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ORIGINAL PAPER

Left atrial fibrosis correlates with extent of left ventricular myocardial delayed enhancement and left ventricular strain in hypertrophic cardiomyopathy

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Abstract

Hypertrophic cardiomyopathy (HCM) is associated with increased left ventricular (LV) mass, decreased myocardial strain, and the presence of LV fibrosis and scar. The relationship between LV scar and fibrosis with left atrial (LA) fibrosis in the setting of HCM has not been examined. The purpose of this study is to demonstrate a correlation between the degree of LA fibrosis and LV parameters in subjects with HCM. Twenty-eight subjects with HCM were imaged on a 1.5T MRI scanner with cine, LV and LA late gadolinium enhancement (LGE) sequences. LA LGE and LA measurements were correlated with LV measurements of volumes, mass, strain, and LGE. Other clinical conditions and medication usage were also examined and evaluated for correlation with LA and LV parameters. LV LGE was identified in 24 (86%) of the cases and LA LGE was identified in all of the cases. Extent of LA fibrosis significantly correlated with percent LV LGE ($r = 0.64$, $p = 0.001$), but not with indexed LV mass or maximum wall thickness. Extent of LA fibrosis also moderately correlated with decreased LV global strain (radial, $r = -0.50$, $p = 0.013$; circumferential, $r = 0.47$, $p = 0.02$; longitudinal, $r = 0.52$, $p = 0.013$). Increased LA systolic volume correlated moderately with LV end diastolic volume ($r = 0.50$, $p = 0.006$). Patients on therapy with Renin-Angiotensin-Aldosterone System (RAAS) Inhibition had significantly less LA LGE compared to those without (18.6% vs 10.8%, $p = 0.023$). LA fibrosis, as measured by LGE, is prevalent in HCM and is correlated with LV LGE. The correlation between LA and LV LGE might suggest either that LA fibrosis is a consequence of LV remodeling, or that LA and LV fibrosis are both manifestations of the same cardiomyopathic process. Further study is warranted to determine the causality of LA scar in this population.

Keywords Left atrial fibrosis · Hypertrophic cardiomyopathy · Left ventricular late gadolinium enhancement · Left ventricular strain

Abbreviations

ACE-I	Ace inhibitors
AF	Atrial fibrillation
ARB	Angiotensin receptor blockers
CMR	Cardiovascular magnetic resonance
ECG	Electrocardiogram
EF	Ejection fraction
GRAPPA	Generalized auto calibrating partially parallel acquisition
HCM	Hypertrophic cardiomyopathy
LA	Left atrium/atrial
LGE	Late gadolinium enhancement
LIFE	Losartan intervention for end point reduction in hypertension study
LV	Left ventricle/ventricular
mm	Millimeter
mm^3	Millimeter cubed
mmol/kg	Millimole/kilogram
PACS	Picture archiving and communication system
RAAS	Renin–Angiotensin–Aldosterone system
SCD	Sudden cardiac death
SSFP	Steady state free precession

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STE	Speckle tracking echocardiography
TDI	Tissue Doppler imaging
TE	Echo time
TR	Repetition time

Introduction

Hypertrophic cardiomyopathy (HCM) is one of the most common cardiovascular genetic disorders. Since the first patient was formally diagnosed in 1958, HCM is increasingly being recognized in a wide array of patients [1–3]. Clinically, HCM manifests with significant genotypic and phenotypic heterogeneity. At the histologic level, it is characterized by left ventricular hypertrophy, myocyte disarray, and interstitial fibrosis. The form of fibrosis in HCM (interstitial fibrosis and replacement fibrosis) is distinct from that which is seen in ischemic heart disease and its extent has been correlated with clinical risk for sudden death and arrhythmias, and is predictive of adverse outcomes including heart failure [4].

Increasingly, cardiovascular magnetic resonance (CMR) imaging is being used as a non-invasive assessment of HCM, and in particular for fibrosis in HCM patients using the LGE imaging technique [5]. Myocardial fibrosis quantification by CMR correlates well to histopathologic samples [4]. In a recent meta-analysis, it was demonstrated that quantitative assessment of LGE on CMR is predictive of multiple adverse events, including sudden cardiac death (SCD), heart failure, cardiovascular mortality, and all-cause mortality [6]. In HCM specifically, the presence of LV scar is a strong independent predictor of all-cause and cardiac mortality in this population. Bruder, et al. followed 220 patients over a period of 3 years and found that, despite being asymptomatic, the presence of scar was significantly associated with a hazard ratio of 5.47 for all-cause mortality [7].

