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NEW RESEARCH PAPERS

Hypertrophic Cardiomyopathy Patients With Paroxysmal Atrial Fibrillation Have a High Burden of Left Atrial Fibrosis by Cardiac Magnetic Resonance Imaging

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ABSTRACT

OBJECTIVES This study hypothesized that paroxysmal atrial fibrillation (PAF) reflects the presence of a more severe cardiac hypertrophic cardiomyopathy (HCM) phenotype.

BACKGROUND HCM is characterized by myocyte hypertrophy, fibrosis, and a high prevalence of PAF. It is currently unresolved whether atrial fibrillation (AF) is a marker or a mediator of adverse outcomes in HCM.

METHODS This study retrospectively examined 45 HCM patients who underwent cardiovascular magnetic resonance (CMR) imaging in sinus rhythm. The function of all 4 cardiac chambers was assessed, as well as late gadolinium enhancement (LGE) in the left atrium (LA) and left ventricle (LV), as indicators of fibrosis. A fat-saturated, 3-dimensional inversion recovery-prepared, fast-spoiled, gradient-recalled echo sequence, and the image intensity ratio method were used to measure LA-LGE; LGE in the LV was quantified using a semi-automated threshold technique.

RESULTS HCM patients (n = 45) were divided into 2 groups (PAF, no AF) based on history of PAF. All HCM patients had LGE in the LA posterior wall. The PAF group (n = 18) had higher LA volume, a lower LA ejection fraction, a lower global peak longitudinal LA strain (PLAS), and a higher amount of LA-LGE compared with the no AF group (n = 27). A modest inverse association was noted between the LA ejection fraction, PLAS, and LA-LGE; a positive association was present between LV-LGE and LA-LGE. The PAF group had lower ejection fractions in the LV, right atrium, and right ventricle compared with those in the no AF group.

CONCLUSIONS PAF is associated with a greater degree of structural LA remodeling and global myopathy, which suggests a more severe cardiac HCM phenotype. (J Am Coll Cardiol EP 2019;5:364–75) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Hypertrophic cardiomyopathy (HCM), which is most frequently caused by mutations in genes that encode sarcomeric proteins, manifests as myocyte hypertrophy, disarray, and fibrosis (1). Expression of mutant contractile proteins in atrial and ventricular myocytes predisposes to contractile dysfunction and electrical remodeling, which could contribute to an increased risk of atrial and ventricular arrhythmias in HCM patients.

Atrial fibrillation (AF) is the most common arrhythmia in HCM patients, with a prevalence of 19% to 30% (2–4). Left atrial (LA) imaging studies in HCM patients demonstrate that increased LA size (≥45 mm) is a strong predictor of AF (5–7). However, not all HCM patients with LA dilation have AF, and HCM patients can develop AF in the absence of LA dilation. Hence, there is a need for noninvasive characterization of the arrhythmogenic substrate in the LA and for biomarkers that improve AF prediction in HCM.

It is now possible to assess replacement fibrosis in the LA noninvasively by quantifying late gadolinium enhancement (LGE) in the LA (LA-LGE) wall using cardiovascular magnetic resonance (CMR) imaging (8,9). LA CMR imaging has revealed greater amounts of LA-LGE and functional impairment of the LA, in non-HCM patients with permanent AF compared with patients who have paroxysmal atrial fibrillation (PAF) (5,10). However, the prevalence of LA-LGE and its association with AF has not been investigated in HCM.

It is currently unresolved whether AF drives adverse outcomes or whether AF is a marker of a more severe cardiac phenotype in HCM. Previous studies have demonstrated an association between AF and adverse outcomes (e.g., heart failure, stroke, and death) (2,3,4,11) in HCM patients. Interestingly, there was no difference in mortality between HCM patients with PAF and patients with permanent AF (3,11), which suggests that the hemodynamic effects of AF might not be driving adverse outcomes in HCM patients. Furthermore, because most HCM patients are treated with beta blockers or calcium channel blockers, ventricular rates are usually well controlled during episodes of PAF, thus reducing the likelihood of tachycardia-mediated cardiomyopathy. This led us to hypothesize that HCM patients with a history of PAF have a more severe cardiac phenotype, which manifests as a greater degree of structural remodeling of the LA and global myopathy, compared with HCM patients without a history of AF. To test this hypothesis, we assessed LA mechanics, measured LGE in the LA and left ventricle (LV), and measured ejection fractions (EFs) of all 4 cardiac chambers during sinus rhythm in HCM patients with and without a history of PAF by CMR, using sequences that were validated previously (12) by electroanatomic mapping in the LA.

METHODS

HCM PATIENTS. The HCM Registry is approved by the institutional review boards of the Johns Hopkins Hospital and the University of California San Francisco. Patients were enrolled in the HCM Registry during their first clinic visit. All HCM patients underwent CMR imaging, exercise echocardiography (ECHO), and 24-h Holter monitoring before their first clinic visit. Patients underwent 24-h Holter monitoring, implantable cardioverter-defibrillator (ICD) interrogation, and exercise ECHO at yearly follow-up visits. All patients were advised to meet with a genetic counselor and were offered clinical genotyping.

Inclusion criteria. HCM patients who underwent contrast-enhanced CMR imaging with the fat-saturated 3-dimensional inversion recovery-prepared, fast-spoiled, gradient-recalled echo sequence and who were in sinus rhythm during imaging were included in the study. PAF was defined as AF that terminated spontaneously or with intervention in ≤7 days of AF onset (13,14). History of PAF before CMR imaging was confirmed by examination of electrocardiographic and Holter recordings. Patients with PAF had confirmed termination of AF within the 7-day window, either by Holter monitoring or electrocardiography. Review of Holter monitoring and/or event recorder examinations, and of medical records was performed in patients from the no AF group to ensure there was no documented history of AF before the first clinic visit.

