Archives of Cardiovascular Disease (2020) xxx, xxx—xxx

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

CLINICAL RESEARCH

Left atrial dysfunction as marker of poor outcome in patients with hypertrophic cardiomyopathy

Valeur pronostique de la dysfonction atriale gauche dans la cardiomyopathie hypertrophique

Benjamin Essayagh[a,g], Noémie Resseguier[b], Nicolas Michel[a], Anne-Claire Casalta[a], Sébastien Renard[a], Valeria Donghi[a], Andreina Carbone[a], Chiara Piazzai[a], Pierre Ambrosi[a], Franck Levy[c], Hélène Martel[a], Hilla Gérard[a], Jean-François Avierinos[a], Karine N'Guyen[d,e], Gilbert Habib[a,f,*]

[a] *Cardiology Department, La Timone Hospital, AP—HM, 13005 Marseille, France*
[b] *CEReSS, Aix-Marseille University, 13005 Marseille, France*
[c] *Cardiothoracic centre of Monaco, 98000 Monaco, Monaco*
[d] *Département de génétique médicale, hôpital d'enfants de la Timone, AP—HM, 13005 Marseille, France*
[e] *Faculté de médecine, Marseille Medical Genetics, Aix-Marseille University, INSERM, 13005 Marseille, France*
[f] *IHU-Méditerranée Infection, Aix-Marseille University, IRD, AP—HM, MEPHI, 13005 Marseille, France*
[g] *Cardiology Department, Simone Veil Hospital, 06400 Cannes, France*

Received 1st March 2020; received in revised form 18 May 2020; accepted 27 June 2020

Abbreviations: BNP, B-type natriuretic peptide; CI, confidence interval; HCM, hypertrophic cardiomyopathy; HR, hazard ratio; ICD, implanted cardioverter defibrillator; LA, left atrial; LASR, left atrial strain rate; LASRa, left atrial peak strain rate (A-wave); LASRe, left atrial peak strain rate (E-wave); LASRs, left atrial peak strain rate (S-wave); LAVI, left atrial volume index; LV, left ventricle/ventricular; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; OR, odds ratio; PALS, peak atrial longitudinal strain; PACS, peak atrial contraction strain; SCD, sudden cardiac death.

* Corresponding author at: Service de cardiologie, 10e étage, CHU la Timone Adulte, 264, rue Saint-Pierre, 13005 Marseille, France.
E-mail address: gilbert.habib3@gmail.com (G. Habib).

https://doi.org/10.1016/j.acvd.2020.06.004

Please cite this article in press as: Essayagh B, et al. Left atrial dysfunction as marker of poor outcome in patients with hypertrophic cardiomyopathy. Arch Cardiovasc Dis (2020), https://doi.org/10.1016/j.acvd.2020.06.004

KEYWORDS
Hypertrophic cardiomyopathy;
Left atrial strain;
Atrial fibrillation;
Outcome;
Sudden cardiac death

