Chapter 11

Left atrial size and function in hypertrophic cardiomyopathy patients and risk of new onset atrial fibrillation

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ABSTRACT

Objectives

Atrial fibrillation (AF) in hypertrophic cardiomyopathy (HCM) patients is highly prevalent, implies dismal prognosis, rendering risk stratification a priority. Whether LA volume and LA strain yield incremental value over LA diameter to risk stratify HCM patients for AF is unknown. The value of LA diameter, volume and strain to risk stratify HCM patients for new onset AF was explored.

Methods and results

A total of 243 HCM patients without AF history were retrospectively evaluated by (speckle tracking) echocardiography to assess LA diameter, volume and strain. New onset AF comprised the primary endpoint. During mean follow-up of 4.8±3.7 years, 40 patients (16%) developed AF. Multivariable analysis showed LA diameter (HR=1.07, 95%CI 1.02-1.13, p=0.011), LA volume (HR=1.03, 95%CI 1.01-1.06, p=0.007) and LA strain (HR=0.91, 95%CI 0.86-0.96, p<0.001) as independent AF correlates. Importantly, 58% (n=23) of AF events occurred despite a baseline LA diameter <45mm, observed in 186 patients. In this patient subset, LA strain (AUC 0.73, p<0.001) and LA volume (AUC 0.70, p=0.004) showed good predictive value for new onset AF. Furthermore, patients with LA volume <36 versus ≥36mL/m² (median value) and LA strain >23.4 versus ≤23.4% (median value) had superior 5-year AF-free survival of 92% versus 80% (p=0.013) and 98% versus 74% (p=0.001), respectively. Importantly, LA volume <36mL/m² and strain >23.4% yielded high negative predictive value (93% and 94%, respectively) for new onset AF. Likelihood ratio test indicated incremental value of LA volume assessment (p<0.001) on top of LA diameter to predict new onset AF in HCM patients with LA diameter <45mm, which further increased by addition of LA strain (p=0.042).

Conclusion

LA diameter, volume and strain all independently relate to new onset AF in HCM patients. In patients with normal LA size, however, both LA volume and strain further refine risk stratification for new onset AF.

INTRODUCTION

Primary hypertrophic cardiomyopathy (HCM), caused by sarcomeric gene mutation(s), encompasses increased risk for arrhythmia, heart failure and (sudden) cardiac death.[1,2] Atrial fibrillation is more prevalent than in the general population, typically affecting about 20% of HCM patients at an annual incidence of over 2%.[3-5] Importantly, one third of patients are diagnosed before the age of 50 years old.[3] HCM patients who develop atrial fibrillation are vulnerable to symptoms, impaired exercise tolerance, hospitalization for heart failure and, importantly, are prone to dismal prognosis.[3,4] Atrial fibrillation increases by 4-fold the risk of mortality independent of other known mortality risk factors, mainly due to heart failure and stroke related death.[3,4,6] In addition atrial fibrillation is associated with an 8-fold increased risk of thromboembolism in HCM patients, occurring at an annual incidence of 3.75%.[5,6] Early mortality or persistent neurologic disability are common in these patients, even more if onset of atrial fibrillation occurs at younger age.[3] Therefore accurate risk stratification for new onset atrial fibrillation in HCM patients should be a priority and may have an impact on follow-up and management strategies.

Left atrial (LA) diameter has consistently been identified as a strong predictor of atrial fibrillation development in HCM patients.[3,5] It has been suggested that the extent of atrial remodeling and therefore risk for atrial fibrillation, might be better reflected by 2-dimensional assessed LA volume rather than uni-dimensional LA diameter.[7,8] Two-dimensional (2-D) speckle tracking echocardiography is a novel method for accurate assessment of LA function, expressed as reservoir strain, more sensitive than LA size or volume. To date only one small study in HCM patients linked impaired LA strain to atrial fibrillation requiring hospitalization.[9] We hypothesized that LA volume and/or LA strain may yield incremental value over LA diameter to risk stratify HCM patients for new onset atrial fibrillation. The aim of current study is to explore the clinical value of all three LA parameters in relation to new onset atrial fibrillation in a large HCM population.

METHODS

Patient population

Patients ≥18 years with a clinical diagnosis of HCM based on otherwise unexplained ventricular hypertrophy, comprising a LV wall thickness of ≥15 mm were selected from an ongoing echocardiographic and clinical database. Patients with a history of atrial fibrillation before or at the moment of echocardiography, no

additional clinical follow-up visit after baseline echocardiography and insufficient image quality to allow LA strain assessment were excluded.

