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ORIGINAL PAPER

Prognostic value of left atrial function by cardiovascular magnetic resonance feature tracking in hypertrophic cardiomyopathy

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Abstract

Left atrium (LA) size has an important role in determining prognosis and risk stratification in hypertrophic cardiomyopathy (HCM). Cardiovascular magnetic resonance myocardial feature tracking (CMR-FT) is a novel technique for the quantification of LA function. Our aim was first to evaluate LA function by CMR-FT and volumetric analysis in patients with HCM; and secondly we sought to determine the association of LA-longitudinal strain (LA-LS) with major cardiovascular outcomes, particularly all cause mortality and heart failure. 75 patients with HCM and 75 control subjects underwent a conventional CMR study including assessment of LA function by CMR-FT (LA-LS) and volumetric analysis. A primary endpoint of all-cause mortality and secondary combined endpoint of hospital admission related to heart failure, lethal ventricular arrhythmias or cardiovascular death were defined. Compared to controls, LA-LS and all volumetric indices of LA function were significantly impaired in HCM even in patients with normal LA volume and normal LV filling pressures. LA-LS showed moderate-high correlation with LA-emptying fraction (total, active and passive LA-EF, $r = 0.68$, $r = 0.67$, $r = 0.31$, $p < 0.001$ for all) and with parameters of diastolic function (E/é, $r = 0.4$, $p < 0.001$). The age, minimum LA volume and % of LGE were independent predictors of LA-LS ($p < 0.01$ for all). During a mean follow-up of 3.3 ± 1.2 years LA-LS was associated with the primary (HR: 0.85 (0.73–0.98), $p = 0.02$) and the secondary end-point (HR: 0.88 (0.82–0.96), $p = 0.003$). LA-LS by CMR-FT provides accurate measurements of LA function in HCM patients. LA-LS may become a novel potential predictor of poor cardiac outcomes, particularly cardiovascular mortality and HF.

Keywords Hypertrophic cardiomyopathy · Cardiac magnetic resonance · Left atrial strain · Outcomes · Heart failure

Introduction

Hypertrophic cardiomyopathy (HCM) is a complex and the most common inheritable cardiovascular disease, associated with increased cardiovascular morbidity and mortality. Left atrial (LA) size is a marker of disease severity and independently predicts adverse long-term clinical outcomes, including atrial fibrillation, systemic thromboembolic events, and heart failure [1–3]. Recent European guidelines have incorporated LA diameter into the stratification risk model to predict sudden cardiac death at 5 years in patients with HCM. However, in addition to LA dimension, the importance of LA contractile function is increasingly recognized as an earlier parameter of the functional status of the LA. In HCM, improvement of LA function correlates with the decrease in the left ventricular (LV) outflow gradient after alcohol-induced septal ablation or septal myectomy and decreased

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LA function independently predicts new-onset atrial fibrillation [4–7].

LA deformation was firstly studied with echocardiographic speckle tracking allowing detailed evaluation of LA phasic function in HCM by volumetric and strain measurements [6–9]. Cardiovascular magnetic resonance feature tracking (CMR-FT) represents a novel approach to assess LA deformation directly from standard steady-state free precession (SSFP) cine CMR. CMR-FT makes use of offline tracking of tissue voxel motion allowing the evaluation of longitudinal atrial deformation. The technique has been used to study LA longitudinal strain and can discriminate between health and disease in patients with heart failure [10]. LA assessment by CMR-FT has demonstrated to be feasible and highly reproducible with higher tracking quality compared to echocardiographic speckle tracking [11]. LA deformation assessed by LA-LS can detect an earlier stage of LA dysfunction. While evidence exists that LA enlargement is predictor of adverse cardiovascular outcomes in HCM, there is no data regarding the prognostic implication of impaired left atrial contractile function to predict heart failure or cardiovascular death in this population. The aim of the present study is to evaluate the LA function by CMR-FT in patients with HCM compared to controls and secondly, to test the association with major outcomes, particularly all-cause death and heart failure.

Methods

Patients with unequivocal diagnosis of HCM referred for a clinically indicated CMR study were included in this study. An HCM diagnosis was made by demonstration of increased LV wall thickness (≥ 15 mm) in one or more LV myocardial segments associated with a non-dilated LV that was not explained solely by loading conditions that could result in a similar magnitude of hypertrophy [1, 11, 12]. Age and gender matched subjects without history of cardiac disease or symptoms and normal CMR findings (including normal biventricular volumes and mass, normal atrium volume and absence of late gadolinium enhancement) served as the control group [13, 14].

All individuals were in sinus rhythm at the time of imaging. Exclusion criteria for all subjects were history of athletic activity, known diagnosis of amyloidosis or Anderson-Fabry disease, as well as the generally accepted contraindications to CMR (implantable devices, cerebral aneurysm clips, cochlear implants, severe claustrophobia), or a history of renal disease with a current eGFR < 30 mL/min/1.73 m^2.