Exclusion criteria. We excluded HCM patients with history of persistent or permanent AF because of a documented association between these forms of AF with a high burden of LA fibrosis (15,16). We also excluded patients with poor CMR image quality, ICD implantation, a history of ablation for

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
CMR = cardiac magnetic resonance
ECHO = echocardiography
EF = ejection fraction
HCM = hypertrophic cardiomyopathy
ICD = implantable cardioverter-defibrillator
IIR = image intensity ratio
LA = left atrium
LGE = late gadolinium enhancement
LV = left ventricle
PAF = paroxysmal atrial fibrillation
PLAS = peak longitudinal LA strain
SR-ed = strain rates during early ventricular diastole
SR-ld = strain rates during late ventricular diastole
SR-s = strain rates during ventricular systole

All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

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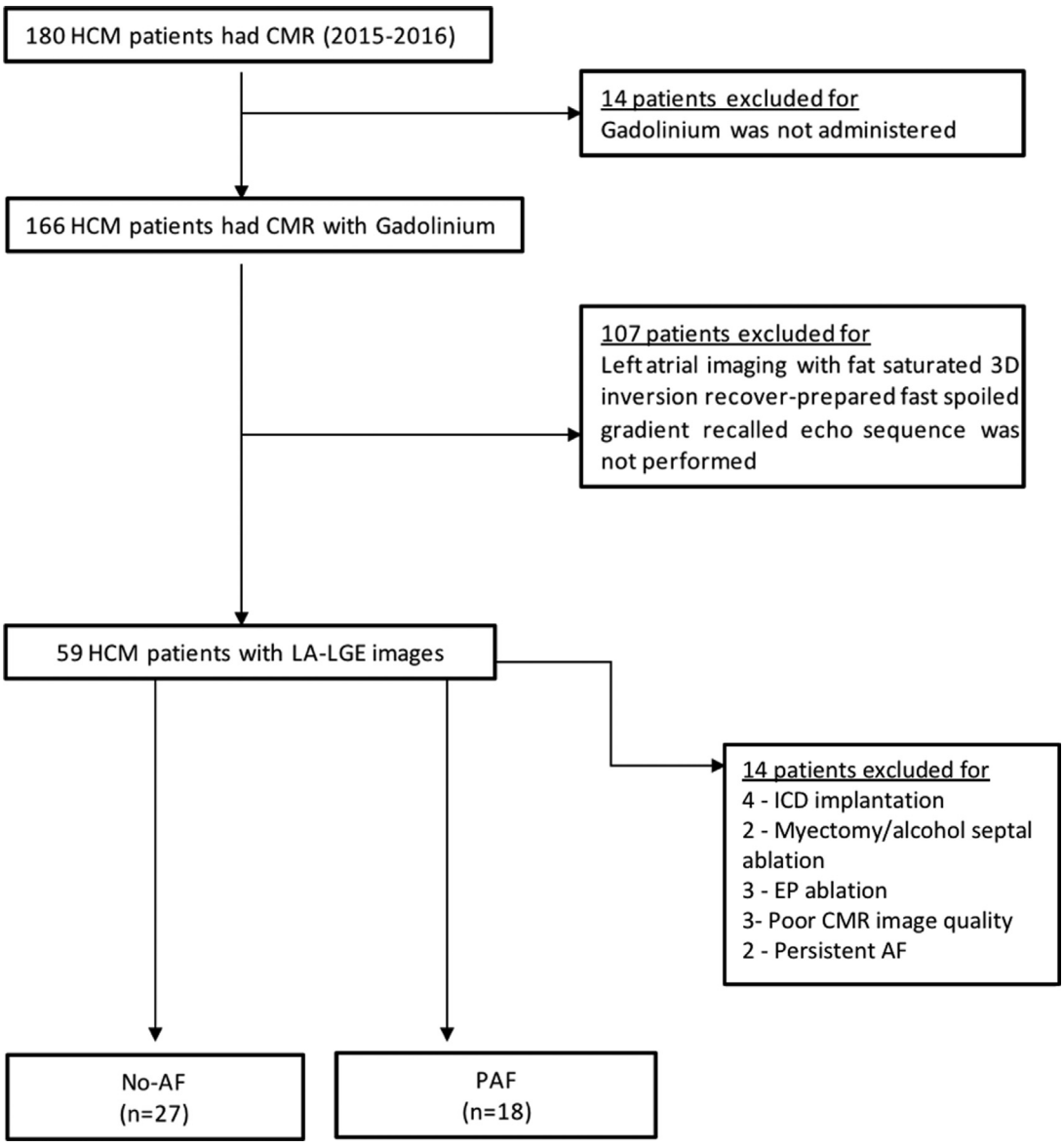
FIGURE 1 Flowchart of HCM Patient Selection



The selection process and reasons for patient exclusion from the study. AF = atrial fibrillation; CMR = cardiac magnetic resonance; EP = electrophysiology; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; LA-LGE = left atrial late gadolinium enhancement; PAF = paroxysmal atrial fibrillation.

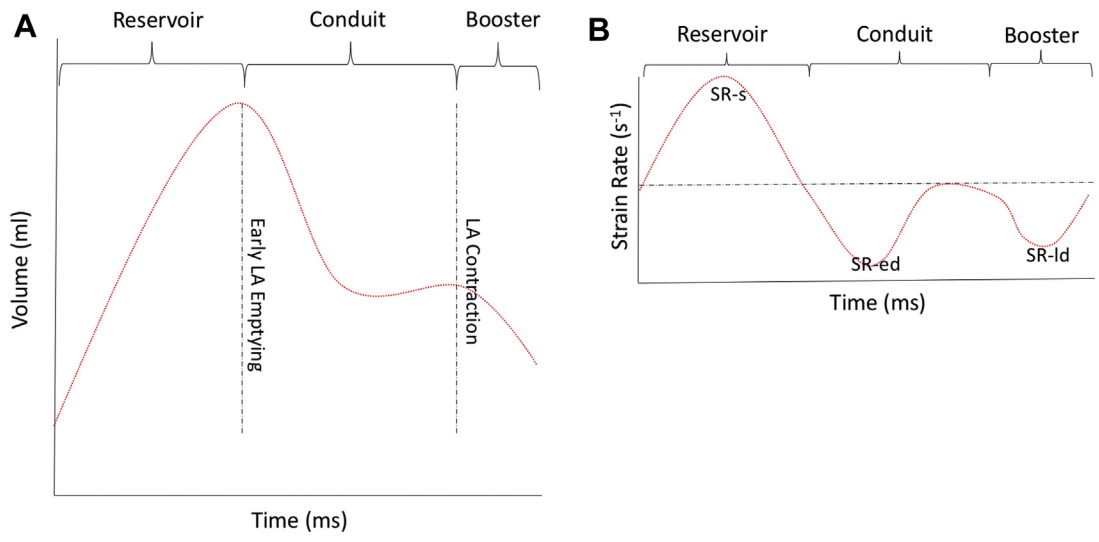
supraventricular arrhythmias, septal myectomy, and alcohol septal ablation before their first clinic visit.