Besides LV fibrosis, another finding in HCM is abnormalities of myocardial strain. Strain is a sensitive measure of LV function that has traditionally been measured using echocardiography to assess for subclinical LV dysfunction in cardiomyopathies. Strain can be measured using tissue Doppler imaging (TDI) or speckle tracking echocardiography (STE) [8], and recently using CMR feature tracking. In HCM, decreased longitudinal, circumferential, and radial strain have been described, even in the absence of abnormal LGE [9]. Interestingly, Popovic, et al. and Saito, et al. both demonstrated that decreased strain is associated with myocardial fibrosis and adverse cardiac events [9, 10] in HCM. Macron, et al. reported that, in patients with a diagnosis of HCM, increase in LV mass is significantly associated with impairment in global peak circumferential strain [11].

Beyond the attention paid to the left ventricle in HCM, it has been noted that there are also changes in the left atrial (LA) size and function. It is well established that with dilatation of LA volume in patients with HCM, there is an increased risk of sudden death, advanced NYHA classification symptoms, and cardiac arrest [12, 13]. Additionally, combination of AF and HCM is associated with markedly increased risk of stroke [14]. While LA fibrosis and scar imaging have been studied in the context of recurrent atrial fibrillation after therapy [15], the findings of LA fibrosis and their relationship with other described features of HCM is unknown. The purpose of this study is to demonstrate a correlation between the degree of LA fibrosis and LV fibrosis and strain in patients with HCM.

Methods

Study population

A retrospective chart review was performed of all consecutive CMR imaging studies of patients with a known diagnosis of HCM from January 2012 to June 2016 who had 3D LA LGE imaging. Selection of patients with HCM included: (1) individuals with wall thickness ≥ 15 mm without history of hypertension, and (2) individuals with wall thickness ≥ 15 mm with history of hypertension, but had LGE at the thickened segments in a nonischemic pattern. Patients with a history of prior cardiac surgery, moderate or severe mitral regurgitation, or prior AF ablation were excluded from the study. Twenty-eight total patients were identified. 3D LA LGE was excluded from analysis for 5 patients due to suboptimal image quality. After initial identification of subjects in our picture archiving and communication system (PACS) data-base, chart review of the electronic medical record was conducted to extract subjects' clinical information, including medical history and medication use at the time of the scan.

Cardiac imaging and analysis

CMR imaging was performed on Siemens 1.5T MR scanners at our institution (Aera, Siemens Healthcare, Erlangen Germany). Subjects were imaged with steady state free precession (SSFP) cine in the vertical long-axis view, horizontal long-axis view, LV outflow tract view, along with contiguous short axis slices of the left ventricle from the base to apex. Scan parameters include: Balanced SSFP cine with retrospective ECG-triggering, TR/TE/$\theta = 3$ ms/1.5 ms/60°, 30 cardiac phases, $1.4 \times 1.4 \times 8$ mm resolution. LV LGE was performed 8–10 min after administration of 0.2 mmol/kg gadolinium contrast agent (Gadobutrol, Bayer Healthcare, Leverkusen, Germany). A Look-Locker sequence (T1 scout) was performed to determine the myocardium null time. Two-dimensional LV LGE was performed in the long

axis views and of contiguous short axis slice of the left ventricle, using inversion recovery gradient echo (TR/TE = 6 ms/3.16 ms, 1.64 × 1.64 × 8 mm) resolution. Left atrial LGE imaging was subsequently acquired after LV LGE imaging. A second Look-Locker sequence was performed to determine the myocardial null time. LA LGE was obtained during mid ventricular diastole using an ECG-triggered and respiratory navigator-gated, fat-saturated 3D gradient echo inversion recovery sequence, 15–20 min after gadolinium contrast. Acquisition time varied from 3 to 10 min, depending on heart rate and diaphragmatic motion variability as determined by the respiratory navigator. Voxel size was 1.32 × 1.32 × 3.0 mm^3 with interpolation to 0.66 × 0.66 × 1.5 mm^3. Axial slabs were acquired with phase-encoding in the right-left direction. Additional scan parameters were: TR/TE/θ = 5.3 ms/2.1 ms/15°, 25 views per segment were acquired, in a ky-centric order. A generalized autocalibrating partially parallel acquisition (GRAPPA) factor of 2 was used.

