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Assessment of left atrial electro-mechanical delay to predict atrial fibrillation in hypertrophic cardiomyopathy

Catherina Tjahjadi, Yasmine L Hiemstra, Pieter van der Bijl, Stephan M Pio, Marianne Bootsma, Nina Ajmone Marsan, Victoria Delgado, and Jeroen J Bax*

Department of Cardiology, Leiden University Medical Center, Albinusdreef 2, 2300 RC Leiden, The Netherlands

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Aims Atrial fibrillation (AF) is frequently observed in hypertrophic cardiomyopathy (HCM) and is associated with poor clinical outcome. Total atrial conduction time, estimated by tissue Doppler imaging (TDI), the so-called PA-TDI duration, reflects the left atrial (LA) structural and electrical remodelling. The aim of this study was to evaluate the association between PA-TDI and new-onset AF in patients with HCM.

Methods and results From a large cohort of patients with HCM, 208 patients (64% male, mean age 53 ± 14 years) without AF were selected. PA-TDI duration was measured from the onset P wave on electrocardiogram to the peak *A′* wave of the lateral LA wall using TDI. The incidence of new-onset AF was 20% over a median follow-up of 7.3 (3.5–10.5) years. Patients with incident AF had longer PA-TDI duration when compared with patients without AF (133.7 ± 23.0 vs. 110.5 ± 30.0 ms, $P < 0.001$). PA-TDI duration was independently associated with new-onset AF (hazard ratio: 1.03, 95% confidence interval: 1.01–1.05, $P < 0.001$).

Conclusion Prolonged PA-TDI duration was independently associated with new-onset AF in patients with HCM. This novel parameter could be useful to risk-stratify patients with HCM who are at risk of having AF.

Keywords hypertrophic cardiomyopathy • atrial fibrillation • total atrial conduction time

Introduction

Atrial fibrillation (AF) is the most common arrhythmia observed in hypertrophic cardiomyopathy (HCM).[1–4] The association between AF and increased morbidity and mortality is well described in this population, independently of the type of AF (paroxysmal or permanent). Early recognition of AF is of paramount importance to initiate appropriate preventive therapeutic measures and improve clinical outcome.[5] Patients with subclinical AF identified on cardiac implantable electronic device (CIED) interrogation may carry similar risks of thromboembolism, heart failure, or mortality as the clinically symptomatic individuals.[6–9] It is noteworthy that patients with silent AF but without CIED will not be diagnosed unless they present with complications such as heart failure or stroke.

Atrial remodelling is frequently observed in HCM as adaptive change in response to left ventricular (LV) diastolic dysfunction with chronic elevated filling pressures and myocardial fibrosis formation. This process results in myocardial structural and functional changes that promote the development of AF.[10] Rapid atrial tachyarrhythmia also causes atrial remodelling that contributes to the maintenance of the arrhythmia itself.[5,11] Understanding the predictive factors of AF that indicate the extent of atrial remodelling before AF develops, is of benefit for implementing preventive therapeutic strategies. Left atrial (LA) diameter, volume, and strain have been identified as predictors of AF in HCM.[12] Similarly, PA-TDI duration is a risk marker that measures the total atrial conduction time (TACT) of the LA and prolongs when atrial dilatation occurs. The association between PA-TDI duration and AF was

* Corresponding author. Tel: +31 71 526 2020; Fax: +31 71 526 6809. E-mail: j.j.bax@lumc.nl