STUDY POPULATION. HCM. We retrospectively identified 59 HCM patients from the HCM Registry who were in sinus rhythm during contrast-enhanced CMR imaging with the 3-dimensional LA-LGE sequence. We excluded 14 patients using the previously mentioned exclusion criteria, which resulted in a total of 45 HCM patients (18 in the PAF group and 27 in the no AF group) in this study (**Figure 1**).

Control subjects. Twelve asymptomatic subjects with no risk factors for coronary artery disease and no documented history of cardiovascular disease were recruited as healthy control subjects.

CMR IMAGING ACQUISITION AND ANALYSIS. All patients were in sinus rhythm during CMR imaging. Imaging was performed on a 1.5-T scanner. Please see the Online Appendix for detailed methods related to CMR image acquisition and analysis.

FIGURE 2 LA Volume and Strain Rate Curves



(A) Schematic of left atrial (LA) volume curve. **(B)** Schematic of LA strain rate curve using the ventricular cycle. SR-ed = strain rates during early ventricular diastole; SR-ld = strain rates during late ventricular diastole; SR-s = strain rates during ventricular systole.

Briefly, electrocardiographically-gated cine images covering the entire LV and RV, as well as single plane 4-chamber and 2-chamber views, were acquired using a standard balanced steady-state free precession sequence. A fat-saturated, 3-dimensional inversion recovery-prepared, fast-spoiled, gradient-recalled echo sequence with electrocardiographic gating and respiratory navigation was used to image LA-LGE. The optimal inversion time was identified with a scout scan (median: 270 ms; range 240 to 290 ms) to maximize nulling of the LA myocardium.

LA image analysis. Images were processed offline using Mass Research (Leiden University, Leiden, the Netherlands), MTT (Toshiba, Tokyo, Japan), and QMass (Medis, Leiden, the Netherlands) software. All image analyses were blinded to clinical data.

LA volumes. LA function was assessed from cine images. MTT software generated LA volume curves during the cardiac cycle (Figure 2A). Measurements for maximum LA volume (LAVmax), LA volume before LA contraction (LAVpre-a), and minimum LA volume (LAVmin) were extracted from the volume and/or time curves. LA passive and active emptying fractions were calculated as follows:

LA passive emptying fraction:

$$100 \times (\text{LAVmax} - \text{LAVpre} - \text{a})/\text{LAVmax}$$

LA active emptying fraction:

$$100 \times (\text{LAVpre} - \text{a} - \text{LAVmin})/\text{LAVpre} - \text{a}$$

LA strain. Global peak longitudinal LA strain (PLAS) was measured from the longitudinal strain curves in all LA segments obtained in 2-chamber and 4-chamber views. Longitudinal strain rate curves were used to compute LA strain rates during ventricular systole (SR-s), early ventricular diastole (SR-ed), and late ventricular diastole (SR-ld); SR-s, SR-ed and SR-ld represented the LA reservoir, conduit, and booster pump function, respectively (Figure 2B).

LA-LGE. LA endocardial and epicardial contours were segmented manually, excluding the LA appendage and pulmonary veins (Figure 3). Mean blood pool intensity was determined from a multi-slice image histogram. The mean blood pool intensity value was multiplied by a factor of 1.22 to obtain the threshold value for LA-LGE (1.22 represents the image intensity ratio [IIR] threshold corresponding to the bipolar voltage of <0.3 mV).

Inter-observer and intra-observer variability. LA contouring was repeated for a random sample of 10 patients by the primary (S.S.) and second independent (T.Z.) observer respectively. The inter- and intra-observer correlation coefficients for measuring LA-LGE were 0.78 to 0.97 (Online Table 1).

STATISTICAL ANALYSIS. HCM patients were divided into 2 groups (PAF and no AF) based on documentation of PAF. Continuous variables are expressed as mean ± SD, and categorical variables are presented as number and percentage. Student's *t*-test was used to compare normally distributed data, and the Mann-Whitney *U* test was used for non-normally distributed data. Statistical significance was a p value of <0.05.

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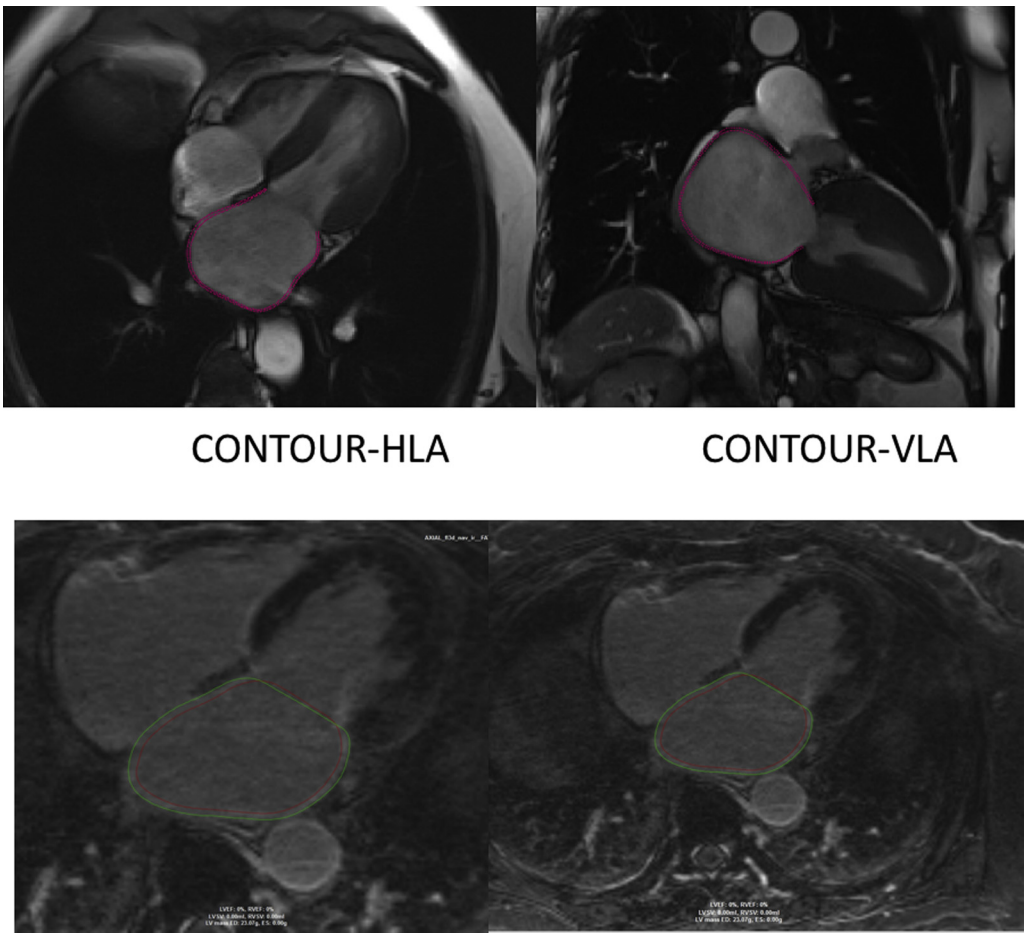
FIGURE 3 LA Segmentation