Baseline characteristics including age, gender, cardiovascular risk factors, medication use, presence of implantable cardioverter defibrillator (ICD) and results of sarcomere mutation testing, if performed, were extracted from the departmental electronic patient information system (EPD-Vision®, Leiden University Medical Center, Leiden, the Netherlands). In addition, at baseline all HCM patients had 12-lead electrocardiography (ECG) and 24-hour ambulatory electrocardiography (Holter) registration.

As recommended, patients were followed-up on a yearly basis at our and/or the referring institution, comprising a clinical visit and 12-lead ECG.[1,2] Repeated ECG or Holter recordings were performed at the discretion of the treating physician based on symptoms, presence of enlarged LA or for sudden cardiac death risk stratification. Device interrogation was performed every 3 to 6 months in ICD recipients.

The study was approved by the internal review board that waived the need for written informed consent for retrospective evaluation of prospectively collected clinical data.

Echocardiographic analysis

Comprehensive 2-D transthoracic echocardiography was performed in all patients in the left lateral decubitus using commercially available ultrasound systems (System-5, Vivid-7 and E9, GE-Vingmed, Milwaukee, WI) equipped with a 3.5 MHz or M5S transducers. Conventional ECG-triggered 2-D B-mode, M-mode, pulsed wave, continuous wave and color-Doppler images were acquired in still or cine-loop format and analyzed off-line (EchoPAC version 112, GE Medical Systems, Horten, Norway). From a short-axis view at basal, mid and apical level the maximal LV end-diastolic wall thickness was assessed. Septal LV wall thickness and LV diameters were calculated from parasternal long-axis views, as recommended.[10] Simpson's biplane method was used for evaluation of LV volumes and to calculate LV ejection fraction. Diastolic parameters, including E/A and E/e' were assessed using pulsed wave Doppler at the tips of the mitral leaflets and from tissue Doppler imaging at the level of the lateral annulus, respectively. A multi-integrative approach was used to grade presence of mitral regurgitation as grade 1 (trivial), 2 (mild), 3 (moderate) or 4 (severe), as recommended.[11] In addition systolic anterior movement of the anterior mitral leaflets was evaluated from M-mode parasternal acquisition. Presence of LV resting intraventricular or outflow tract gradient was systematically explored by pulsed wave Doppler and quantified by continuous wave Doppler.

LA analysis

LA diameter was derived from parasternal long axis B-mode view and LA volume was measured at end-systole with the Simpson's biplane rule. All volumes were indexed to body surface area. LA 2-D speckle tracking longitudinal strain was measured as peak systolic reservoir strain, as previously reported.[12] The smallest region of interest was set to include the thin atrial wall. The average value of both the apical 2-chamber and 4-chamber views was used. Mean frame rate for LA strain analysis was 57 frames per second. The intra- and interobserver variability for LA strain analysis in our department has been previously reported.[12]

Endpoint

New onset atrial fibrillation at out-patient or emergency room visit, defined as an irregular heart rhythm without distinct P-waves documented on ECG, Holter registration (if duration ≥30 seconds) or after expert analysis from device recordings in patients with ICD, comprised the study endpoint.[13]

Statistical analysis

Normally distributed and skewed continuous data are presented as mean ± standard deviation and median ± interquartile range, respectively, while percentages are used for categorical data. Comparison between groups was based on Student-T, Mann-Whitney U, Fisher exact or χ^2-test, when appropriate. Receiver Operator Characteristic (ROC) curve analysis was performed to test all 3 LA parameters (diameter, volume and strain) for prediction of the study endpoint. The study population was stratified based on LA diameter < or ≥45 mm, a cut-off value proposed by most recent HCM guidelines.[2] Stratification based on LA volume and strain was performed by their median value, given current lack of generally accepted cut-off in this patient population. Kaplan-Meier cumulative survival curves free of atrial fibrillation were constructed for all LA parameters, stratified according to their cut-off values, and compared by log-rank test. In addition sensitivity, specificity, positive and negative predictive values for the study endpoint prediction were calculated. Subsequently Cox proportional hazards regression analysis was performed to identify associates of new onset atrial fibrillation. Parameters at a significance threshold of $p<0.1$ at univariable level were entered into the multivariable analysis using a backward elimination approach. Multivariable testing was performed for each LA parameter of interest separately (diameter, volume and strain). Finally, similar statistical analysis was performed, restricting the study population to patients with LA diameter <45 mm, generally regarded as being at low risk for new onset atrial fibrillation.[2] In addition, likelihood ratio test was used to explore the potential incremental value of adding LA volume and strain on top

of LA diameter in relation to the study endpoint for this patient subset. SPSS version 20.0. (SPSS Inc., Chicago, Illinois) was used for statistical analysis. A p-value of <0.05 was considered statistically significant, all tests being two-sided.