All identified CMR studies were then independently processed by experienced CMR readers using a vendor-independent post-processing software CMR42 (v5.2.3 Circle Cardiovascular Imaging, Calgary, Alberta, Canada). LV contouring for LV volumes, LV ejection fraction (EF) analysis, and LV mass were performed using the semi-automated edge detection feature, with manual adjustment, on short axis stack images, excluding trabeculations and papillary muscles from the volume. Linear LV wall thickness measurements were performed based on the 16-segment model of the left ventricle [16].

LV strain analysis was performed in radial, circumferential and longitudinal orientations using SSFP cine in short axis, 2-chamber, 3-chamber, and 4-chambe slices using tissue feature tracking module in CMR42 [17]. Tissue tracking recognizes patterns of features or irregularities in the image that can be tracked in successive images of a cine sequence. The software identifies a small window on one image and searches for a comparable image in a window of the succeeding frame of the cine. This displacement of the comparable frame between the slices is interpreted as displacement [18].

LV scar quantification was performed on the 2D short axis LGE images using a semi-automated detection feature, with manual adjustment, using a cutoff value of 6 standard deviations (SD) above a normal reference of myocardium [7] (Fig. 1).

Atrial LGE volume was quantified by a single experienced observer blinded to all other data, as previously described [19]. Briefly, 3D Slicer software (http://www.slicer.org, NA-MIC) was used to define thresholds and segment LA LGE. Thresholds were set using mitral/aortic valve enhancement as the reference for each image, while attempting to exclude blood pool enhancement and include visually apparent LGE (Fig. 2). The volume of segmented LGE enhancement was obtained using summation of segmented areas of enhancement in each axial slice, and normalized by estimated LA myocardial volume. This volume was calculated using a 2 mm LA myocardial thickness [20], and estimating LA area as a scalene ellipsoid. Quantitative measurement of the LA LGE volume was performed on 3D LGE images using 3D Slicer, an open source medical informatics and post-processing software to manually segment LA LGE and determine total volume of LA LGE [21]. Inter and intraobserver reliability of this method was reported to be good to excellent, with ICC = 94% (intra-observer); 71% (inter-observer) by our group [22] and similar to others [23].

Statistics

The patient characteristics were described in absolute numbers and percentages. In describing the relationship between LA LGE with clinical and cardiac variables, LGE was analyzed as a percentage of estimated LA tissue volume. Spearman's rho correlations were used to describe the relationship between continuous variables such as LA LGE, LV LGE, LV mass, and LV strain. Student's *t* tests were used to compare LA LGE percentage among patients with and without usage

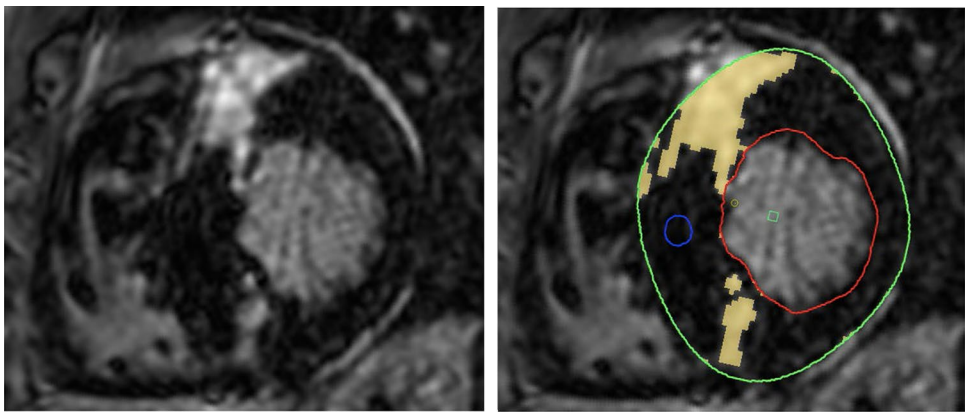

Fig. 1 Myocardial delayed enhacement is demonstrated at the anteroseptal and inferoseptal segments (left). Yellow overlay depicts LV LGE on semi-automated quantification (right)