The study protocol was reviewed and approved by the local institutional ethics committees. All procedures were carried out in accordance with the Declaration of Helsinki (2000).

Cardiovascular magnetic resonance

All subjects underwent a routine clinical scan protocol for volumes and mass and tissue characterisation with LGE using a 1.5-Tesla MRI scanner equipped with advanced cardiac package and multi-transmit technology (Achieva, Philips Healthcare, Best, The Netherlands) following professional recommendation for standardized acquisition [15]. Details of CMR sequence parameters and image postprocessing are included in Supplementary Material.

LA function

a. CMR-feature tracking LA myocardial feature tracking was performed offline using dedicated software (CMR 42®, Circle, Calgary, Canada). Endocardial and epicardial LV borders were manually drawn in end-diastole of standard cine SSFP short and long axis images. LA endocardial borders were manually traced in long axis views of the cine images when the atrium was at its minimum volume and the fully automated tracking algorithm was applied. LA-longitudinal strain (LA-LS) was measured as peak systolic reservoir strain (Fig. 1). Impaired myocardial global LV longitudinal strain (GLS) and LA-LS were defined as the value above 2 SDs of the normal range (control group).

b. Volumetric analysis Manual tracings of the LA area and length were performed in the 2-and 4-chamber view. LA volumes were calculated using the previously validated biplane area-length method [14] according to the formula:

LA volume (ml) = 0.85*A2C*A4C/L, where A2C and A4C are the LA areas on the 2- and 4-chamber views, respectively, and L is the shorter long-axis length of the LA from either the 2- or the 4-chamber views.

The following volumetric calculations were performed [14]:

- Maximum LA volume (LAV_{max}) assessed at LV end-systole the time at which atrial volume was largest just before mitral valve opening.
- Minimum volume (LAV_{min}): at late LV end-diastole, the time at which atrial volume is at its nadir before mitral valve closure, after LA contraction.
- Volume before atrial contraction (LAV_{preA}): the last frame before mitral valve reopening.

Total LA emptying fraction (LAEF Total, corresponding to atrial reservoir function), passive LA emptying fraction (LAEF passive, corresponding to atrial conduit function) and LA active emptying fraction (LAEF active, corresponding to atrial contractile booster pump function)