RESULTS

Patient population

A total of 243 HCM patients comprised the final population after excluding patients for age <18 years old (n=18), history of atrial fibrillation (n=43), no follow-up visit (n=4) and insufficient image quality for LA strain assessment (n=54, 15%). Baseline demographic, clinical and echocardiographic characteristics of these patients (65% male, mean age 53±13 years) are provided in Table 1. The patient population showed typical characteristics of HCM such as increased wall thickness (median 21 mm), small LV cavities and preserved LV function (ejection fraction 68±8 %). In addition the presence of systolic anterior movement of the mitral valve or a significant LV outflow tract obstruction (≥30 mmHg) were noted in one third of the patients. Median LA size was slightly or moderately increased, when expressed as diameter [40 mm (36-44)] or volume [36 mL/m² (28-46)], respectively.[10] Median LA reservoir function measured with speckle tracking was 23.4% (16.9-29.1). By definition all patients were in sinus rhythm at baseline.

Study endpoint

During a mean follow-up of 4.8±3.7 years (range 1.7-7.1) 40 out of 243 patients (16%) experienced new onset atrial fibrillation. Particularly, more than half of these events (23/40, 58%) occurred in the sub-group of 186 HCM patients with a baseline LA diameter of <45 mm.

Atrial fibrillation in the overall population

Patients with versus without new onset atrial fibrillation had a larger LA size (diameter and volume) and more impaired LA function (strain), as shown in Table 2 (all p<0.001). ROC curve analysis, indicated a moderately higher predictive value for LA volume and LA strain than for LA diameter, to predict the occurrence of new onset atrial fibrillation (Table 2, all p<001).

Survival free from new onset atrial fibrillation was higher in patients with an LA diameter <45 versus ≥45 mm yielding a 5-year atrial fibrillation free survival of 88% versus 74%, respectively (p=0.005) (Figure 1). Similarly, survival free from new onset atrial fibrillation was higher in patients with an LA volume <36 versus ≥36 mL/m² (5-year survival 92% versus 78% respectively, p=0.001) and LA strain

Table 11.1
Baseline characteristics.

	Study population (n = 243)	LA <45 mm (n=186)	LA ≥45 mm (n=57)	p-value
Clinical characteristics				
Age, years	53 ± 13	53 ± 13	52 ± 14	0.544
Men, n (%)	157 (65)	108 (58)	49 (86)	<0.001
Systolic BP, mmHg	139 ± 23	138 ± 23	142 ± 21	0.432
Diastolic BP, mmHg	81 ± 11	81 ± 10	80 ± 11	0.512
Hypertension, n (%)	94 (39)	73 (39)	21 (37)	0.624
Diabetes, n (%)	20 (8)	17 (9)	3 (6)	0.773
Smoking history, n (%)	65 (27)	51 (27)	14 (24)	0.212
Hyperlipidemia, n (%)	73 (30)	60 (32)	13 (23)	0.325
ICD, n (%)	20 (8)	14 (8)	6 (10)	0.581
For primary prevention	14 (6)	10 (5)	4 (7)	-
For secondary prevention	6 (2)	4 (2)	2 (4)	-
Echocardiography				
IVS, mm	20 ± 5	19 ± 5	22 ± 6	<0.001
Maximal LVH, mm	21 (18-24)	20 (17-23)	24 (21-26)	<0.001
LVEDD, mm	43 ± 6	42 ± 6	47 ± 6	<0.001
LVESD, mm	24 ± 6	23 ± 6	26 ± 7	0.001
LV EDVI, mL/m^2	51 ± 16	49 ± 14	57 ± 18	0.001
LV ESVI, mL/m^2	16 ± 7	15 ± 6	19 ± 9	0.001
LV EF, %	68 ± 8	69 ± 8	67 ± 8	0.171
LA diameter, mm	40 ± 6	38 ± 5	48 ± 3	<0.001
LA volume, mL/m^2	38 ± 14	35 ± 12	50 ± 15	<0.001
LA strain, %	23.2 ± 8.0	24.6 ± 7.6	18.7 ± 7.4	<0.001
E/A	1.0 (0.7-1.4)	0.9 (0.7-1.4)	1.2 (0.9-1.6)	0.018
E/e'	10 (8-15)	10 (8-15)	13 (10-17)	0.011
Systolic anterior motion of MV, n (%)	90 (37)	62 (33)	28 (49)	0.041
MR grade	1.02 ± 0.71	0.98 ± 0.74	1.18 ± 0.69	0.075
Resting LV outflow gradient, mmHg	9 (6-20)	9 (6-17)	10 (7-55)	0.051
Resting LV outflow gradient >30 mmHg, n (%)	39 (16)	24 (13)	15 (26)	0.021
Sarcomeric mutation (n=119 tested), n (%)	61 (51)	43 (48)	18 (56)	0.541