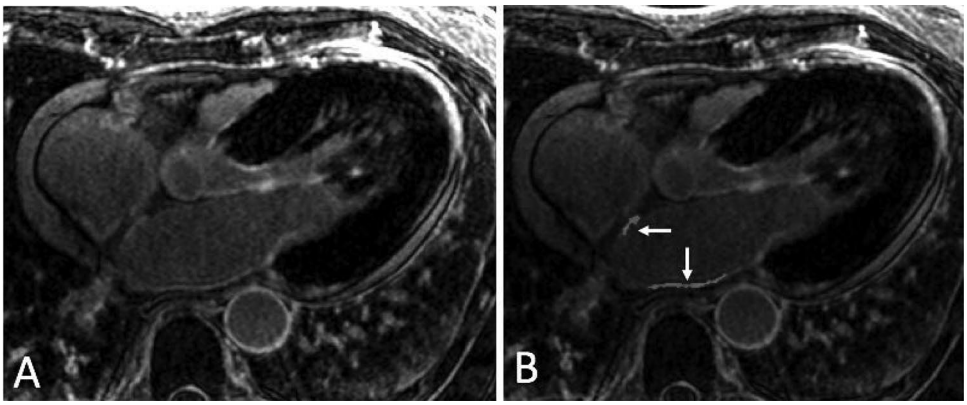

Fig. 2 **a** 3D LGE Image in one study subject. **b** LA LGE was segmented using the method described by our group previously [19], which used a subject specific threshold selected to include signal from the enhanced mitral valves in the 3D LGE volume. Enhanced atrial wall signal was segmented in each slice. Enhancement extending to the antrum of the pulmonary vein was included as previously described [24]. On average, 5 mm of the PV ostia was included. Manual correction was used to exclude enhanced pixels from extra-atrial tissues and artifacts

of ace inhibitors (ACE-I) or angiotensin receptor blockers (ARB). Values of $p < 0.05$ was considered significant, and all p values are results of 2-tailed tests. Statistical analysis was performed using an independent statistical analysis software (SPSS v23). Biserial correlation was employed to determine association between LA fibrosis and CMR parameters, medications, and comorbidities.

Results

Baseline characteristics

After reviewing consecutive cases between January 2012 to June 2016, twenty-eight cases met the above criteria (Table 1). The mean age was 59 years old ± 18.9, and 57% were male. Significant cardiovascular risk factors included hypertension (39%), diabetes (7%), hyperlipidemia (36%), former tobacco use (29%), atrial fibrillation (18%) and history of ventricular tachycardia (25%) (Table 1). Nine patients had genetic testing, 5 of whom had mutations identified (Table 2). Morphological findings of hypertrophy included 22 patients with asymmetric septal hypertrophy, 5 with apical hypertrophy, and 1 with a mixed pattern. 32% of patients were on therapy with an ACE-I or ARB at the time of CMR imaging.

Table 1 Baseline characteristics

Baseline characteristics	No. (%)
Age (average)	59
Male	16 (57)
ACE-I/ARB use	9 (32)
Genetic testing	9 (32)
Positive	5 (18)
Negative	4 (14)
Comorbidities	
Atrial fibrillation	5 (18)
Congestive heart failure	1 (4)
Coronary artery disease	2 (7)
Diabetes	2 (7)
Family history of HCM	4 (14)
Hyperlipidemia	10 (36)
Hypertension	11 (39)
Tobacco use, active	4 (14)
Tobacco use, former	8 (29)
Ventricular tachycardia history	7 (25)

ACE-I Angiotensin converting enzyme inhibitors, *ARB* angiotensin II receptor blocker, *no*. number of patients, ± standard deviation

Follow up events

Patients were followed on average 3.4 years from the time of CMR. Two of the 28 patients died in follow up, one of which was attributed to sudden cardiac death (Table 3). Nine patients required hospitalization in follow-up, 6 of whom carried cardiovascular diagnosis at discharge. Of the 28 patients, 8 had ICDs implanted and 7 had a prior diagnosis of ventricular arrhythmia. There were no new ICDs implanted or ventricular arrhythmias detected in extended follow up. Of the 8 patients with ICDs implanted, none received ICD shocks in extended follow up. There were 3 out of 28 patients who underwent surgical septal myectomy.

Even though only 5 tested positive for a genetic variant of HCM, 2 of the 4 patients who tested negative for a genetic variant required septal myectomy, and one these 4 patients experienced sudden cardiac death.