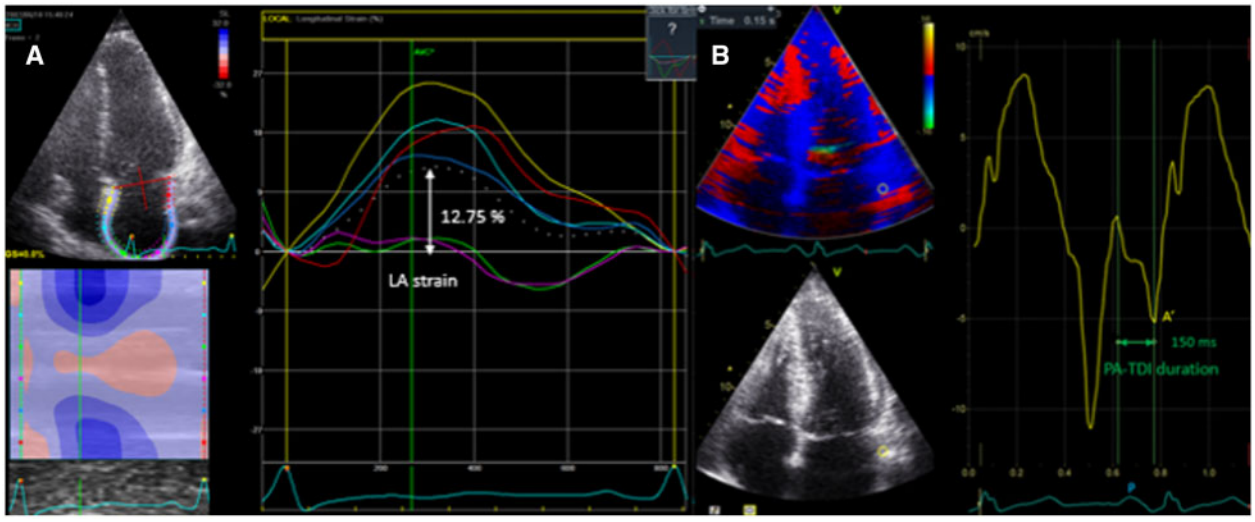

Figure 1 Assessment of LA reservoir strain and total atrial conduction time by means of PA-TDI duration. (*A*) The peak LA reservoir strain measured in the apical four-chamber view is shown, (*B*) whereas the measurement of PA-TDI duration is shown. (*A*) LA reservoir strain (12.75%) of a patient with hypertrophic cardiomyopathy (HCM) prior to developing AF. The dashed curve represents the mean LA reservoir (longitudinal) strain of the six segments. (*B*) The PA-TDI duration (150 ms) of the same patient as measured from the onset of the P wave on the electrocardiogram to the peak *A′* wave of the LA lateral wall above the mitral annulus.

demonstrated in various populations,[13–15] but it remains unexplored in HCM patients. In this study, we hypothesize that a long PA-TDI duration is associated with AF in HCM patients.

Methods

Patient population

Adult patients with phenotype-positive HCM and no previous history of AF were included. The diagnosis of HCM was defined in accordance to the international guidelines.[16,17] A recorded episode of absolutely irregular RR intervals and no discernible, distinct P waves on an electrocardiogram (ECG) for at least 30 s was diagnostic of AF according to current guidelines.[18] Documentation of new-onset AF was obtained from clinical assessment confirmed by ECG, external cardiac monitor analysis, or CIED interrogation. Clinical data were collected retrospectively from the departmental electronic health record system, and echocardiographic measurements were performed offline. The institutional review board approved the study and waived the need for written informed consent. The data that support the findings of this study are availableon reasonable request to the corresponding author.

Echocardiography

Comprehensive transthoracic echocardiographic assessment was performed for each patient. Two-dimensional and Doppler data were acquired as per contemporary guidelines.[16,17] Measurements of the LV wall thickness at end-diastole were performed on the three levels in the parasternal short-axis views. The LA dimensions were obtained from an end-systolic frame: the LA diameter was measured in the parasternal long-axis view, whereas the LA volume was measured from the apical two- and four-chamber views and indexed to body surface area.[19] Two-dimensional speckle tracking echocardiographic data of the LA were analysed offline (EchoPac version 202, GE Medical Systems) on the apical four-chamber view at end-diastole. The LA endocardial border was manually traced and the software divided the LA endocardium into six segments. The final LA reservoir strain value was the average of the segmental values (*Figure 1*).[20] PA-TDI duration was measured on tissue Doppler Imaging (TDI) data from the onset of the P wave on the surface ECG to the peak *A′* wave velocity recorded at the lateral LA wall just above the mitral annulus. PA-TDI is an estimation of the TACT (*Figure 1*).[15,21]

The patient population was divided according to reference cut-off values for LA diameter (≥45 mm) and LA volume index (≥34 mL/m^2) that define LA dilation,[16,17] and according to the median values for LA reservoir strain (<21.3%) and PA-TDI duration (≥115 ms) which, respectively, define impaired LA function and prolonged TACT.