BP: blood pressure, EDD: end-diastolic diameter, EDVI: end-diastolic volume index, EF: ejection fraction, ESD: end-systolic diameter, ESVI: end-systolic volume index, ICD: implantable cardioverter defibrillator, IVS: interventricular septum, LA: left atrium, LV: left ventricle, LVH: left ventricular hypertrophy, MR: mitral regurgitation, MV: mitral valve

>23.4 vs ≤23.4 % (5-year survival of 94% versus 75%, respectively, p<0.001). Table 2 shows the higher sensitivity at cost of lower specificity of LA volume and strain compared to LA diameter to predict new onset atrial fibrillation. Cox regres-

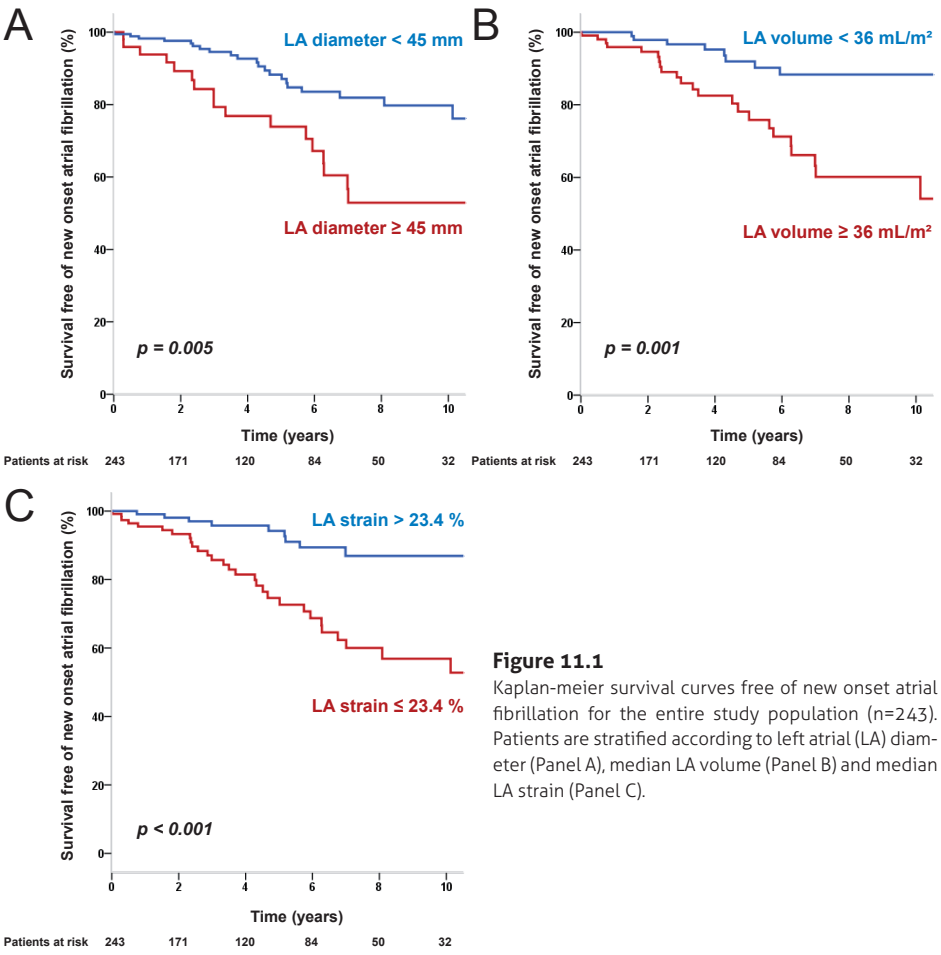

Figure 11.1
Kaplan-meier survival curves free of new onset atrial fibrillation for the entire study population (n=243). Patients are stratified according to left atrial (LA) diameter (Panel A), median LA volume (Panel B) and median LA strain (Panel C).

sion analysis identified age, diabetes, E/e', mitral regurgitation grade and all LA parameters (diameter, volume and strain) as univariate associates of new onset atrial fibrillation (all p<0.10) (Table 3). Moreover, multivariable analysis showed that all LA parameters were independently associated with the study endpoint: LA diameter (HR 1.07, 95% CI 1.02-1.13, p=0.011), LA volume (HR 1.03, 95% CI 1.01-1.06, p=0.007) and LA strain (HR 0.91, 95% CI 0.86-0.96, p<0.001) (Table 4).