Table 2 Mutations identified by genetic testing

Patient (n = 9)	Genetic test	Variant pathogenicity
1	MYBPC3 Intron 23 c.2309-2A > G	Pathogenic
2	MYBPC3 c.3064C > T (p.Arg1022Cys)	VUS
3	MYBPC3	Pathogenic
4	MYH7 c.161G > A (p.Arg54Gln)	VUS
5	MYBPC3 c.1895delT (p.Met632fs)	Pathogenic
6–9	No mutations identified	

VUS variant of undetermined significance

Table 3 Clinical outcomes

Outcomes	No. of patients (%)
All cause death	2 (7)
Sudden cardiac death	1 (4)
Hospitalizations	9 (32)
Cardiac related	6 (21)
New atrial fibrillation	3 (11)
Diagnosis prior to CMR	5 (18)
New ICDs implanted	8 (29)
Septal myomectomy	3 (11)
Ventricular arrhythmias	0

Overall, half [14] of subjects had either positive genetic testing, required interventions for HCM including septal myectomy or ICD placement, or suffered from death attributed to a cardiovascular cause.

Left ventricular and left atrial characteristics

On average, LVEF was within normal limits, indexed LV end diastolic volume was normal, indexed LV mass was moderately increased, and average maximal wall thickness was 21 mm (Table 4). LV LGE was identified in 24 (86%) of the cases and the mean percentage of LV LGE was 9.67%.

LA LGE was identified in all of the cases. A significant amount of left atrial fibrosis was identified in this HCM population with an average of 15 ± 13%. All LV and LA parameters were interrogated for correlation. The extent of LA fibrosis significantly correlated with the percent LV LGE (r = 0.64, p = 0.001) (Fig. 3). It did not, however, correlate with indexed LV mass or maximum wall thickness. Extent of LA fibrosis also moderately correlated with decreased LV global radial strain (r = −0.50, p = 0.013,), global circumferential strain (r = 0.47, p = 0.02), and global longitudinal strain (r = 0.52, p = 0.013). Increased LA systolic volume (maximum LA volume; immediately preceding mitral open opening) moderately correlated with LV end diastolic volume (r = 0.50, p = 0.006). Presence of atrial fibrillation did not affect amount of left atrial fibrosis (Table 5).

Table 4 Left ventricular and left atrial parameters

LA/LV parameters	Mean ± standard deviation
LVEF (%)	70 ± 8
LVEDV (ml)	128 ± 43
LVEDI (ml/m^2)	61 ± 13
LVESV (ml)	40 ± 22
LVESVI (ml/m^2)	19 ± 8
LVSV (ml)	88 ± 26
LVSVI (ml/m^2)	42 ± 8
LV mass index (g/m^2)	102 ± 35
Cardiac output (l/min)	6.07 ± 2.18
Cardiac index	2.88 ± 0.68
Maximum wall thickness (mm)	21 ± 4
LV LGE—% of total LV mass	9.67 ± 9.70
LV LGE—no. of pts (%)	23 (82%)
Global radial strain (mean)	31.46 ± 10.10
Global circumferential strain (mean)	− 15.53 ± 3.65
Global longitudinal strain (mean)	− 14.74 ± 3.70
LA systolic volume (ml)	38 ± 34
LA systolic volume index (ml/m^2)	19 ± 22
LA fibrosis (%)	15 ± 0.13

L liters, *LVEF* left ventricular ejection fraction, *ml* millliters, *min* minute

Upon investigation of medication usage, patients on therapy with Renin–Angiotensin–Aldosterone System (RAAS) Inhibition had significantly less LA LGE compared to those without (18.6% vs 10.8%, p = 0.023) (Fig. 4). Other medications were not associated with extent of LA fibrosis (Table 6). With regards to association of LA LGE with clinical conditions and medication usage, only the use of ACE-I and ARB correlated significantly with extent of LA LGE (r = 0.51, p = 0.019). There was no correlation between RAAS inhibition and LV LGE.