LA segmentation in an HCM patient using QMass software. HLA = horizontal long-axis view; VLA = vertical long-axis view; other abbreviations as in Figure 1.

The inter-observer and intra-observer agreement were assessed using the intraclass correlation coefficient. Spearman's correlation test was used to test for correlation between numerical continuous variables and LA-LGE percentage. The analyses were performed using Stata software version 14 (StataCorp, College Station, Texas). Patients with the lowest quartile of PLAS (<7), SR-ld (<−0.6), SR-s (<0.4), SR-ed (<−0.4) were considered to have severe LA myopathy.

RESULTS

PATIENT CHARACTERISTICS. We retrospectively studied 45 HCM patients (age range 19 to 86 years), and 12 healthy subjects, who were the control group (Table 1). Eighteen HCM patients (40%) were diagnosed with PAF before CMR imaging. HCM patients were divided into 2 groups (PAF and no AF) based on documentation of PAF. All patients in the PAF group had at least 1 episode of PAF within 12 months of imaging (average of 6.1 ± 4.3 episodes after PAF diagnosis). Most HCM patients in both groups were receiving beta blockers, and 44% of patients in the PAF group were receiving antiarrhythmic therapy. Patients with obstructive and nonobstructive HCM were equally distributed in the 2 groups.

The median follow-up duration was 18 months. Two patients from the PAF group developed permanent AF, and 1 patient developed heart failure. None of the HCM patients in the no AF group developed AF during follow-up. Five patients underwent ICD implantation during follow-up.

A subset of HCM patients (n = 14) underwent clinical genotyping. Pathogenic variants were found in the *MYBPC3* (myosin binding protein C), *MYH7* (myosin heavy chain beta 7), *MT-ND5* (NADH dehydrogenase 5), *TNNT2* (cardiac troponin T), *RYR2* (ryanodine receptor 2), *ACTN2* (actinin alpha 2), *MYPN* (myopalladin), *FKTN* (fukutin), and *DMD* (dystrophin) genes. Genotype data stratified by PAF status is presented in Online Table 2.

LA PROFILE IN HCM PATIENTS. HCM patients with history of PAF had a larger LA, characterized by higher LA diameter and/or volume and a lower LA ejection fraction (LA-EF) compared with those in HCM patients in the no AF group. The PAF group also had evidence of lower LA compliance, which was reflected by a significantly lower global PLAS, SR-s, and SR-ed compared with those in the no AF group (**Table 2, Figures 4A to 4D**). Notably, one-third (6 of 18) of patients in the PAF group had the lowest quartile of LA strain and strain rate (PLAS: <7; SR-s: <0.4; SR-ld: <−0.6; and SR-ed: <−0.4), which indicated low LA compliance and contractility (Online Table 3, **Figure 4A and 4B**).

All HCM patients had evidence of LA-LGE, but the PAF group had a significantly higher amount of LA-LGE compared with that of the no AF group (**Table 2, Figure 5A**). The posterior wall of the LA was involved in all patients, with the region near the left inferior pulmonary vein being the most frequent location of LGE (**Figure 5B**). The LA anterior wall and/or septum was affected in 42% of HCM patients, but the extent of LGE in this region was significantly less than that observed in the LA posterior wall.

Modest inverse correlations were observed between LA-EF, global PLAS, resting LV outflow tract gradients and LA-LGE (**Figure 6A to 6C**).

RA, RV, AND LV FUNCTION IN HCM PATIENTS. HCM patients with history of PAF had lower EFs of the LV, right ventricle, and right atrium compared with those in the no AF group (**Table 3**). A modest positive association was present between LV-LGE and LA-LGE (**Figure 6D**).

LA PROFILE IN HEALTHY CONTROL SUBJECTS. Control subjects ranged in age from 35 to 55 years of age. Control subjects had significantly lower LA size and/or volumes and significantly higher LA-EFs, global PLAS, and systolic, early diastolic, and late diastolic strain rates compared with those in HCM patients (**Table 2**). Four healthy control subjects (33%) had no evidence of LA-LGE (**Figure 5A and 5B**). The LA posterior wall was the most common site for LGE; only 1 control subjects had evidence of LGE in the LA anterior wall and/or septum. As in the case of HCM patients, LGE was most frequently located in the region of the left inferior pulmonary vein, but the extent of LA-LGE was markedly lower than that seen in HCM patients (**Figure 5A**).