Atrial fibrillation in patients with left atrial diameter <45 mm

Although HCM patients with LA diameter <45 mm are generally considered to be at relatively low risk for new onset atrial fibrillation, 58% (23 out of 40) of these events occurred in this subset of 186 patients (Figure 2), implicating a prevalence

Table 11.2

Left atrial parameters for prediction of new onset atrial fibrillation using the pre-specified cut-off values. Note superior sensitivity of LA volume and strain versus diameter to predict atrial fibrillation in entire study population. In the patient sub-group with preserved LA diameter (<45 mm, 186 patients), comprising 58% (n=23/40) of the atrial fibrillation events, both LA volume and LA strain show high negative predictive value.

Entire study population (n=243)	No AF (n=203)	AF (n=40)	p-value	AUC ROC	Cut-off	Sens %	Spec %	PPV %	NPV %
LA diameter, mm	40 ± 6	44 ± 6	<0.001	0.68	≥ 45	43	80	30	88
LA volume, mL/m²	36 ± 13	48 ± 16	<0.001	0.72	≥36	73	54	22	92
LA strain, %	24.1 ± 7.8	18.4 ± 7.3	<0.001	0.71	≤23.4	75	55	25	85
Patients with LA diameter <45 mm (n=186)	**No AF (n=163)**	**AF (n=23)**	**p-value**	**AUC ROC**	**Cut-off**	**Sens %**	**Spec %**	**PPV %**	**NPV %**
LA volume, mL/m²	34 ± 11	44 ± 16	<0.001	0.70	≥36	63	62	17	93
LA strain, %	25.4 ± 7.3	18.9 ± 7.5	<0.001	0.74	≤23.4	74	61	21	94

Abbreviations, see Table 1. AF: atrial fibrillation. AUC: area under the curve, NPV: negative predictive value, PPV: positive predictive value, ROC: receiver operating curve analysis, Sens: sensitivity, Spec: specificity

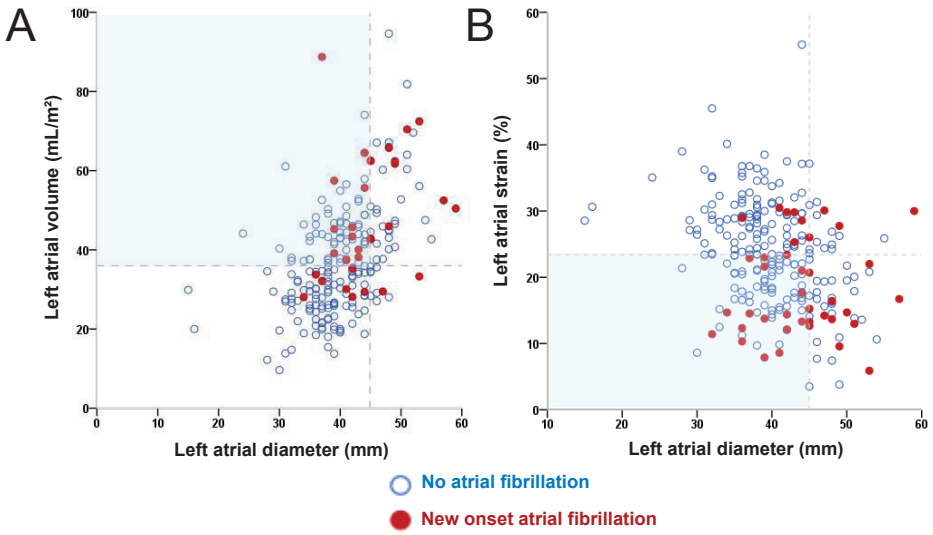

Figure 11.2

New onset atrial fibrillation according to left atrial size and function. Left atrial (LA) diameter versus volume (Panel A) and versus strain (panel B). Dashed vertical line represents the 45 mm LA diameter cut-off. The dashed horizontal line represents the 36 mL/m² and 23.4% cut-off for LA volume (panel A) and strain (panel B), respectively. A significant proportion of new onset atrial fibrillation events occurs despite 'normal' LA diameter (<45 mm) of which a significant part is detected based on the cut-offs set for enlarged LA volume and impaired LA strain (light blue area), explaining higher overall sensitivity. Relative few events occur in patients with preserved LA diameter without enlarged LA volume or preserved LA strain, explaining the high negative predictive value of the latter two parameters.

Table 11.3
Univariable Cox regression analysis to predict new onset atrial fibrillation. Abbreviations, see Table 1. LVOT: left ventricular outflow tract.