Follow-up

Follow-up visits to the outpatient clinics were scheduled on a 6- to 12-monthly basis, or earlier when required. Standard ECG was performed on each presentation, Holter monitoring was requested according to patient's condition and at the discretion of the treating physician. CIED interrogation was performed as per institutional patient care programme. The follow-up period of this study was from the first ECG obtained (coinciding with the time of the echocardiogram where the PA-TDI was measured) to the first onset of AF documented on ECG, Holter analysis or CIED interrogation. The study endpoint was new onset AF documented on the ECG at presentation to outpatient clinic or emergency department, ECG Holter registration, and CIED analysis. There was no loss to follow-up.

Statistical analysis

Statistical data analysis was performed with SPSS statistical software for Windows, version 23 (SPSS, Armonk, NY, USA). Data with normal

distribution were expressed as mean ± SD and median ± interquartile range, respectively. Percentages were used to report categorical data. The distinction between continuous and categorical variables was made, and the appropriate tests (Student's *t*-test or Fisher's exact test) were applied accordingly to compare patients with and without AF during follow-up. The cumulative event-free survival was assessed with Kaplan–Meier analysis. The follow-up period was set at the first ECG obtained concomitantly with the echocardiogram where the various LA parameters were assessed and lasted until the episode of new onset AF or last visit of follow-up (whichever occurred first). Differences between the groups were evaluated by the log-rank test. Logistic regression was used to test the association between various echocardiographic variables and new-onset AF during follow-up. Variables with significant association were then included in a multivariable model for the assessment of the independent association between PA-TDI and occurrence of AF. A *P* value <0.05 was considered to be statistically significant.

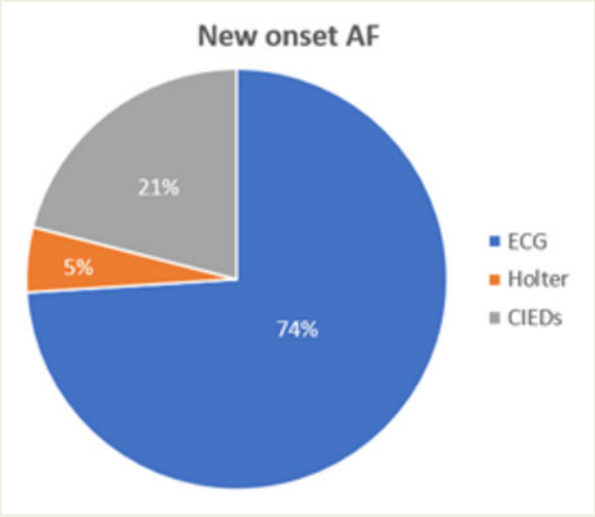

Figure 2 New-onset AF as detected by different diagnostic devices. AF, atrial fibrillation; CIEDs, cardiac implantable electronic devices.

Results

A total of 208 patients with HCM who did not have AF prior to their baseline echocardiography were included in this analysis. The mean age was 53 ± 14 years and 64% were men. During the median follow-up period of 7.3 (3.5–10.5) years, 42 patients (20%) developed new-onset AF. The new-onset AF was detected by ECG (74%), ECG Holter (5%), and CIEDs (21%) as demonstrated in *Figure 2*. Baseline characteristics are shown in *Table 1*. Patients in the AF group were older and had more cardiovascular risk factors (hypertension, dyslipidaemia, diabetes, and being former smokers) compared to patients without AF.

The baseline echocardiography of the patients who later developed AF showed greater interventricular septal thickness and LV filling pressure than the group that remained in sinus rhythm. Patients with AF had larger LA diameter, larger LA volume index, more impaired LA reservoir strain, and longer PA-TDI duration. As shown in *Figure 3*, patients who developed new onset AF had more frequently a dilated LA, impaired LA function, and prolonged TACT when compared with patients who remained in sinus rhythm (*Table 2*).