TABLE 1 Clinical Profile of HCM Patients and Control Subjects

	PAF-HCM (n = 18)	No-AF-HCM (n = 27)	p Value	Controls (Non-HCM) (n = 12)
Demographics				
Age, yrs	61 ± 14	64 ± 13	NS*	45 ± 10
Male	10 (56)	17 (63)	NS*	8 (67)
Clinical characteristics				NA
Nonobstructive	9 (50)	9 (33)	NS†	
Labile obstructive	4 (22)	7 (26)	NS†	
Obstructive	5 (28)	11 (41)	NS†	
NYHA functional class I	9 (50)	21 (78)	NS†	
NYHA functional class II	5 (28)	5 (19)	NS†	
NYHA functional class III	4 (22)	1 (3)	NS†	
Hypertension	12 (67)	18 (67)	NS†	
Diabetes	1 (6)	5 (19)	NS†	
Angina	4 (22)	9 (33)	NS†	
Dyspnea	12 (67)	12 (44)	NS†	
Syncope	5 (28)	3 (11)	NS†	
Palpitations	7 (41)	12 (44)	NS†	
Dizziness	7 (41)	8 (30)	NS†	
Medications				None
Beta-blocker	16 (89)	22 (81)	NS†	
Ca-channel blocker	4 (22)	9 (33)	NS†	
ACEi/ARB	8 (44)	9 (33)	NS†	
Statin	13 (72)	17 (63)	NS†	
Diuretic agents	3 (17)	1 (3)	NS†	
DOAC	12 (67)	0 (0)	—	
Warfarin	1 (6)	0 (0)	—	
Anti-arrhythmics	8 (44)	0 (0)	—	
ECHO characteristics				ECHO not performed
LVEF (%)	63 ± 9	70 ± 4	0.04*	
Max wall thickness, mm	21 ± 0.7	20 ± 0.4	NS*	
Rest LVOTG at rest, mm Hg	37 ± 40	52 ± 52	NS†	
Stress LVOTG, mm Hg	52 ± 37	90 ± 65	NS†	
E/A ratio	1.7 ± 1.4	1.1 ± 0.4	NS†	
E/e′	17 ± 9	20 ± 11	NS†	

Values are mean ± SD or n (%). Control subjects were healthy, asymptomatic individuals who were not taking any cardiac medications and did not undergo echocardiography. *Student's *t*-test. †Mann-Whitney *U* test.

ACEi/ARB = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; DOAC = direct oral anticoagulant agent (includes factor Xa inhibitors such as apixiban and direct thrombin inhibitors such as dabigatran); ECHO = echocardiography; HCM = hypertrophic cardiomyopathy; LVEF = left ventricular ejection fraction; LVOTG = peak left ventricular outflow tract gradient; NYHA = New York Heart Association; PAF = paroxysmal atrial fibrillation.

DISCUSSION

This is the first study to investigate LA-LGE and LA function by CMR in HCM patients. We found evidence of LA-LGE in all HCM patients. Notably, HCM patients with PAF had a greater degree of LA structural

TABLE 2 LA Imaging in HCM Cohort and Control Subjects

	PAF-HCM (n = 18)	No AF-HCM (n = 27)	p Value (PAF vs. no AF)	All HCM (n = 45)	Controls Non-HCM (n = 12)	p Value (all HCM vs. Controls)
LA size/function						
LA diameter, cm	5.8 ± 1.0	5.1 ± 0.7	0.01*	5.4 ± 0.9	4.4 ± 0.4	<0.0001†
Max LA volume, ml	110 ± 45	86 ± 15	0.03†	89 ± 24	81 ± 12	NS†
Min LA volume, ml	73 ± 48	45 ± 12	0.01†	48 ± 19	36 ± 8	0.0003†
Max LA volume index, ml/m^2	51 ± 19	44 ± 7	0.01†	47 ± 10	39 ± 6	NS†
Min LA volume index, ml/m^2	32 ± 23	23 ± 5	0.01†	25 ± 8	17 ± 4	0.0008†
LA stroke volume, ml	33 ± 15	37 ± 14	NS*	35 ± 14	45 ± 9	0.01†
LA EF, %	31 ± 15	41 ± 11	0.008*	37 ± 13	56 ± 7	<0.0001†
LAV pre-a, ml	95 ± 43	70 ± 17	0.02†	77 ± 20	49 ± 11	0.001†
LAPEF, %	10 ± 5	13 ± 6	NS†	13 ± 5	25 ± 6	0.003†
LAAEF, %	21 ± 15	31 ± 12	0.04†	29 ± 13	53 ± 5	<0.0001†
LA strain						
PLAS, %	8.4 ± 8.9	19.5 ± 4.4	0.005†	18.3 ± 9.3	30.4 ± 6.7	0.0003†
SR-s, s^{-1}	0.6 ± 0.4	1.03 ± 0.3	0.01*	0.8 ± 0.4	1.23 ± 0.2	0.007†
SR-ed, s^{-1}	−0.2 ± 0.1	−0.5 ± 0.2	0.01†	−0.4 ± 0.2	−1.41 ± 0.5	<0.0001†
SR-ld, s^{-1}	−1.03 ± 0.8	−1.4 ± 0.6	NS*	−1.2 ± 0.7	−1.89 ± 0.5	0.006†
LA-LGE						
LA mass, g	31 ± 10	27 ± 8	NS*	29 ± 9	-	-
LGE mass, %	30 ± 11	20 ± 7	0.03†	22 ± 8	4 ± 4	<0.0001†
LGE mass, g	10.2 ± 3.4	4.9 ± 2.7	0.01†	6.6 ± 3.3	0.6 ± 0.7	<0.0001†

Values are mean ± SD. *Student's *t*-test. †Mann-Whitney *U* test.

LA = left atrial; LAAEF = left atrial active emptying fraction; LAPEF = left atrial passive emptying fraction; LGE = late gadolinium enhancement; PLAS = peak global left atrial longitudinal strain; SR-s = systolic strain rate; SR-ed = early diastolic strain rate; SR-ld - late diastolic strain rate; vol = volume; other abbreviations as in Table 1.

remodeling and lower EFs in all 4 cardiac chambers, which suggested a global myopathic process and a more severe cardiac HCM phenotype.