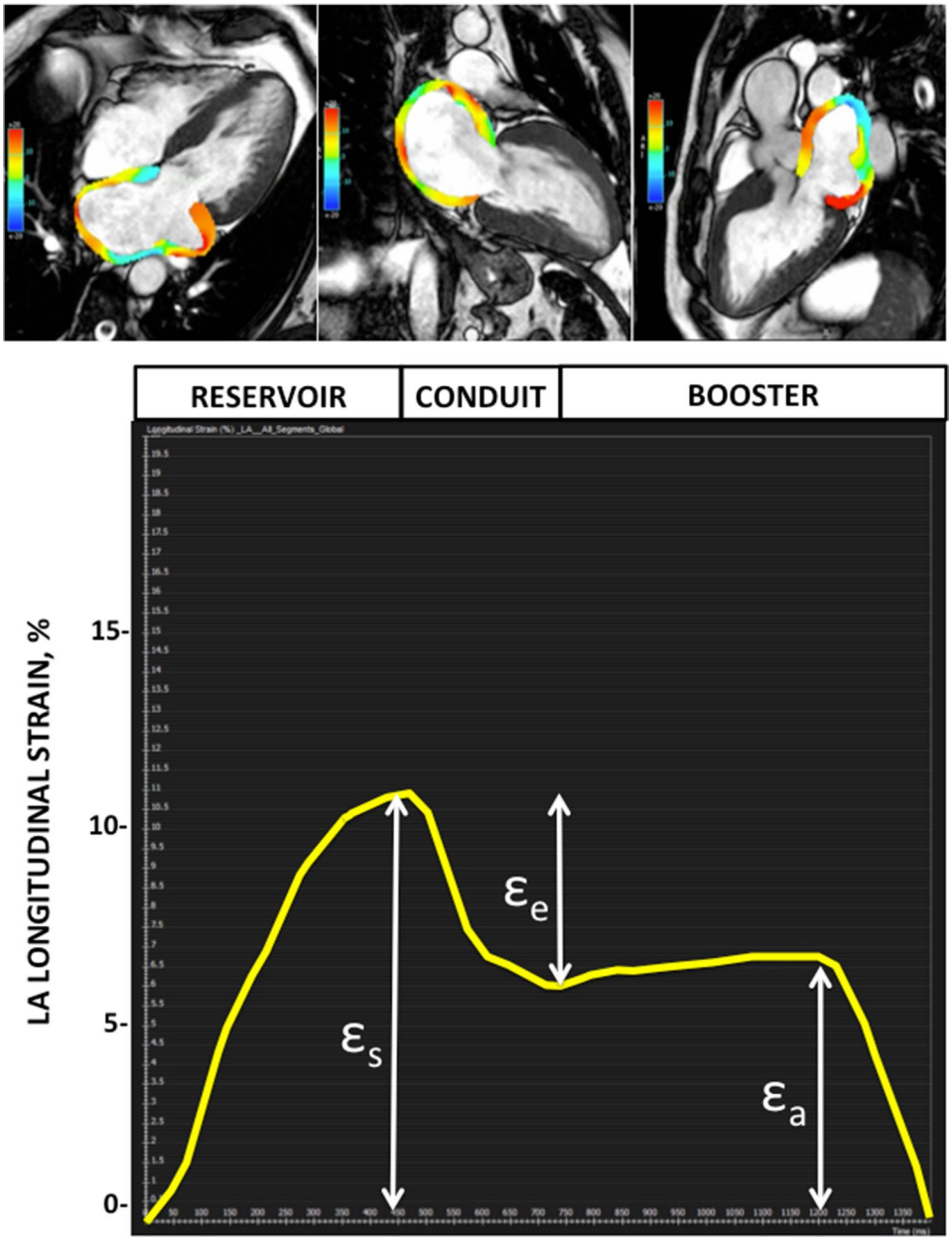

Fig. 1 Composite figure showing measurement of total peak left atrial longitudinal strain using CMR-FT from an apical 4, 2 and 3-chamber view in a representative patients with obstructive HCM. Lower: LA strain profiles. Three aspects of LA strain are displayed: passive strain (εe, corresponding to atrial conduit function), active strain (εa, corresponding to atrial contractile booster pump function), and total peak strain, the sum of passive and active strain (εs, corresponding to atrial reservoir function)

were assessed from above LA volumetric parameters (Supplementary Table S2).

Echocardiography

All patients underwent clinical transthoracic echocardiography (TTE) according to the recommendations from the European Association of Cardiovascular Imaging [16]. Early myocardial tissue Doppler relaxation velocities (E') were measured at the lateral and septal wall of the mitral annulus. In addition, those variables included in the risk stratification model were collected [1]. Maximum LV wall thickness was defined as the greatest thickness using parasternal short-axis plane in 2-D echocardiography. Left atrial (LA) diameter was determined by M-Mode or 2D-echocardiography in the parasternal long axis plane. The maximum LV outflow gradient was determined at rest and with Valsalva provocation using pulsed and continuous wave Doppler from the apical three and five chamber view. Peak outflow tract gradients were determined using the modified Bernoulli equation: $\Delta P = 4*V2^2$, where V is the peak aortic outflow velocity.

Outcomes

At least 6 months following the CMR, clinical data was obtained from hospital's records and from direct communication with the patients. A primary endpoint of all-cause

mortality and secondary combined endpoint (development or progression of heart failure requiring hospitalization, lethal ventricular arrhythmias or cardiovascular death) were defined. When a patient experienced > 1 secondary endpoint, the first event was chosen. When > 1 secondary endpoint occurred simultaneously, the worse event was chosen (CV death > ventricular arrhythmias > congestive heart failure). All CMR measurements were performed blinded to patients' outcomes.

Statistical analysis

Statistical analysis was performed using SPSS software (version 21.0; SPSS, Chicago, IL, USA). Normality of distributions was tested with the Kolmogorov–Smirnov statistic. Categorical data are expressed as percentages, and continuous variables as mean ± SD or median (interquartile range), as appropriate. For comparison of two and more than two normally distributed variables, Student's *t*-test, and the Chi square test were employed as appropriate. Correlations were assessed using Pearson's correlation coefficient for normally distributed variables and Spearman's correlation coefficient for non-parametric data. Associations were explored by single and multivariate linear regressions. The multivariate model was based on those variables that were significant in the univariate model. The differences in event-free survival according to normal and abnormal LA-LS strain were evaluated by Kaplan–Meier survival analysis and were compared by log-rank tests. Inter- and intraobserver reproducibility and agreement of LA deformation post-processing approach was assessed in 30 randomly selected subjects (15 HCM + 15 controls) by the coefficient of variation (CoV) and intraclass correlation coefficient (ICC). All tests were two-tailed and a P value of less than 0.05 was considered significant.

Results

Seventy-five HCM patients and seventy-five controls subjects were included in the study. Subject characteristics are presented in Supplementary Table S1. 46 patients (61%) exhibited asymmetrical septal HCM, 18 apical variant (24%), four symmetric type (5%), three mid-ventricular type (4%) and four sigmoid type (5%). Nearly one-third of HCM patients were in NYHA class II or greater, but the majority of patients had a low-estimated risk of SCD at 5 years (median SCD score: 1.87 (1.33–1.87); 80% of patients with an estimated risk below 4%) [1].