The Kaplan–Meier analyses computed for the development of new-onset AF demonstrated that patients with an LA diameter ≥45 mm and an LA volume index ≥34 mL/m^2 had significantly more cumulative rates of AF as compared to their counterparts (*Figure 4*). Similarly, patients with more impaired LA reservoir strain (<21.3%) and patients with more prolonged PA-TDI duration (≥115 ms) had significantly more cumulative rates of AF as compared to patients with preserved LA reservoir strain or shorter PA-TDI (*Figure 4*). On proportional hazard Cox regression analyses, age, *E*/*e*′, presence of systolic anterior motion of the mitral valve, moderate to severe MR, significant obstruction

Table 1 Clinical characteristics of study population

	Total population (*n* = 208)	AF (*n* = 42)	No AF (*n* = 166)	*P* value
Age (years)	53.1 ± 13.7	58.5 ± 9.7	51.8 ± 14.3	0.005
Male, *n* (%)	132 (63.5)	25 (59.5)	107 (64.5)	0.593
Positive genotype, *n* (%)	83 (39.9)	9 (21.4)	74 (44.6)	0.080
Family history of HCM, *n* (%)	107 (51.4)	16 (38.1)	91 (54.8)	0.072
Body mass index (kg/m^2)	27.1 ± 4.3	27.2 ± 4.4	27.1 ± 4.2	0.861
Systolic blood pressure (mmHg)	139.7 ± 19.7	139.3 ± 21.4	139.8 ± 19.2	0.899
Diastolic blood pressure (mmHg)	80.8 ± 10.3	80.7 ± 9.1	80.6 ± 10.6	0.972
Hypertension, *n* (%)	90 (43.3)	21 (50)	69 (41.6)	0.387
Dyslipidaemia, *n* (%)	59 (28.4)	17 (40.5)	42 (25.3)	0.057
Diabetes, *n* (%)	16 (7.7)	6 (14.3)	10 (6.0)	0.102
Current smokers, *n* (%)	59 (28.4)	12 (28.6)	47 (28.3)	1.000
Former smokers, *n* (%)	16 (7.7)	5 (11.6)	11 (6.6)	0.326

Values are expressed as mean ± SD or *n* (%).
AF, atrial fibrillation; HCM, hypertrophic cardiomyopathy.