	Univariable	
	HR (95% CI)	p-value
Age, per year	1.04 (1.01-1.07)	0.002
Male gender	0.70 (0.37-1.31)	0.266
Systolic BP, per mmHg	1.00 (0.98-1.02)	0.808
Diastolic BP, per mmHg	1.02 (0.98-1.05)	0.409
Hypertension	1.42 (0.73-2.74)	0.300
Diabetes	2.66 (1.09-6.46)	0.031
Smoking history	0.79 (0.36-1.77)	0.577
Hypercholesterolemia	0.94 (0.47-1.89)	0.855
Maximal LVH, per mm	1.02 (0.97-1.07)	0.383
E/e'	1.04 (1.02-1.07)	0.003
MR grade	2.09 (1.38-3.15)	<0.001
Resting LV(OT)gradient, per mmHg	1.01 (1.00-1.02)	0.130
Resting LV(OT)gradient >30 mmHg	1.34 (0.61-2.91)	0.464
LVEDD, per mm	0.98 (0.93-1.03)	0.389
LVESD, per mm	1.01 (0.96-1.07)	0.606
LVEDVi, per ml/m²	0.99 (0.97-1.01)	0.243
LVESVi, per mL/m²	1.01 (0.98-1.05)	0.579
LVEF, per %	0.97 (0.94-1.01)	0.112
LA diameter, per mm	1.09 (1.04-1.14)	0.001
LA volume, per mL/m²	1.05 (1.03-1.07)	<0.001
LA strain, per %	0.92 (0.89-0.96)	<0.001

Table 11.4
Multivariable Cox regression analysis to predict new onset atrial fibrillation for different left atrial parameters. Univariate predictors p<0.10 in univariable model were included in the multivariable model. Separate models were created for each left atrial parameter to avoid co-linearity. Abbreviations, see Tables 1 and 2.

	Multivariable LA diameter		Multivariable LA volume		Multivariable LA strain	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.03 (1.00-1.06)	0.071	1.01 (0.97-1.04)	0.635	1.01 (0.98-1.07)	0.732
Diabetes	1.70 (0.58-5.00)	0.332	1.78 (0.60-5.32)	0.302	1.17 (0.40-3.38)	0.779
E/e'	1.02 (0.99-1.06)	0.207	1.03 (1.00-1.07)	0.079	1.02 (0.98-1.05)	0.440
MR grade	1.66 (0.97-2.83)	0.063	1.40 (0.72-2.73)	0.322	1.67 (1.02-2.71)	0.041
LA diameter	1.07 (1.02-1.13)	0.011	-	-		
LA volume	-	-	1.03 (1.01-1.06)	0.007		
LA strain	-	-	-	-	0.91 (0.86-0.96)	<0.001

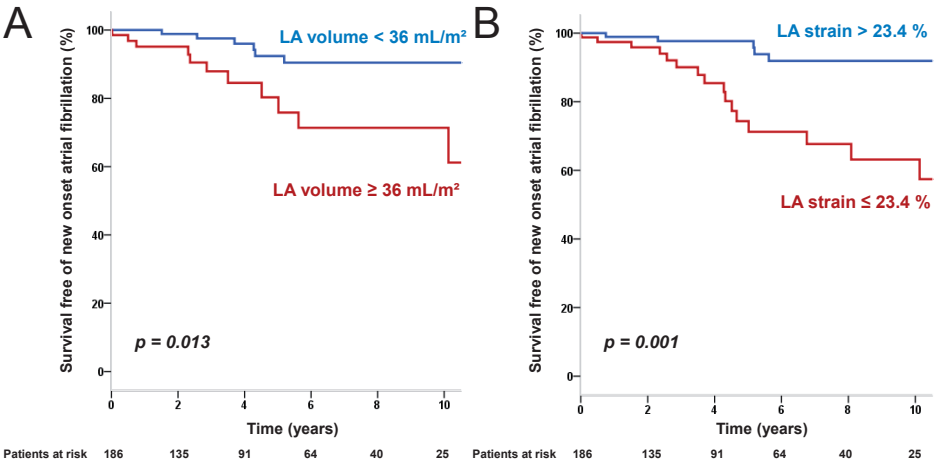

Figure 11.3
Kaplan-meier survival curves free of new onset atrial fibrillation in patients with left atrial diameter <45 mm (n=186). Patients are stratified according to median left atrial (LA) volume (Panel A) and LA strain (Panel B).

of 12% (23/186) versus 30% (17/57) in patients with LA diameter <45 mm versus ≥45 mm, respectively.[2]