Five of 28 patients had a diagnosis of atrial fibrillation prior to the index CMR. Of the remaining 23 patients, 3 had a new diagnosis of AF. One patient underwent

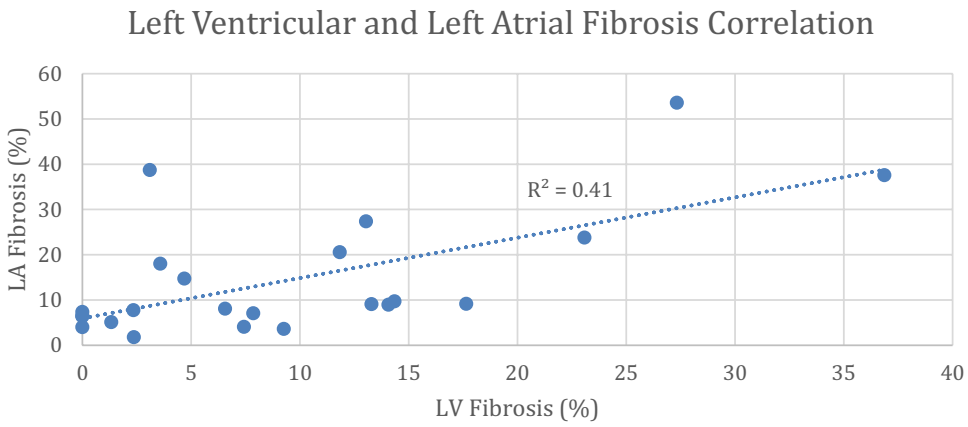

Fig. 3 Scatter plot demonstrating correlation between percent left ventricular fibrosis and left atrial fibrosis ($R^2 = 0.41$)

Table 5 Impact of atrial fibrillation on amount of left atrial fibrosis

	Afib	N	Mean (%)	Std. deviation (%)	Std. error mean (%)
%LA fibrosis	Yes	6	15	13.60	5.50
	No	17%	14.30	13.80	3.35

invasive attempt at rhythm control, which included a MAZE procedure.

Limitations

Limitations include the retrospective nature of the study design and the small number of patients.

Although LGE is currently the clinical gold standard for scar and fibrosis assessment, there is an inherent limitation of this technique for scar quantification in disease processes with diffuse involvement of the myocardium, such as HCM, since it a normal reference myocardium is required discriminate the

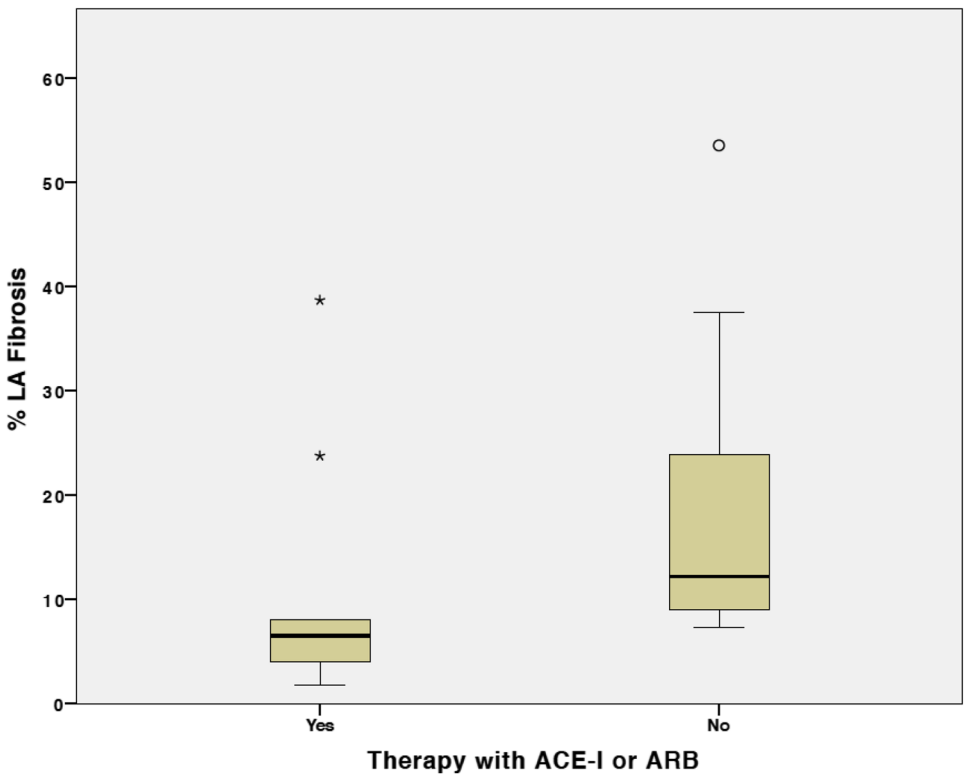

Fig. 4 Tukey boxplot shows extent of atrial fibrosis in association with ACE-I or ARB. Median is marked by horizontal line inside box. Interquartile ranges are the ends of the box. The upper and lower whiskers extend to 1.5 times the interquartile range from the hinge. Data beyond the end of the whiskers are outliers