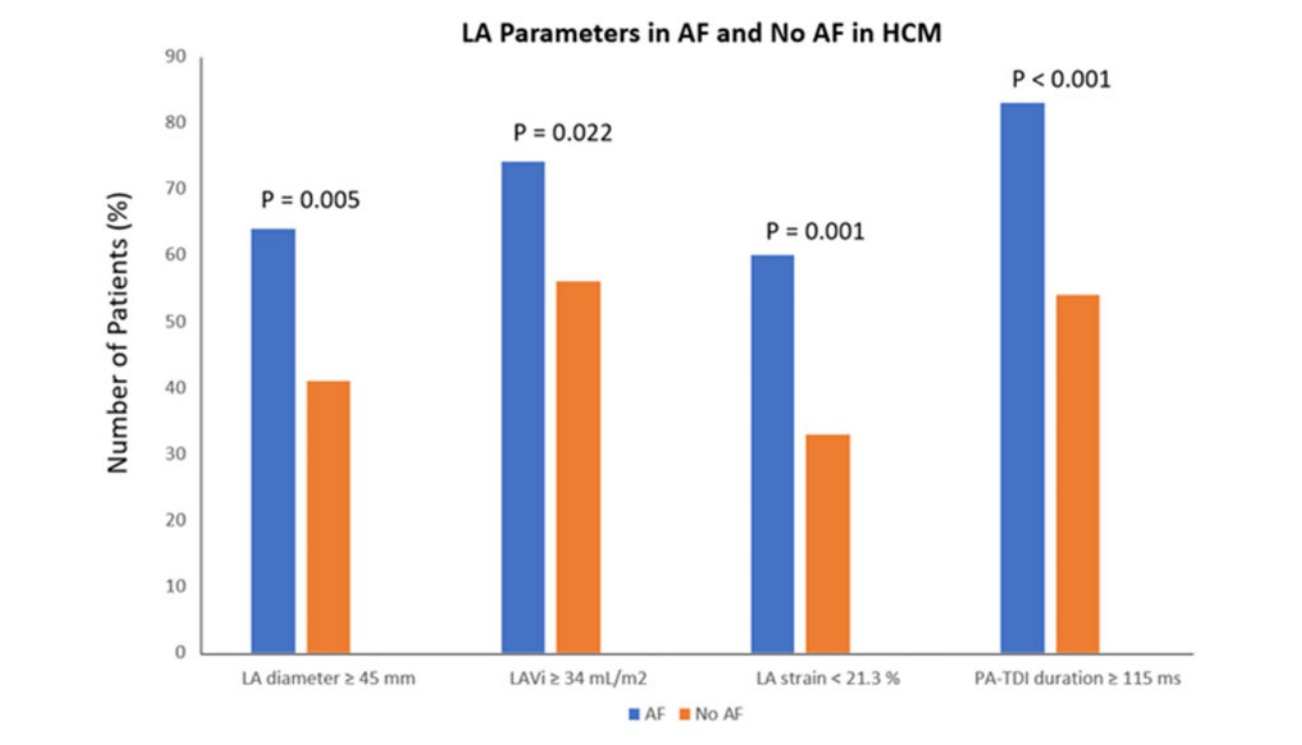

Figure 3 Distribution of LA anatomical and functional abnormalities among patients with hypertrophic cardiomyopathy who developed atrial fibrillation and who remained in sinus rhythm. AF, atrial fibrillation; HCM, hypertrophic cardiomyopathy; LA, left atrium; PA-TDI, peak *A′* on tissue Doppler imaging of the atria.

Table 2 **Echocardiographic characteristics of the population**

	Total population (*n* = 208)	AF (*n* = 42)	No AF (*n* = 166)	*P* value
IVSd (mm)	20.50 (16.0–3.0)	20.50 (16.0–3.0)	17.0 (15.0–21.0)	0.011
Maximum LVH (mm)	20.0 (17.0–23.0)	22.5 (18.0- 7.0)	19.0 (17.0–23.0)	0.011
LVEDD (mm)	43.3 ± 6.7	42.9 ± 7.0	43.4 ± 6.6	0.643
LVEF (%)	66.4 ± 8.2	66.5 ± 8.2	66.4 ± 8.2	0.928
E/A	1.0 (0.8–1.3)	0.9 (0.7–1.3)	1.0 (0.8–1.4)	0.205
E/e'	10.0 (7.4–14.9)	13.0 (8.9–17.2)	9.7 (6.9–13.9)	0.002
SAM of MV, *n* (%)	90 (43.3)	29 (69)	61 (36.7)	0.000
Moderate to severe MR, *n* (%)	43 (20.7)	16 (38.1)	27 (16.3)	0.005
LVOT gradient >30 mmHg, *n* (%)	39 (18.8)	16 (38.1)	23 (13.9)	0.001
LA diameter (mm)	44.7 ± 6.5	47.7 ± 6.6	43.9 ± 6.3	0.001
LAVI (mL/m^2)	36.0 (29.0–45.0)	44.7 (33.5–54.4)	35.0 (28.0–44.0)	0.000
LA reservoir strain (%)	25.8 ± 11.8	20.1 ± 8.2	27.1 ± 12.1	0.001
PA-TDI duration (ms)	115.2 ± 29.8	133.7 ± 23.0	110.5 ± 30.0	0.000

Values are expressed as mean ± SD, median (interquartile range), or *n* (%).
AF, atrial fibrillation; GLS, global longitudinal strain; IVSd, interventricular septum end diastole; LA, left atrium; LAVi, left atrial volume index; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVOT, left ventricular output tract; MR, mitral regurgitation; MV, mitral valve; PA TDI, peak *A′* on tissue Doppler imaging of the atria; SAM, systolic anterior motion.

of the LV outflow tract, and LA parameters were significantly associated to the occurrence of new onset AF (*Table 3*). Due to the limited number of patients with new-onset AF at follow-up, the number of variables included in the multivariate analysis was limited to a maximum of 4. On multivariate analysis, larger LA diameter and volume, impaired LA reservoir strain and prolonged PA-TDI duration were all independently associated with the occurrence of new onset AF (*Table 4*).