Compared to controls, HCM showed higher maximal LV wall thickness, higher LV mass and increased E/é ratio (Table 1). LV-end-diastolic volumes were lower and LA size (LA volumes and LA diameter) higher in patients compared to controls ($p < 0.001$). Biventricular ejection fraction was significantly higher but global longitudinal strain (GLS) impaired in HCM patients. LGE was present in 73% of HCM patients, with a median extension of 6% (2–11) of the LV mass. 32% of patients have significant mitral regurgitation (≥ grade II), mainly due to the systolic anterior motion of the valve.

LA Function

A- LA volumetrics

Maximal and minimal LA volumes were larger in HCM compared to controls. In addition, total, active and passive LA-ejection fractions (reservoir, conduit and contractile atrial function respectively) were significantly impaired in HCM (Table 2). In subgroups analysis, those patients with normal LA volume (n = 31) or normal LV filling pressures (septal E/é<8) (n = 41) showed impaired total, active and passive LA-ejection fractions ($p < 0.001$ for all). Those patients exhibiting areas of LGE did not show different LA volumes or LA function ($p > 0.05$ for all).

B- LA strain

Compared to controls, LA longitudinal strain was significantly reduced in HCM (Table 2) ($p < 0.001$ for all). Similarly to volumetric analysis, those patients with normal LA volume or normal LV filling pressures showed impaired LA-LS ($p < 0.001$ for both) (Fig. 2). 48% of patients with normal LA volume (n = 15) and 34% of patients with normal LV filling pressures (n = 13) exhibited an abnormal LA-LS. In addition, LA-LS was also more reduced in those HCM with areas of LGE (HCM_{LGE+} vs. HCM_{LGE-}, LA-LS, %: 16.0 ± 7 vs. 22.5 ± 9, $p = 0.005$). Patients with obstructive HCM (LVOT gradient ≥ 30 mm Hg) exhibited a trend of lower LA-LS (obstructive HCH vs. non-obstructive HCM, LA-LS, %: 14.5 ± 3 vs. 17.2 ± 8, $p = 0.14$).

Analysis of relationships

In patients with HCM, LA-LS showed moderate negative correlation with parameters of diastolic function (E/é) ($r = -0.43$, $p < 0{,}001$), LV mass ($r = -0.46$, $p < 0{,}001$), maximum LV wall thickness ($r = 0.38$, $p < 0.001$), amount of LGE ($r = -0.47$, respectively, $p < 0.001$), GLS ($r = 0.65$, $p < 0{,}001$) and with the current SCD risk prediction model ($r = -0.33$, $p = 0.005$). Furthermore, a strong-to-moderate relation was found between LA function by volumetric indexes, LA volume and LA-LS (Table 3).

Table 1 Global morphological and functional measures based on CMR measurements and on echocardiography

Variable	Controls (n = 75)	HCM (n = 75)	p-value
CMR variables			
LV-EDV index (ml/m^2)	75 ± 14	43 ± 17	< 0.001
LV-ejection fraction (%)	62 ± 7	66 ± 8	0.01
LV-GLS (%)	− 19 ± 2.8	− 13 ± 4.2	< 0.001
RV-ejection fraction (%)	63 ± 6	69 ± 7	< 0.001
LV Mass Index (mg/m^2)	53 ± 14	85 ± 19	< 0.001
Maximal LVWT (mm)	8 ± 1	18,8 ± 5	< 0.001
Maximum LA volume index, ml/m^2	44 ± 10	63 ± 20	< 0.001
LGE			
Present, n (%)	0 (0)	55 (73)	< 0.001
LGE extent (as % LV mass), median (interquartile range)	0 (0)	6 (2–11)	< 0.001
Echocardiographic variables			
Maximal LVWT (mm)	9 ± 1	18.7 ± 5	< 0.001
LA diameter	29 ± 5	43 ± 7	< 0.001
LVOT gradient (mm Hg)	4.8 ± 5	10 (6–17)	NA
Significant LVOT gradient (≥ 30 mm Hg)	0 (0)	11 (15)	< 0.001
Mitral regurgitation (≥ grade II), n (%)	0 (0)	24 (32)	< 0.001
Septal E/é	7.9 ± 2.9	13 ± 5	< 0.001
Lateral E/é	6 ± 3	19 ± 5	< 0.001
Diastolic function normal or type I, n (%)	70 (100)	41 (55)	< 0.001
Diastolic function II, III, IV, n (%)	0 (0)	34 (45)	< 0.001

Diastolic parameters (E/é ratio) based on echocardiography

LV left ventricular, *EDV* end-diastolic volume, *RV* right ventricular, *GLS* global longitudinal strain. *LVWT* LV wall thickness, *LGE* late gadolinium enhancement

Table 2 LA function

	Controls (n = 75)	HCM (n = 75)	p-value
LA volumetric			
Maximum LA volume index (ml/m^2)	44 ± 10	63 ± 20	< 0.001
Minimum LA volume index (ml/m^2)	20 ± 6	41 ± 23	< 0.001
Total LA-EF (%)	55 ± 9	40 ± 16	< 0.001
Passive LA-EF (%)	24 ± 13	16 ± 11	0.001
Active LA-EF (%)	41 ± 11	27 ± 14	< 0.001
LA speckle tracking			
ALS (%)	30 ± 6	17 ± 8	< 0.001

LA-EF left atrial ejection fraction. *ALS* atrial longitudinal strain

By multivariable linear regression, the age, minimum LA volume, and % of LGE were independent predictors of LA-LS ($p < 0.01$ for all) (Supplementary Table S3).