Table 6 Imaging and clinical parameters and associated correlation coefficient (r)

Parameters and correlate to LA fibrosis	r value	p value
CMR parameters		
LV mass index	−0.152	0.488
LVEDVI	−0.339	0.114
LVESVI	−0.171	0.403
LV LGE	0.64	0.001
LVEF	0.147	0.504
LAEF[a]	−0.096	0.664
LA systolic volume	−0.24	0.27
Medications		
ACE inhibitor/ARB	0.51	0.019
Aldosterone	0.185	0.423
Aspirin	0.205	0.373
Beta blocker	−0.146	0.528
Calcium channel blocker	−0.031	0.89
Cormorbidities		
Age	−0.202	0.354
CAD	−0.257	0.236
DM	0.22	0.337
Dyslipidemia	−0.05	0.829
Family history of HCM	−0.138	0.53
Tobacco smoking, active	0.421	0.058
Tobacco smoking, former	0.402	0.071
History of ventricular tachycardia	−0.013	0.952
Hypertension	−0.166	0.448
Sex	0.224	0.304
Statin use	0.001	0.995

ACE-I Angiotensin converting enzyme inhibitors, *ARB* angiotensin II receptor blocker, *CAD* coronary artery disease, *DM* diabetes mellitus, *HCM* hypertrophic cardiomyopathy, *LAEF* left atrial ejection fraction, *LVEDVI* left ventricular end-diastolic volume index, *LVEF* left ventricular ejection fraction, *LVESVI* left ventricular end-systolic dimension index, *LV LGE* left ventricular late gadolinium enhancement

[a](Mid diastolic volume – end diastolic volume) ÷ mid diastolic volume [25]

regions of enhancement on Look-Locker sequence. We did not have T1 mapping images for calculation of extracellular volume quantification, which may overcome this limitation in assessment of the fibrotic process.

Additionally, clinical characteristics and medication usage were obtained through medical chart review, and were not available for all patients who were referred from outside the institution. Therefore, only 21 of the 28 patients had full medication usage data available for analysis.

Discussion

HCM is an active area of investigation with the goals of elucidating the underlying pathophysiology, improving diagnosis, understanding prognostic factors and guiding clinical management. The majority of the focus on HCM research has been, until recently, on characterizing the left ventricle. In a recent meta-analysis, Weng, et al. demonstrated a strong correlation between LV LGE with all-cause mortality, cardiovascular mortality, and SCD [6]. Similarly, Chan, et al. demonstrated that LV LGE ≥ 15% was an associated with a two-fold increase in SCD risk in patients who would otherwise be considered low risk by standard clinical parameters [26].

Only recently, investigators have begun to look beyond the left ventricle to explore the impact of HCM on other cardiac structures. It is well established that LA functional abnormalities are present in HCM. Kowallick et al. recently demonstrated that decline of LA function is associated with extent of LV LGE [27]. Debonnaire et al. demonstrated increased LA size and decreased LA function in HCM [28]. Interestingly, Farhad, et al. showed that LA dysfunction was present even without LVH in preclinical HCM (genotype-positive/LVH-negative) [29]. The induction of atrial fibrosis results from profibrotic signals such as angiotensin II (Ag II) and transforming growth factor beta 1 (TFG-β1). Transgenic mice with cardiac-specific upregulation of cardiac Ag II had left and right atria three times the normal size with attendant atrial fibrosis [30]. TFG-β1 is a key mediator of in the signaling cascade of cardiac fibrosis. Overexpression of TFG-β1leads to selective left atrial fibrosis but not ventricular fibrosis [31, 32]. Increased levels of Ag II and TFG-β1induces cardiac fibroblast extracellular matrix protein synthesis. Atrial mechanical stimulation, such as wall tension and pressure promotes collagen formation, Ang II and TFG-β1 expression, and atrial remodeling [33]. In our study, a significant amount of left atrial fibrosis was identified (15 ± 13%). This is substantially increased in comparison to an average of 3 ± 3% in a relatively healthy reference population previously published from our group [34]. We showed a significant correlation between the extent of LA fibrosis and LV fibrosis, as well as abnormal LV function via strain analysis. The correlation between LA LGE and LV LGE may suggest that LA fibrosis is secondary to LV remodeling and increased filling pressure. Alternatively, LA and LV abnormalities may be manifestations of the same cardiomyopathic process as suggested by the finding of abnormal left atria in phenotype negative HCM subjects by Farhad et al., although LA fibrosis was not investigated in that study. Regarding the relationship between LV mass and extent of LV fibrosis, prior work did not find