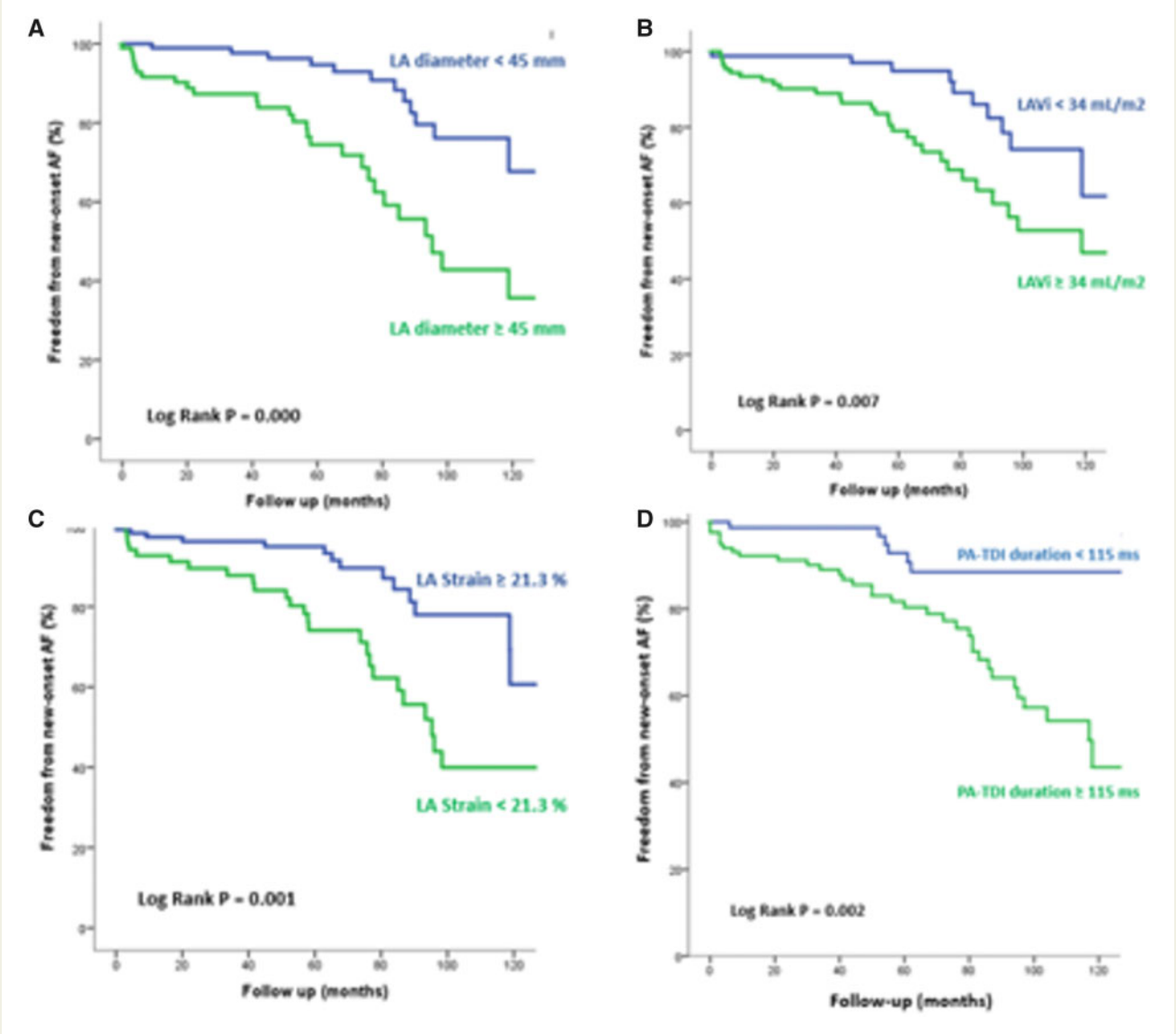

Figure 4 Kaplan–Meier curves for freedom from new-onset AF in the study population according to LA diameter (A), left atrial volume (B), left atrial reservoir strain (C), and PA-TDI duration (D). AF, atrial fibrillation; LA, left atrium; LAVi, left atrial volume index; PA-TDI, peak *A′* on tissue Doppler imaging of the atria.

Discussion

The novelty of this study is the demonstration that PA-TDI duration is independently associated with the occurrence of new-onset AF in HCM patients besides previously known factors such as dilation of the LA and impaired LA reservoir strain.