Outcome data

No patient was lost to follow-up. Mean follow-up time was 3.3 ± 1.2 years. During follow-up, 9 patients (12%) were admitted due to development or progression of heart failure (HF) and only 1 patient suffered sustained ventricular arrhythmias. A total of 4 patients (5.3%) died during the follow-up. Cause of death was cardiovascular in all of them (3 due to progression of heart failure and 1 patient suffered sustained ventricular arrhythmia). LA-LS parameter was significantly impaired in subjects with primary and secondary endpoints (primary endpoint, LA-LS%: 8 ± 5 vs. 19 ± 8, $p < 0.05$; secondary endpoint, LA-LS%: 10 ± 5 vs. 19 ± 8, $p < 0.05$). All patients with primary and secondary endpoints exhibited abnormal LA-LS (< 18%) (Supplementary Table S4). Among volumetric indices, total and active LA-EF were impaired

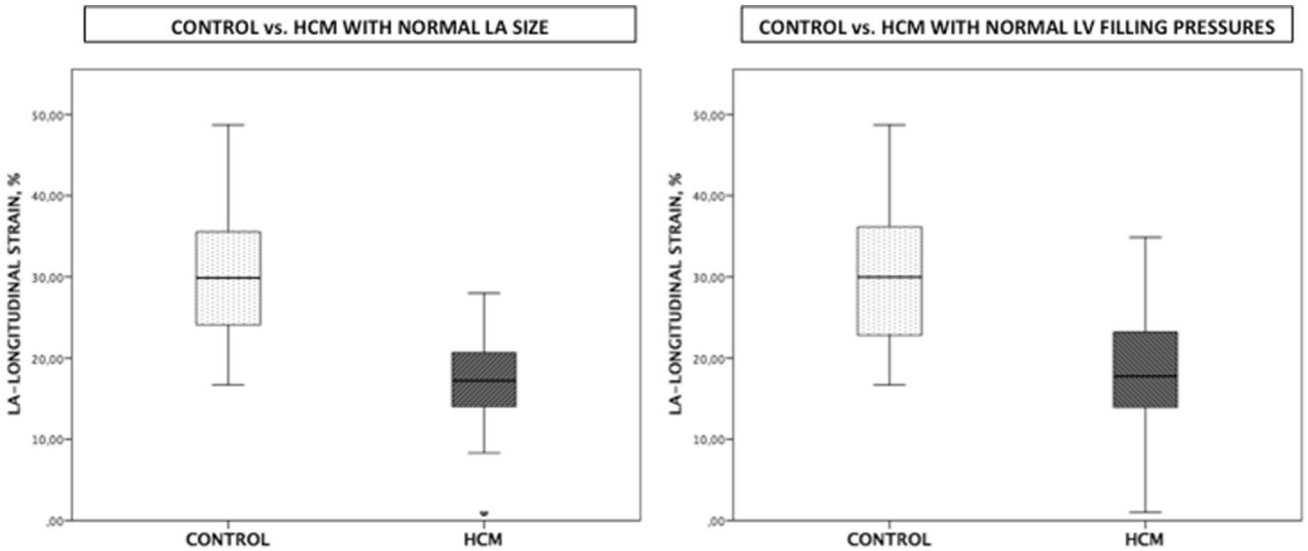

Fig. 2 LA longitudinal strain in HCM with normal LA size and normal LV filling pressures compared to controls

Table 3 Bivariate correlation between LA-LS, LA function assessed by volumetric analysis and LA size

	LA-LS (%)	p-value
Minimum LA volume index (ml/m^2)	r = 0.67	< 0.001
LA diameter	r = 0.65	< 0.001
Total LA-EF (%)	r = 0.68	< 0.001
Passive LA-EF (%)	r = 0.33	< 0.001
Active LA-EF (%)	r = 0.60	< 0.001

in patients with secondary end-points (total LA-EF %: 25 ± 15 vs. 40 ± 18, p < 0.015; active LA-EF %: 17 ± 15 vs. 29 ± 13 p < 0.006). No differences were found for the primary endpoint. All 9 patients who were admitted due to HF had a LVEF > 50% and impaired LA-LS strain (Supplementary Table S4).

In univariate Cox regression analyses, LA-LS and total LA-EF were significantly associated with the primary end-point and with the secondary end-point (Table 4). In multivariate analysis LA-LS were associated to adverse outcomes independently of LA volume, GLS and RVEF.