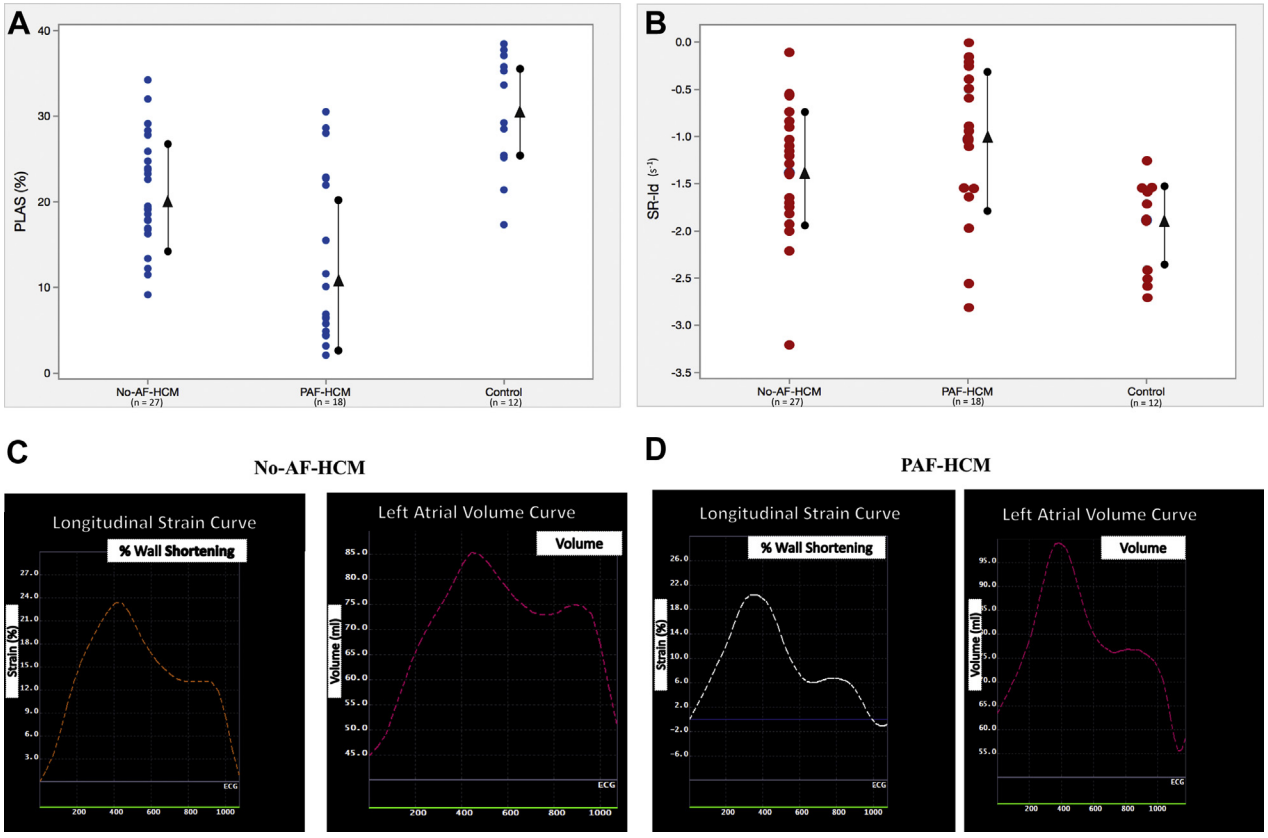
CMR IMAGING OF LA FIBROSIS AND FUNCTION. A high burden of LA fibrosis (17) has been reported in autopsy studies of HCM patients with LV dysfunction and heart failure. However, LA fibrosis has not been investigated in HCM patients with preserved LVEFs (18). In this study, we used the image intensity ratio method developed by Khurram et al. (12) as an indicator of LA fibrosis. The IIR method has been validated by electroanatomic mapping of the LA and has the advantage of using the mean intensity of the LA blood pool as the denominator in the LGE calculation, rather than a standard deviation based scar threshold for computing LGE (12,19). The IIR method was developed with the intent of reducing interpatient and interscan variability that result from variations in the proximity of the surface coil, body mass index, contrast dose, timing of image acquisition, hematocrit, and renal function (12).

We found evidence of LGE in the LA posterior wall in all HCM patients. A previous study that used electroanatomic mapping in non-HCM patients with PAF also reported regional variation in LA fibrosis (20). The authors found significantly more low voltage points in the posterior and septal walls of the LA in patients with PAF compared with that in patients with atrial tachycardia (20). Greater structural remodeling in the LA posterior wall (compared with the LA appendage) was also observed in a pathological study of patients with mitral valve disease and permanent AF who underwent open heart surgery (21). The mechanisms underlying regional variations in fibrosis are unknown and could include higher wall stress related to low wall thickness of the LA posterior wall.

We detected LA-LGE in healthy control subjects using our method, which quantified the signal in the LA wall. Notably, LA-LGE in control subjects and HCM patients was most frequently located in the LA posterior wall near the left inferior pulmonary vein, which was similar to that reported in non-HCM patients with AF (22). Although LA-LGE reflected areas of low voltage reflecting fibrosis, there was likely overlap in signal intensity between normal and fibrotic myocardium, especially on the lower end of the fibrosis scale, which could have contributed to our observed results.

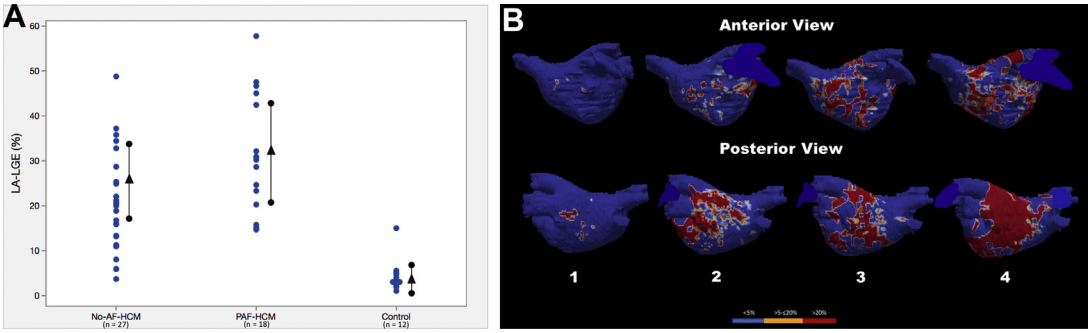
CMR provides accurate measurements of LA volume and also permits tracking of myocardial motion