Incidence of AF in HCM and echocardiographic risk factors

AF is a common arrhythmic event complicating HCM with increased morbidity and mortality.[2,22] The prevalence of AF in HCM was reported ranged between 17% and 28% in different study populations.[1,2,4,21,23] Our data shows 20% of patients with HCM developed new-onset AF, in line with previous studies.

Earlier studies have reported the association of echocardiographic parameters reflecting LA remodelling with risk of AF in HCM patients.[12,24] Debonnaire *et al.*[12] showed that LA diameter, volume, and strain were associated with new-onset AF in this group of patients. The association between large LA volume and paroxysmal AF was demonstrated by Tani *et al.*[24] in a retrospective study of 187 patients with HCM. This association is confirmed by the findings in the current study. The novelty of the present study compared to those studies is that we also identified a significant correlation between prolonged PA-TDI duration and new onset AF in this population.

Table 3 Univariate Cox regression analysis

	Univariable		
	Hazard ratio	95% confidence interval	*P* value
Age (years)	1.05	1.02–1.08	0.000
Male gender	0.94	0.50–1.77	0.839
Systolic blood pressure (mmHg)	1.00	0.98–1.01	0.560
Diastolic blood pressure (mmHg)	1.00	0.96–1.03	0.828
Hypertension	0.91	0.49–1.71	0.774
Dyslipidaemia	1.43	0.76–2.71	0.268
Diabetes	1.26	0.49–3.24	0.625
Current smoker	1.32	0.67–2.61	0.424
Body mass index (kg/m^2)	0.99	0.91–1.07	0.785
Positive genotype	1.21	1.01–1.45	0.045
Positive family history of HCM	0.63	0.33–1.20	0.158
LV IVSd (mm)	1.04	0.99–1.09	0.101
Maximum LV wall thickness (mm)	1.03	1.00–1.07	0.161
LVEDD (mm)	1.00	0.96–1.05	0.980
LVEF (%)	1.00	0.96–1.04	0.841
E/*A*	0.83	0.45–1.55	0.554
E/e'	1.04	1.01–1.06	0.005
SAM	4.23	2.14–8.36	0.000
Moderate to severe MR	2.71	1.42–5.15	0.002
LVOT gradient >30 mmHg	2.92	1.54–5.55	0.001
LA diameter (mm)	1.11	1.05–1.16	0.000
LAVI (mL/m^2)	1.03	1.02–1.05	0.000
LA reservoir strain (%)	0.94	0.91–0.97	0.000
PA-TDI duration (ms)	1.04	1.02–1.05	0.000

GLS, global longitudinal strain; HCM, hypertrophic cardiomyopathy; IVSd, interventricular septum end diastole; LA, left atrium; LAVi, left atrial volume index; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVOT, left ventricular output tract; MR, mitral regurgitation; MV, mitral valve; PA TDI, peak *A*′ on tissue Doppler imaging of the atria; R, reservoir; SAM, systolic anterior motion.

Table 4 Multivariable cox regression analysis

	Multivariable LA diameter		Multivariable LAVi		Multivariable LA strain		Multivariable PA-TDI	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (year)	1.05 (1.02–1.08)	0.000	1.05 (1.02–1.09)	0.000	1.04 (1.01–1.07)	0.020	1.03 (1.00–1.07)	0.032
E/e'	1.01 (0.98–1.03)	0.734	1.01 (0.97–1.04)	0.765	1.01 (0.97–1.05)	0.782	1.02 (0.99–1.05)	0.226
Moderate to severe MR	2.88 (1.45–5.71)	0.002	2.53 (1.24–5.15)	0.010	2.53 (1.24–5.15)	0.002	2.60 (1.30–5.20)	0.007
LA diameter (mm)	1.09 (1.04–1.14)	0.000						
LAVi (mL/m^2)			1.03 (1.01–1.05)	0.001				
LA reservoir strain (%)					0.94 (0.91–0.98)	0.003		
PA-TDI duration (ms)							1.03 (1.01–1.05)	<0.001

LA, left atrium; LAVi, left atrial volume index; MR, mitral regurgitation; MV, mitral valve; PA TDI, peak *A*′ on tissue Doppler imaging of the atria.