Kaplan–Meier curves (stratified by an abnormal value of LA-LS = < 18%) for the primary and secondary end-point event-free survival are demonstrated in Figs. 3 and 4. Patients with abnormal global LA-LS (< 18%) experienced a significantly higher rate of all cause-death and higher rate of the combined end-point (particularly development or progression of heart failure) (p = 0.04 and p = 0.002 respectively).

Inter- and intra-observer reproducibility

Intra- and inter-observer agreements for LA-LS (intraclass coefficient of correlation r = 0.95 (0.91–0.98) and r = 0.92 (0.81–0.96) p < 0.001 for both) values were high. Similarly, the intra- and inter-observer coefficients of variation (CoV = 3 and 5.6% respectively) were low.

Discussion

Results of the present study reveal a promising role of CMR to quantify left atrial (dys) function in patients with HCM. Firstly, we demonstrate impaired LA function assessed either by volumetric analysis (total, passive and active LA emptying fraction) or by novel deformation CMR feature tracking (LA-longitudinal strain) even in patients with normal LA volume and LV filling pressures. Secondly, we show that impaired global longitudinal LA strain is associated with major cardiac outcomes, particularly with cardiovascular mortality and HF.

HCM patients commonly exhibited dilated LA, frequently associated to SAM-related mitral regurgitation and elevated LV filling pressures. LA size assessed predominantly with echocardiography has been associated with increased morbidity and mortality in this population [17–19]. Recently, LA function, in top of the LA dimension, is gaining considerable interest [4–8, 20–24], although studies focusing on HCM are still scarce. LA dilatation represents the latest stage of LA performance; studying LA function in this population may be more sensitive than LA volume, and an earlier parameter to detect LA abnormalities.

Table 4 Results of univariate and multivariate analyses in prediction of the outcome endpoints

All cause mortality (n, %)				
4 (5.3%)	Univariate analysis			
	LR Chi^2 (p-value)	Wald	Unadj HR (95% CI)	Sig. (p-value)
LA parameters				
Minimum LA volume (per 1 ml/m^2)	3.78 (0.052)	3.39	1.02 (0.99–1.03)	0.06
Maximum LA volume (per 1 ml/m^2)	1.56 (0.21)	1.52	1.02 (0.99 – 1.06)	0.21
Total LA-EF (per 1%)	5.37 (0.02)	4.99	0.96 (0.93–0.99)	0.025
Passive LA-EF (per 1%)	4.32 (0.04)	4.74	0.94 (0.90–0.99)	0.029
Active LA-EF (per 1%)	2.45 (011)	2.35	0.95 (0.89–1.01)	0.12
LA-LS (per 1%)	5.13 (0.02)	5.01	0.85 (0.73–0.98)	0.02
LV myocardial parameters				
LVEF (per 1%)	0.05 (0.82)	0.05	0.99 (0.9–1.08)	0.82
GLS (per 1%)	5.85 (0.016)	4.84	0.75 (0.59–0.97)	0.03
LV mass (index, per g/m^2)	1.82 (0.17)	1.66	1.01 (0.99–1.02)	0.19
RVEF (per 1%)	0.18 (0.66)	0.18	1.03 (0.89 – 0.19)	0.66
LGE extent (per % change)	0.26 (0.60)	0.26	0.96 (0.83–1.11)	0.6
Combined endpoint (n, %)	Univariate analysis			
12 (16%)				
	LR Chi^2 (p-value)	Wald	Unadj HR (95% CI)	Sig. (p-value)
LA parameters				
Minimum LA volume (per 1 ml/m^2)	3.21 (0.07)	3.19	1.01 (0.99–1.02)	0.07
Maximum LA volume (per 1 ml/m^2)	0.76 (0.38)	0.75	1.01 (0.98–1.03)	0.38
Total LA-EF (per 1%)	6.36 (0.012)	6.29	0.97 (0.95–0.99)	0.012
Passive LA-EF (per 1%)	1.36 (0.24)	1.40	0.97 (0.94–1.01)	0.24
Active LA-EF (per 1%)	8.92 (0.003)	8.52	0.94 (0.91–0.98)	0.003
LA-LS (per 1%)	8.36 (0.004)	8.55	0.88 (0.82–0.96)	0.003
LV myocardial parameters				
LVEF (per 1%)	1.12 (0.28)	1.13	0.97 (0.91–1.02)	0.29
GLS (per 1%)	8.43 (0.004)	7.76	0.83 (0.72–0.94)	0.005
LV mass (index, per g/m^2)	0.82 (0.36)	0.80	1.005 (0.99–1.01)	0.37
RVEF (per 1%)	8.57 (0.003)	8.29	0.91 (0.86–0.97)	0.004
LGE extent (per % change)	3.37 (0.06)	3.19	1.06 (0.99–1.12)	0.07
Variables	Multivariate analysis			
	LR Chi^2 (p-value)	Wald	Adj HR (95%CI)	Sig. (p-value)
Model 1 (LA-LS + minimum LA volume*)*	8.39 (0.015)			
LA-LS (per 1%)		6.76	0.84 (0.74–0.96)	0.009
Minimum LA volume (per 1 ml/m^2)		1.19	0.99 (0.97–1.008)	0.27
Model 2 (LA-LS + GLS)	11.11 (0.004)			
LA-LS (per 1%)		3.5	0.92 (0.84–1.004)	0.06
GLS (per 1%)		2.17	0.88 (0.76–1.04)	0.14
Model 3 (LA-LS + RVEF)	16.43 (< 0.001)			
LA-LS (per 1%)		6.49	0.90 (0.83–0.98)	0.01
RVEF (per 1%)		5.59	0.93 (0.88–0.98)	0.02