FIGURE 4 **LA Strain in HCM Patients and Control Subjects**



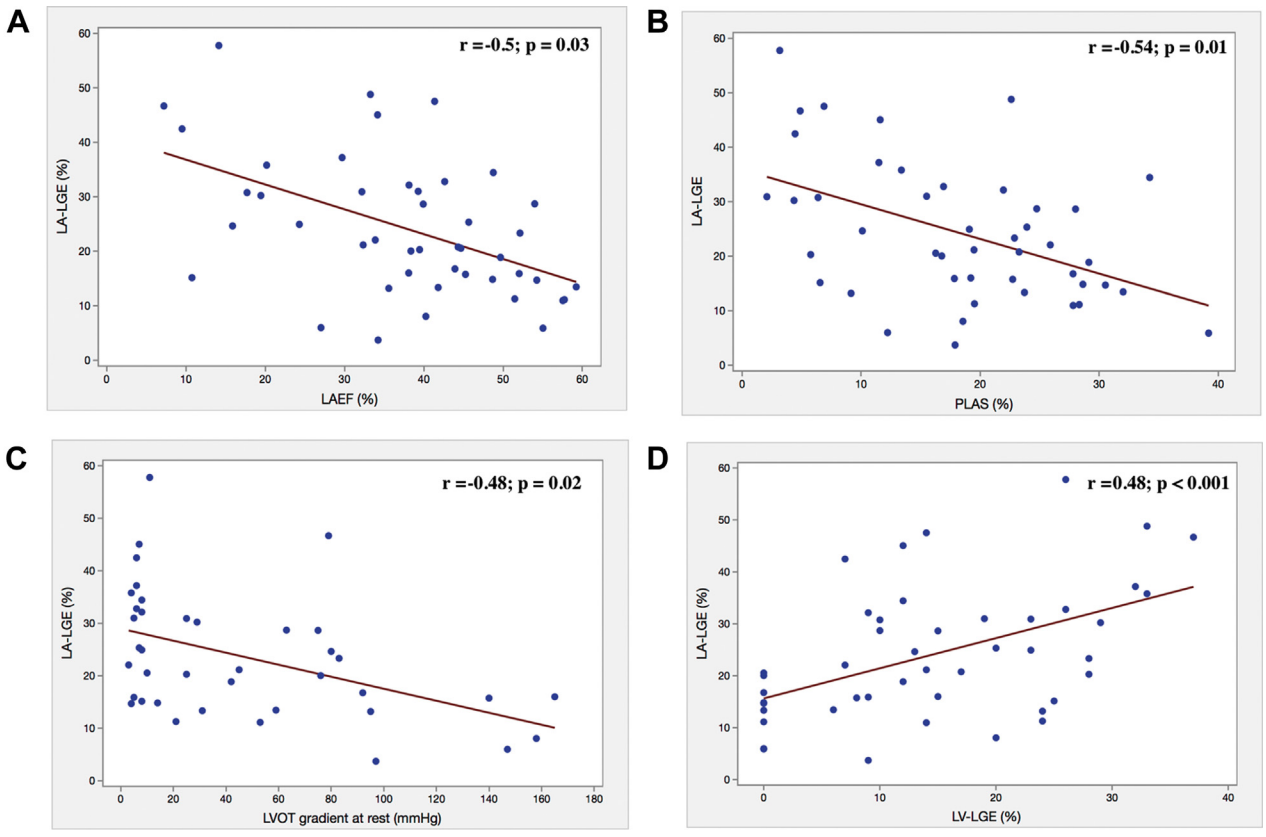
(A) Distribution of global peak longitudinal LA strain (PLAS) in PAF-HCM, no AF-HCM and control groups. **(B)** Distribution of SR-ld in PAF-HCM, no AF-HCM, and control groups. **(C)** Representative LA strain and LA volume curves in HCM patient without AF and **(D)** a patient with PAF. Abbreviations as in Figures 1 and 2.

FIGURE 5 **LA-LGE in HCM and Controls Subjects**



(A) The PAF-HCM group had significantly higher amounts of LA LGE (calculated as percentage of LA mass) compared with the no AF-HCM and control groups. **(B)** Representative 3-dimensional LA-LGE maps of the posterior wall and anterior and/or septal wall in **(1)** control subject, **(2 to 3)** 2 HCM patients from the no AF group, and **(4)** an HCM patient with a history of PAF. **Color bar** represents percentage of transmural LGE in the LA wall. Abbreviations as in Figure 1.

FIGURE 6 Correlations With LA-LGE in HCM



Statistically significant inverse correlations of **(A)** LA ejection fraction (EF), **(B)** global PLAS, and **(C)** resting left ventricular outflow tract (LVOT) gradient and LA-LGE. **(D)** Modest positive correlation between LV-LGE and LA-LGE. Abbreviations as in Figure 1.

because of its ability to accurately define endocardial and epicardial borders (23). We used a feature tracking technique that uses cine CMR images to measure LA strain and the strain rate. We found lower values for LA reservoir strain (global PLAS) for HCM patients in the PAF group compared with those in the no AF group, which reflected lower LA compliance. Patients in the PAF group also had greater amounts of LA-LGE, which could contribute to lower LA compliance. Beta-blocker use, which was associated with impairment of LA strain (24), was similar in both groups; hence, it was unlikely to have contributed to the differences in LA strain observed between the PAF and no AF groups.

We found a modest inverse correlation between LV outflow tract gradients at rest and LA-LGE, which suggested that high LV and LA pressures generated by LV outflow tract obstruction might not be the main driver of LA-LGE. These results were supported by a previous study from our group that reported a greater extent of LV-LGE (>20% of LV mass) and a greater degree of LV myopathy in HCM patients with non-obstructive HCM (25). Interestingly, pathology studies also reported lower amounts of LA fibrosis in patients with severe mitral valve disease (without AF) compared with HCM patients with systolic dysfunction and/or heart failure, which suggested that mechanical overload might not be sufficient to cause marked fibrotic changes in the LA (17). In the case of HCM, because expression of mutant sarcomeric proteins in cardiac myocytes can lead to contractile dysfunction and promote cardiac fibrosis (26,27), we hypothesized that the extent of LGE, which reflects replacement fibrosis, could reflect the degree of myopathy in HCM patients. Our hypothesis of a global myopathic process in HCM was supported

TABLE 3 Summary of Biventricular and RA Characteristics by CMR in HCM Patients and Control Subjects