Summary
Background. — The incremental prognostic value of left atrial (LA) dysfunction, emerging in various clinical contexts, remains poorly explored in hypertrophic cardiomyopathy (HCM).
Objective. — To assess LA strain correlation with outcome in HCM.
Methods. — A cohort of all 307 consecutive patients presenting with HCM between 2007 and 2017 (54 ± 17 years; 34% women), with comprehensive echocardiography at diagnosis and LA peak longitudinal strain (PALS) and LA peak contraction strain (PACS) measurement, was enrolled and occurrence of HCM related cardiac events analysed.
Results. — Clinically, atrial fibrillation (AF) was present in 13%, New York Heart Association functional class II—III in 54%, and B-type natriuretic peptide (BNP) concentration was 199 ± 278 pg/mL. By echocardiography, left ventricular (LV) ejection fraction (EF) was 67 ± 10%, LV thickness 21 ± 5 mm and European Society of Cardiology HCM risk score 3 ± 3%, with 109 patients (36%) presenting obstructive HCM (LV outflow gradient 21 ± 32 mmHg). LA diameter was 41 ± 8 mm [with 109 (36%) presenting LA diameter ≥ 40 mm], LA volume index 50 ± 26 mL/m^2, PALS 24 ± 13%, PACS 11 ± 7% and LA peak systolic strain rate (LASRs) 1.7 ± 0.6 s^{-1}. In addition to AF, age, BNP, LVEF and LV thickness were all independent determinants of lower PALS, with odd ratios almost unchanged after adjustment (all $P \leq 0.0004$). At a mean follow-up of 21 (range 18—23) months, patients with adverse cardiac events ($n = 65$) presented with more impaired LA function (all $P \leq 0.0005$), with a significant association between impaired PALS and worse outcome, hazard ratio 0.94 [95% confidence interval (CI) 0.92—0.97, $P < 0.0001$]. After comprehensive adjustment, PALS remained strongly associated with worse outcome, adjusted hazard ratio 0.86 (95% CI 0.79—0.94; $P = 0.0008$).
Conclusions. — The present study, by gathering a unique HCM cohort, suggests a strong link between LA dysfunction and poor outcome, to be further investigated.

MOTS CLÉS
Cardiomyopathie hypertrophique ;
Strain de l'oreillette gauche ;
Fibrillation atriale ;
Pronostic ;
Mort subite

Résumé
Contexte. — La dysfonction de l'oreillette gauche (OG), déjà reconnue comme marqueur de maladie avancée chez les patients atteints de cardiomyopathie hypertrophique (CMH), pourrait être un marqueur pronostic, mais reste mal définie.
Objectif. — Évaluer la corrélation entre strain OG et pronostic dans la CMH.
Méthodes. — Tous les 307 patients consécutivement diagnostiqués porteurs de CMH entre 2007—2017 (âge 54 ± 17 ans, 34% de femmes), avec échocardiographie complète permettant l'étude de la fonction OG incluant pic atrial longitudinal (PALS) et pic atrial de contraction (PACS), ont été inclus et la survenue d'événements cardiaques indésirables analysée.
Résultats. — Cliniquement, 13% présentaient une FA, 54% une dyspnée NYHA II—III et le BNP était de 199 ± 278 pg/mL. Echocardiographiquement, la fraction d'éjection ventriculaire gauche (FE-VG) était de 67 ± 10%, l'épaisseur maximale VG 21 ± 5 mm et le score de risque ESC 3 ± 3%, avec 109 patients (36%) présentant une CMH obstructive de gradient d'obstruction 21 ± 32 mmHg. Le diamètre OG était de 41 ± 8 mm (avec 109 [36%] présentant un diamètre OG ≥ 40 mm), le volume OG indexé 50 ± 26 mL/m^2, PALS 24 ± 13%, PACS 11 ± 7% et LASRs 1.7 ± 0.6 s^{-1}. En plus de la présence d'une FA, l'âge, le BNP, la FE-VG et l'épaisseur maximale VG était tous des déterminants indépendants d'altération du PALS, avec rapport de risques quasiment inchangés après ajustement. Au décours du suivi de 21 (étendue 18—23) mois, les patients présentant des événements cardiaques indésirables ($n = 65$) avaient une fonction OG altérée (tous $p \leq 0.0005$), et l'altération du PALS était significativement associé à la survenue d'événements, rapport de risque 0.94 (IC95% 0.92—0.97) ($p < 0.0001$). Après ajustement, le PALS restait fortement associé à plus mauvais pronostic: rapport de risque ajusté 0.86 (IC95% 0.79—0.94; $p = 0.0008$).
Conclusions. — La présente étude, en rassemblant une cohorte importante et unique de CMH, suggère un lien fort entre dysfonction OG et CMH de plus mauvais pronostic.