For univariate analyses results are presented with unadjusted hazard ratios (unadj HR) with 95% confidence intervals (95% CI). Accounting for the rule of thumb for logistic and Cox models with a minimum of ten outcome events per predictor variable multivariate analysis was not performed for the primary endpoint and we limited the selection to 2 variables for the secondary endpoint

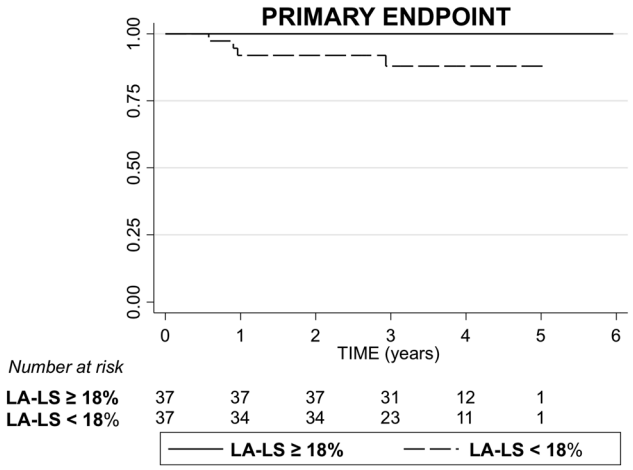

Fig. 3 Primary outcome (all cause-death) Kaplan–Meier survival analysis for patients with normal and abnormal total peak left atrial longitudinal strain (LA-LS). A lower free survival is shown in patients with abnormal LA-LS (p = 0.04)

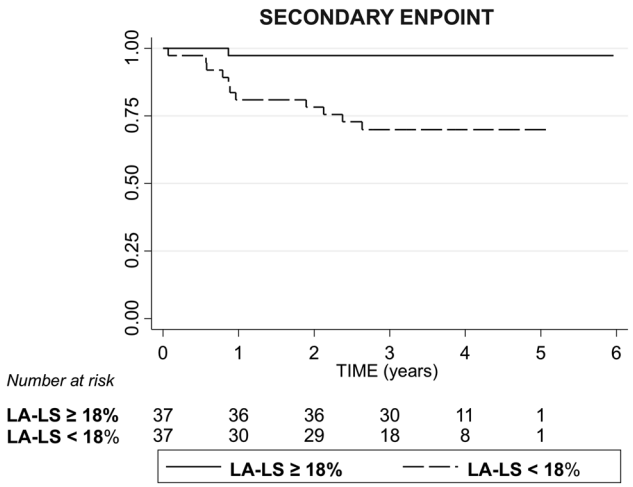

Fig. 4 Secondary composite outcome Kaplan–Meier survival analysis for patients with normal and abnormal total peak left atrial longitudinal strain (LA-LS). A lower free of event survival (hospital admission related to heart failure, lethal ventricular arrhythmias or cardiovascular death) is observed in patients abnormal LA-LS

LA volumetric analysis can study all three components of LA function: in the phase of reservoir component or expansion during systole (total LA-EF), in conduit phase during diastole (passive LA-EF) and in active contractile phase during late diastole (active LA-EF), however they are time consuming and are poorly integrated in clinical practice. There are different methods to noninvasively evaluate LA volume and function such as 2- or 3-dimensional echocardiography, speckle-tracking echocardiography, cine computed tomography, or CMR [25–29]. Initial attempts to assess LA deformation used speckle-tracking echocardiography [22–24]; however given the thin wall of the LA and the requirement of good acoustic windows, LA strain by echocardiography is restricted to expert operators and for the moment its clinical application remains limited.