Within the cohort of patients with LA diameter <45 mm, LA volume was larger and LA strain more impaired in patients that developed new onset atrial fibrillation compared with patients who remained in sinus rhythm (Table 1). Using ROC curve analysis, LA strain (AUC 0.74, p<0.001) provided greater predictive value for new onset atrial fibrillation compared to LA volume (AUC 0.70, p=0.004) in this subset of patients. Importantly, both LA parameters were able to further discriminate risk for new onset atrial fibrillation in patients with LA diameter <45 mm, as illustrated by the survival curves free of new onset atrial fibrillation in Figure 3. Patients with LA volume <36 versus ≥36 mL/m² and LA strain >23.4 versus ≤23.4 % (median values) had better survival free of atrial fibrillation with cumulative 5-year survival of 92% versus 80% (p=0.013) and 98% versus 74% (p=0.001), respectively. As shown in Table 2 and Figure 2, both LA parameters particularly yield high negative predictive value for new onset atrial fibrillation in this HCM sub-population.

Likelihood ratio test indicated significant incremental value of LA volume (p <0.001) on top of LA diameter to predict new onset atrial fibrillation in HCM patients with LA diameter <45 mm (Figure 4). Interestingly, addition of LA strain further increased the predictive value of the model containing LA diameter and LA volume (p =0.042).

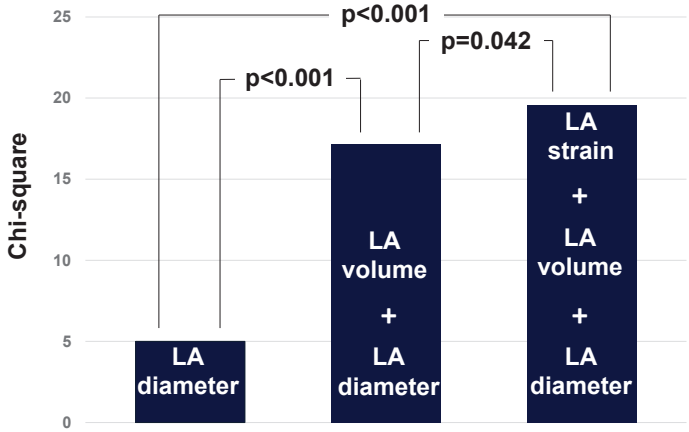

Figure 11.4
Likelihood ratio test in patients with left atrial diameter <45 mm (n=186). Subsequent addition of both left atrial (LA) volume and LA strain on top of diameter assessment provides incremental value for prediction of new onset atrial fibrillation.

DISCUSSION

The main study findings in this HCM population can be summarized as follows: 1) LA size (diameter and volume) and LA function (strain) are independently related to new onset atrial fibrillation, 2) the burden of new onset atrial fibrillation is significant despite the relative young age, even in patients with LA diameter <45 mm, and 3) adding LA volume and/or LA strain assessment on top of LA diameter improves prediction of new onset atrial fibrillation with both parameters yielding high negative predictive value in the subset of patients with LA diameter <45 mm.

Left atrial remodeling comprises structural and functional changes usually preceding atrial arrhythmias. In the current study, patients developing new onset atrial fibrillation had larger LA size (diameter and volume) and more impaired LA function (strain), compared to HCM patients free of atrial fibrillation. HCM patients are particularly prone to adverse atrial remodeling for several reasons. Increased filling pressures due to left ventricular diastolic dysfunction and hypertrophy, mitral regurgitation and outflow tract obstruction are well known determinants of increased LA size in HCM patients.[14,15] Moreover, increased atrial fibrosis contributes to atrial enlargement and functional impairment.[16] Although evidence is scarce, intrinsic atrial myopathy as part of the molecular disease has been suggested as well.[5] Specific sarcomeric gene mutations have recently been described in atypical forms of HCM that relate to juvenile onset of atrial fibrillation in these patients.[17] Even polymorphisms in non-sarcomeric genes, encoding for proteins involved in the renin-angiotensin-aldosterone system and collagen synthesis, have shown to

act as HCM disease modifiers, increasing the likelihood of atrial fibrillation development.[18] Therefore it is not unexpected that atrial fibrillation often complicates the natural course of HCM, translating into a significant morbidity and mortality burden.

Increased LA size, evaluated by uni-dimensional antero-posterior diameter assessment, has consistently been reported as one of the strongest correlates of atrial fibrillation in HCM patients.[3,5] Current guidelines recommend intensification of diagnostic arrhythmia surveillance with 48-hour Holter 6-monthly once LA diameter equals or exceeds 45 mm.[2] As atrial enlargement in the antero-posterior direction is restricted by the presence of the sternum and mediastinum (more specific), structural remodeling may be better described by evaluating atrial volume, often based on a 2-D approach (more sensitive).[8,19] Several reports demonstrate that increased LA volume heralds increased risk of atrial fibrillation and might be preferred over LA diameter.[7,8,20,21] The current study confirms this hypothesis, indicating higher sensitivity and negative predictive value of LA volume versus diameter to identify patients at risk for new onset atrial fibrillation.