	PAF-HCM (n = 18)	No AF-HCM (n = 27)	p Value (PAF vs. no AF)	All-HCM (n = 45)	Controls Non-HCM (n = 12)	p Value (All-HCM vs. Controls)
LV function						
EDV, ml	135 ± 41	138 ± 33	NS*	137 ± 36	157 ± 30	NS†
EDV index, ml/m^2	76 ± 23	71 ± 18	NS*	73 ± 20	78 ± 9	NS†
ESV, ml	50 ± 11	41 ± 6	NS†	43 ± 8	57 ± 14	0.01†
ESV index, ml/m^2	24 ± 4	20 ± 4	0.02†	22 ± 4	28 ± 5	NS†
Stroke volume, ml	86 ± 32	95 ± 24	NS*	91 ± 27	100 ± 20	NS†
LVEF, %	64 ± 4	71 ± 3	0.01†	67 ± 4	64 ± 5	0.02†
Cardiac output, l/min	6.5 ± 1.4	6.4 ± 1.0	NS†	6.5 ± 1.1	6.6 ± 2.0	NS†
Mass, g	161 ± 49	156 ± 44	NS†	158 ± 46	126 ± 14	0.04†
LVMI, g/m^2	84 ± 31	77 ± 19	NS†	80 ± 24	61 ± 9	0.04†
RA function						
EDV, ml	86 ± 31	60 ± 30	NS†	75 ± 31	68 ± 14	NS†
ESV, ml	60 ± 28	36 ± 20	0.001†	45 ± 26	28 ± 5	0.05†
EF, %	33 ± 19	48 ± 21	0.001*	43 ± 25	59 ± 5	<0.0001†
RV function						
EDV index, ml/m^2	55 ± 24	60 ± 22	NS†	58 ± 23	81 ± 10	0.004†
ESV index, ml/m^2	24 ± 12	22 ± 9	NS†	23 ± 10	31 ± 7	0.02†
EF, %	54 ± 7	65 ± 6	<0.0001*	62 ± 10	62 ± 7	NS†
LV LGE						
LGE mass, g	27.6 ± 11.6	15.3 ± 19.5	NS†	20.9 ± 11.6	–	–
LGE volume, ml	26.3 ± 11.0	14.6 ± 18.6	NS†	19.9 ± 11.0	–	–
LGE, % LV mass)	16.8 ± 10.6	13.3 ± 10.9	NS*	14.7 ± 10.8	–	–

Values are mean ± SD. *Student's *t*-test. †Mann-Whitney *U* test.

CMR = cardiac magnetic resonance; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; LV = left ventricle; LVMI = left ventricular mass index; RA = right atrium; RV = right ventricle; other abbreviations as in Tables 1 and 2.

by our finding of a positive association for LGE in the LA and LV.

PAF IS ASSOCIATED WITH A GREATER DEGREE OF MYOPATHY IN HCM. Our study revealed that EFs of the right atrium, right ventricle, LA, and LV were lower in the PAF group compared with those in the no AF group. It was less likely that the lower EFs were the result of a tachycardia-mediated myopathy, because all patients were in sinus rhythm at the time of CMR, and most patients were on beta-blockers (which reduce risk for rapid ventricular response during AF). Instead, the lower EFs in the PAF group could reflect a global myopathic process.

We saw no difference in the amount of LV-LGE, LV outflow tract gradients, and LV diastolic function between the PAF-HCM and no AF-HCM groups. However, we did observe a wide variance of global PLAS in the PAF-HCM group. Furthermore, a significant proportion (6 of 18) patients in the PAF-HCM group had markedly reduced LA compliance (PLAS: <7%; SR-s; <0.4; SR-ed: <−0.4) and LA systolic function (SR-ld: <−0.6) in sinus rhythm, which reflected the presence of severe LA myopathy. Taken together, our results of significantly lower LA reservoir and conduit strain, lower LA contractility, as well as larger LA size and/or volume, and greater amounts of LA-LGE in the HCM-PAF group indicated that PAF is associated with a greater degree of LA myopathy in HCM. The presence of severe LA myopathy could predispose patients to LA appendage thrombus and embolic stroke, as well as reduce the success of catheter ablation of AF.

We observed a positive correlation between replacement fibrosis reflected by LGE in the LV and LA, but the percentage of myocardium involved by LGE was significantly higher in the LA compared with the LV. A greater amount of fibrosis in the LA compared with that in the LV was reported previously in transgenic mouse models that expressed mutant transforming growth factor-β1 in the heart (28,29). Our study illustrated this phenomenon in HCM patients. Because activation of TGF-β1 signaling was implicated in the generation of cardiac fibrosis in HCM (29), we speculated that one mechanism underlying the differences in the amount of LA and LV fibrosis detected in our study could be greater predilection of LA fibroblasts to proliferate and/or

secrete the extracellular matrix (in response to transforming growth factor-β1) compared with LV fibroblasts (30). Another possibility was the differences in the methods used to quantify LGE in the LA and LV in our study.

STUDY LIMITATIONS. This was a retrospective pilot study that excluded HCM patients with persistent and/or permanent AF. Multivariate adjustment was not performed due to the small sample size. We did not implant loop recorders for rhythm monitoring, which could have led to misclassification of HCM patients with subclinical PAF into the no AF group. We acknowledged that the association between voltage and CMR intensities, in validating LA fibrosis, was dependent on several factors and was not 100% sensitive or specific. In addition, we did not measure LGE in the roof of the LA, due to the challenge of capturing the myocardium in its entirety because of the partial volume effect.

CONCLUSIONS

HCM patients had a high prevalence of LA-LGE, which reflected replacement fibrosis by CMR imaging. PAF was associated with a greater degree of LA structural remodeling and global myopathy, which suggested a more severe cardiac HCM phenotype.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Our pilot CMR study revealed that all of our HCM patients had evidence of LGE in the LA posterior wall, which could explain the high prevalence of AF in the HCM patient population. Fibrosis would reduce the velocity of impulse conduction in the LA and predispose to development of conduction block and reentrant arrhythmias such as AF. Based on our results, CMR imaging of LA-LGE and LA function might be useful to identify HCM patients at high risk for developing AF, who could benefit from antifibrotic and/or anticoagulation therapies to prevent strokes.

TRANSLATIONAL OUTLOOK: This was a retrospective pilot study that excluded HCM patients with persistent and/or permanent AF. Multivariate adjustment was not performed due to the small sample size. Our study design did not permit us to assess whether LA fibrosis led to PAF or whether PAF led to LA fibrosis. We did not implant loop recorders for rhythm monitoring, which could have led to misclassification of HCM patients with subclinical PAF into the no AF group. Furthermore, results from our patient cohort might not be extrapolated to asymptomatic HCM patients because our patient population consisted of HCM patients referred for symptom management. We acknowledged that the association between voltage and CMR intensities, in validating LA fibrosis, was dependent on several factors and was not 100% sensitive or specific. In addition, we did not measure LGE in the roof of the LA, due to the challenge of capturing the myocardium in its entirety because of the partial volume effect.

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KEY WORDS **cardiovascular magnetic resonance imaging, hypertrophic cardiomyopathy, late gadolinium enhancement in the left atrium, paroxysmal atrial fibrillation**

APPENDIX **For an expanded Methods section and supplemental tables, please see the online version of this paper.**