CMR is the gold standard modality to quantify right and left atrial and ventricular volumes and systolic function [28]. Faster imaging and increased availability of equipment and imaging expertise, in addition to its ability to non-invasively provide information about the presence and extent of myocardial fibrosis support the use of CMR in the routine evaluation of patients with HCM [1]. CMR- feature tracking (CMR-FT), a technique analogous speckle-tracking echocardiography, derives similar quantitative deformation parameters from conventional steady state free precession (SSFP) cine sequences with inherently better image quality. Despite the commonly lower temporal resolution, myocardial CMR-FT has been validated allowing an in-depth study of cardiomyopathies given its excellent ability to detect border delineation for adequate strain analysis [30–33]. Recently, CMR-FT has been applied to study LA deformation in health and disease, demonstrating to be feasible and reproducible [7, 10]. Furthermore, Williams LK and collaborators demonstrated abnormal LA functional parameters by CMR-FT in patients with HCM, which were significantly worse in those with LVOT obstruction [4]. They further show improved LA function after septal myectomy, suggesting the associated effects of LVOT obstruction and mitral regurgitation in left atrial mechanics. Our results confirm that CMR is able to quantify LA contractile dysfunction in this cohort of patients capturing LA motion throughout the cardiac cycle. We also show that LA strain is impaired even in patients with normal LA volume and apparently normal LV filling pressures (E/é < 8). We expand their evidence, showing that the amount of LGE and the degree of LV hypertrophy (both affecting GLS), in addition to age are independent predictors of impaired LA strain. Lastly, we further demonstrate that impaired global longitudinal LA strain by CMR-FT is associated with cardiovascular mortality and heart failure in HCM.

Previously, LA function had been studied by volumetric indices, however their analysis are time consuming, require higher level of expertise and suffer of lower reproducibility. On the contrary, CMR-FT represents an easy-to-use tool, fast and with very good intra and inter-observer reproducibility.

LA size is an established marker of risk in HCM; however, our results confirm that LA function is more sensitive than LA volume to detect LA abnormalities, suggesting that early detection of LA dysfunction may provide prognostic information beyond measurements of LA volume or diameter.

Heart failure (HF) represents a major complication determining long-term prognosis in HCM. Patients are usually stratified to identify individuals with high-risk of sudden

cardiac death [1]. For the moment, there are no general recommendations or risk scores in terms of prevention of other cardiovascular events related to the condition, particularly HF. HF events in HCM are mainly secondary to three different underlying mechanisms. Firstly, LVOT obstruction, which has been correlated with LA-EF and where LVEF is usually normal or supernormal [5]; secondly, "end stage" HCM ("burnt out" HMC) characterized by systolic impairment with low EF [< 50%] and without LVOT obstruction, which usually reveals extensive replacement myocardial fibrosis. Thirdly, and most importantly, reduced LV compliance and increased LV end-diastolic pressures and atrial fibrillation as common factors in acute heart failure.

In our cohort of patients who developed HF, all had normal LVEF and only one had significant LVOT obstruction. The predominantly underlying mechanism of HF was an increased LV filling pressure. LA-LS as a marker of LA function was impaired in all patients. LA-LS reflects the passive stretching of the LA during LV systole and represents LA compliance and reservoir function. Its strong correlation with LV filling pressure has already been demonstrated [23, 34]. LA size as a sensitive and load-independent marker of LV diastolic dysfunction has been independently associated with AF, and thrombo-embolic events, heart failure or cardiac death in HCM [17, 33, 35–38]. Although LA function, instead of LA enlargement, has been applied to other scenarios (general population, patients with chronic hypertension) demonstrating promising prognostic implications, for the moment no study has been focus on HCM population [7, 21, 39]. Our results add to this knowledge by showing that in patients with HCM, LA deformation represents an additional prognostic tool by characterizing the burden of underlying diastolic dysfunction.

Although our results should be confirmed in future multicentre studies with higher number of patients, our findings bring forward CMR-determined LA function as a promising ongoing biomarker or transducer of sustained elevations in LV filling pressures that may become an important clinical risk stratifier in the clinical evaluation of patients with HCM.

Limitations

First, this was a single center study with small sample size and therefore, low number of events that may limit the overall power of the study. In our cohort, the SCD risk score was low and only one patient experienced lethal ventricular arrhythmias; given the observational nature of the study, a higher risk subset of patients directly derived to ICD implantation (and with contraindication for a CMR study) may have been excluded. These factors may explain the lack of associations between classical predictors of SCD and mortality in our study.

All LA strain measurements were performed with CMR 42® FT software and significant differences in strain measurements between different CMR-FT vendors cannot be excluded. For the moment CMR-FT values by different software cannot consider interchangeably. Given the higher reliability compared to velocity or LA strain-rate values, only LA strain values were reported. Future efforts to standardize available solutions would be desirable to reduce inter-vendor variability and facilitate comparative measures of LA deformation.

Conclusion

LA-LS by CMR-FT provides accurate measurements of LA function in patients with HCM even in patients with normal LA volume and LV filling pressures. LA-LS may become a novel predictor of adverse cardiac events, particularly HF and death in this population. The feasibility and high reproducibility of CMR-FT that is applied to conventional cine CMR images suggest that this tool might be implemented in the routine evaluation of HCM patients. Nevertheless, the relatively small sample size of the study (and the subsequent few events) call for the cross-validation of our results in a larger multicenter study.

Compliance with ethical standards

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

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