a correlation between serum markers of collagen turnover and severity of LV hypertrophy [35]. To extend this disconnect, our study did not show correlation between LA fibrosis and LV parameters of LV mass, LV volume, and LVEF (Table 6). This is in keeping with Farhad's study which demonstrated abnormalities in the LA without phenotypic LV changes in HCM subjects. Therefore, there may be a separate pathologic mechanism for atrial fibrosis independent of LV remodeling in HCM.

A reduction in strain is associated with fibrosis (Circ Cardiovasc Imaging. 2014;7:11–19), [22] HF, and death [23]. Pronounced abnormal mechanical dispersion by myocardial strain is also present in HCM Mechanical dispersion is independently associated with ventricular arrhythmias, which is thought to be related to an increase electrical dispersion, likely related to myocyte disarray and fibrosis [36]. In our myocardial strain analysis, longitudinal, circumferential, and radial were all abnormal despite a preserve average LVEF (70%), indicating subclinical LV dysfunction. Consistent with prior data by Popovich et al. and Saito et al., the decreased strain values in our study was associated with myocardial fibrosis.

The other important finding of note is that patients on ACE-I or ARB had significantly less LA fibrosis as compared with patients who were not on these medications. It is well documented that in animal models of AF, Ag II has a pro-arrhythmic effect and promotes atrial fibrosis. Conversely, treatment with ACE-I or ARB in these same models is associated with less fibrosis and less incidence of arrhythmia [37]. In humans, multiple studies have been notable for demonstrating benefits of RAAS inhibition in preventing clinical arrhythmias. For example, the Losartan Intervention For End Point Reduction in Hypertension (LIFE) study there were fewer episodes of AF and stroke in patients on Losartan as compared to patients on atenolol [38]. Similarly, Maggioni et al. demonstrated that patients on Valsartan had a significant decrease (37%) in clinical AF events [39]. In our study, the decreased LA fibrosis in individuals taking ACE-I or ARB suggests that RAAS inhibition may attenuate the fibrotic response in HCM. It remains to be determined whether decreased LA fibrosis is associated with less incident atrial arrhythmias in patients with HCM. Nonetheless, RAAS inhibition may serve as a potential therapeutic avenue in such patients.

Conclusion

Our study demonstrates that there is an increased amount of LA fibrosis in this HCM population and that there is a significant correlation between LA fibrosis, as manifested by myocardial LGE, and LV fibrosis. It is possible that this correlation between LA fibrosis and LV fibrosis indicates that LA fibrosis is secondary to LV remodeling. However, the lack of correlation between LA fibrosis and LV parameters (LV mass, LV volume, LVEF, see Table 6) suggests that an alternative mechanism may be present. Therefore, it is plausible that a similar pathophysiologic process is involved in the development of LA fibrosis as in LV fibrosis, suggesting that the myocardial derangements of HCM may extend beyond the left ventricle to include the atria as well. Notably, our study showed that individuals on ACE-I or ARB therapy had less LA fibrosis, and the clinical consequence of this finding has yet to be determined. Further study is warranted to determine the causality of LA fibrosis and the role of RAAS inhibition in patients with HCM.

Author contributions SRL, VQN, MLH, KG, DCP, LAB collected imaging data, performed chart review, and performed literature review. SRL, VQN, DCP, and LAB analyzed the CMR studies. LAB, SRL, and DCP conceived of the study, and participated in its design and coordination. SRL, MLH, KG, VQN, DCP, JT, DJH, SH, HM, DD, AJS, JLM, NP, DJ, LAB participated in analysis and interpretation of the patient data and contributed to writing the manuscript. AS and DCP performed intra- and interobserver variability. SRL, VQN, MLH, DCP, and LAB were major contributors in writing the manuscript. All authors read and approved the final manuscript.

Availability of data and material The datasets used and/or analyzed during the current study are available from the corresponding author on request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethics approval This study was approved by the Yale IRBS—Yale University Institutional Review Board, specifically the Human Investigation Committee, and is HIPAA compliant.

Informed consent No informed consent was required since this is a retrospective data review.

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