Functional LA changes may coincide or even precede structural adaptations. Decreased LA ejection fraction, evaluated by echocardiography or cardiac magnetic resonance imaging, has been linked to the occurrence of atrial fibrillation in HCM patients.[7,20] Two-dimensional speckle tracking analysis allows angle independent assessment of LA function by measuring magnitude (strain) or rate (strain rate) of atrial deformation. In particular LA reservoir strain, referring to longitudinal deformation that occurs due to LA distention by pulmonary venous inflow during ventricular systole (reservoir phase) is a highly sensitive technique, able to identify atrial changes even in patients with normal LA size.[22,23] Hence, impaired LA reservoir strain is often noted in HCM patients.[24] A recent cross-sectional report in a limited number of patients indicated more impaired lateral reservoir Doppler-derived strain (rate) in HCM patients with versus without atrial fibrillation.[21] One study in 50 HCM patients indicated that LA reservoir speckle-tracking derived strain independently predicts occurrence of atrial fibrillation requiring hospitalization (odds ratio 0.85, 95% CI 0.75-0.97, p=0.017).[9] The present study, representing the largest cohort of HCM patients evaluated by LA strain so far, demonstrates higher sensitivity of LA strain compared to LA diameter to predict new onset atrial fibrillation and confirms its independent predictive value for this endpoint.

Importantly, 58% of new onset atrial fibrillation events in the HCM patients studied occurred despite a relatively preserved atrial diameter of <45 mm. This is of particular relevance as this subset of HCM patients is generally regarded as being at low risk to develop atrial fibrillation and no additional follow-up measures are recommended.[2] We showed that patients with LA diameter <45 mm who

actually do develop atrial fibrillation have larger LA volume and more impaired LA function compared to patients free of atrial arrhythmia. In particular patients with LA volume ≥36 mL/m² or LA strain ≤23.4 % had worse survival free of atrial fibrillation. Presence of relatively preserved LA volume <36 mL/m² or LA strain >23.4 % virtually excluded the risk of new onset atrial fibrillation (negative predictive value of 93% and 94%, respectively). Not unexpectedly, additional assessment of LA volume and LA strain therefore conveyed a higher predictive value for new onset atrial fibrillation in the subset of HCM patients with LA diameter <45 mm. These findings probably reflect the previously reported higher sensitivity of LA volume and LA strain assessment in comparison with LA diameter.

Clinical implications

Intensified monitoring to detect atrial fibrillation should indeed be offered to HCM patients with dilated LA ≥45 mm, as recommended.[2] Based on current findings, however, this strategy should not be restricted to those patients only, but LA volume and/or strain assessment should additionally be performed in order to rule out increased risk for atrial fibrillation. In those patients with LA volume >36 mL/² and/or LA strain <23.4 % it might therefore be prudent to intensify follow-up aiming for detection of subsequent atrial fibrillation occurrence. In addition, observational data have indicated that patients with only one atrial fibrillation episode have similar risk for thromboembolism versus those with repeated episodes and oral anticoagulation using warfarin significantly decreased that likelihood.[5,6] It has been suggested that prophylactic anticoagulation in HCM patients with increased LA size should be the focus of additional research. In light of current findings it might prove valuable to consider additional assessment of LA volume or strain to facilitate such clinical decision-making. Finally ablation for atrial fibrillation in HCM patients is increasingly reported although the results seem less compared to non-HCM patients.[25,26] The value of LA volume and strain rather than LA diameter to select candidates for ablation and predict success or recurrence of arrhythmia in HCM patients may be the scope of future investigation.

Limitations

Some limitations merit attention. First, this report is a retrospective longitudinal analysis of patients referred to a tertiary HCM center; therefore selection bias cannot be fully excluded. Second, ICD recipients are submitted to continuous heart rhythm monitoring, increasing the likelihood of atrial fibrillation detection. Other patients were followed by annual ECG or Holter monitoring (at discretion of treating physician). Therefore the true prevalence of new onset atrial fibrillation may have been underestimated in our study population.

CONCLUSION

Both LA size (diameter and volume) and function (strain) are independently related to new onset atrial fibrillation in HCM patients. A significant proportion of atrial fibrillation events, however, occurs in patients despite relatively preserved LA diameter <45 mm. Assessment of LA volume and strain have incremental predictive value in this patient subset, in particular to exclude increased risk for atrial fibrillation development based on high negative predictive value. These findings might impact on provision and intensity of follow-up surveillance to detect atrial fibrillation in HCM patients with preserved LA size.

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