Role of PA-TDI in identifying HCM patients at risk of AF

LA remodelling with pathophysiological changes in atrial structure and function (electrical and contractile) is central to AF vulnerability.[12,25] Combined volume and pressure load is responsible for the atrial stretch in HCM patients; however, some of these patients may still have atrial size within the normal range. Changes in the atrium can also disrupt electrical interconnections between muscle bundles resulting in reduced atrial refractory period, shortening of re-entrant wavelength, and lower local conduction velocity, thus promoting the

development of AF.[10,25] It is established that functional remodelling may take place prior to the occurrence of structural changes, and atrial remodelling usually precedes AF.[12] Non-invasive imaging is the corner stone to assess this process, with echocardiography being the most practical option.

LA enlargement reflects the structural remodelling of the atrium and it is more accurately reflected by LA volume than the linear dimension,[12,19] whereas LA strain measurements have been utilized to evaluate atrial function.[19] The TACT represents the time difference between the onset of electrical and mechanical activation.[26] It is prolonged when there is an enlarged atrium or decreased conduction velocity. PA-TDI duration is a reliable marker to estimate TACT that is measured from the initiation of to the last atrial depolarization, represented by the onset of P wave on ECG and *A′* wave at the LA lateral wall on TDI, respectively.[15] Erdem *et al.*[27] compared TACT measured by PA-TDI duration with electrophysiological study in 80 healthy subjects and demonstrated that there was good agreement between the two methods.

The current data support that this new echocardiographic parameter could also be utilised as an independent predictor of future AF in HCM patients.

Pathophysiology of AF in HCM patients

Establishing the causal mechanism of AF in HCM is challenging. The thickened myocardium with impaired LV relaxation gives rise to elevated filling pressures which may lead to atrial stretch. Furthermore, in patients with obstructive HCM, mitral regurgitation secondary to systolic anterior motion of the mitral leaflets can occur, contributing to the increased LA pressure and volume overload, as well as to the LA remodelling process that facilitates the initiation of AF.[5,28,29] The sarcomere mutations related to HCM cause abnormal sarcomere function leading to increased energy consumption across the cardiac cycle.[30] In addition, it has been demonstrated that an increased sensitivity of the myofilaments to calcium and changes in calcium/calmoduline-dependent protein kinase may lead to prolonged action potentials, cellular arrhythmias, prolonged calcium currents, and increased diastolic intracellular calcium and sodium.[31] Although these changes have been demonstrated in the LV myocardium, it could be hypothesized that similar abnormalities may occur in the LA. Therefore, the presence of an atrial cardiomyopathy could be the underlying mechanism explaining the new-onset AF in HCM rather than the LA remodelling alone. Indeed, as shown in the present study, the LA dimensions of patients with HCM and AF are larger than the patients without, still 25–40% of patients with AF may have normal values of LA diameter and volumes. In contrast, the proportion of patients with prolonged PA-TDI is almost 90% among patients with AF suggesting that this parameter may be an earlier reflector of the pathophysiological consequences of the sarcomere mutation in HCM before the anatomical (LA dimensions) and functional (LA strain) consequences of such mutation occur.

Study limitations

This is a retrospective study with a relatively small number of patients. Patients referred to our tertiary centre could have had undetected silent AF resulting in selection bias. Changes in LA dimensions, function and TACT were not recorded over time. These changes may have an influence on the occurrence of new onset AF. However, to further investigate this influence, prospective studies are needed consisting of sequential echocardiograms performed at pre-specified time points.

Conclusion

This study demonstrates that PA-TDI duration is a valuable non-invasive echocardiographic parameter to predict the development of new-onset AF in HCM. PA-TDI may be useful in the selection of HCM patients who require prolonged rhythm monitoring for the detection of incident AF.

Conflict of interest: The Department of Cardiology, Heart Lung Center, Leiden University Medical Centre received research grants from Abbott Vascular, Bioventrix, Biotronik, Medtronic, Boston Scientific Corporation, GE Healthcare, and Edwards Lifesciences. V.D. received speaker fees from Abbott Vascular, Edwards Lifesciences, Medtronic, and GE Healthcare. J.J.B. and N.A.M. received speaker fees from Abbott Vascular. The remaining authors have nothing to disclose.

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