Please cite this article in press as: Essayagh B, et al. Left atrial dysfunction as marker of poor outcome in patients with hypertrophic cardiomyopathy. Arch Cardiovasc Dis (2020), https://doi.org/10.1016/j.acvd.2020.06.004

Background

Hypertrophic cardiomyopathy (HCM) is a frequent genetically transmitted cardiac disease of heterogeneous outcome, observed in 1 in 500 people in the general population [1]. Although HCM is relatively benign in most individuals, it can be associated with an increased risk of heart failure, atrial fibrillation (AF) and sudden cardiac death (SCD), HCM being known as the second most frequent cause of SCD in the USA and Europe [2–4].

Although risk scores [5] to predict SCD have been proposed, with left atrial (LA) diameter and volume holding a key prognostic role [6], they appear to be ineffective in an important subset of patients [7]. In this context, LA strain has been shown to be promising in assessing LA dysfunction and remodelling, and in predicting HCM outcome, with the potential to solve this troublesome situation. However, these pilot proofs of concept were limited by cohorts of small magnitude [8,9] or the inclusion of patients in sinus rhythm only [10]. Thus, it is uncertain whether LA strain measurement assessed in a large cohort of patients with HCM, irrespective of rhythm, may provide similar predictive information.

To fill this knowledge gap, we aimed at gathering a large cohort of patients with HCM and LA strain measurement, irrespective of rhythm at baseline, to assess its additional value in predicting HCM outcome.

Methods

Eligibility criteria were screened in all consecutive patients with:

- a diagnosis at la Timone Hospital (Marseille, France) of HCM, defined as hypertrophied left ventricle (LV) (wall thickness $\geq$ 15 mm) by two-dimensional echography and/or cardiac magnetic resonance imaging (MRI), between 2007 and 2017;
- absence of other cardiac or systemic disease able to produce a similar degree of hypertrophy;
- aged $\geq$ 18 years;
- comprehensive clinical evaluation at diagnosis with symptoms, clinical history, comorbidities and rhythm status record.

Patients with known metabolic disease or syndromic causes were excluded. As this was a low-risk study, the need for written consent was waived by la Timone Institutional Review Board, which gave its approval for the study.

Echocardiographic evaluation

All patients underwent comprehensive two-dimensional echocardiography using dedicated software (two-dimensional strain; EchoPAC™; GE Healthcare, Chicago, IL, USA) to assess left ventricular (LV) and LA myocardial deformation. All measurements were guided by European Society of Cardiology recommendations [11–14]. LA strain in apical four- and two-chamber views was measured according to a previous method demonstrating feasibility and reproducibility [15,16], Peak atrial longitudinal strain (PALS), resulting from maximal LA stretching, and peak atrial contraction strain (PACS), resulting from maximal LA contraction, were expressed as percentages. Time to peak longitudinal strain and time to peak contraction strain were time between the start of QRS and PALS or PACS, respectively, expressed in ms (Fig. 1A). LA peak strain rate (S-wave; LASRs) was determined as a surrogate of LA reservoir function, and LA peak strain rate after contraction (E-wave; LASRe) and (A-wave; LASRa) as a surrogate of LA contractile function [17] (Fig. 1B). Each measurement was reported as an average of both the four- and two-chamber views.

Cardiovascular MRI evaluation

MRI studies performed at 3 ± 15 months around Doppler echocardiography used a 1.5-Tesla magnetic resonance scanner (Symphony™ TIM™, Siemens, Erlangen, Germany). All examinations were transferred to a dedicated workstation, and flow was quantified using Argus™ Flow software (Siemens, Erlangen, Germany). Assessment of cardiac function and measurements were guided by recommendations [18]. Gadolinium administration and delayed enhancement were used according to standard protocol. The final decision to process gadolinium injection was left to the radiologist in charge of the patient.

Clinical evaluation

Rhythm status was determined by electrocardiogram reports and clinical notes. Patients were classified as having AF if they had overt AF by electrocardiogram or, if in sinus rhythm on electrocardiogram, if their clinical notes demonstrated history of proven AF. SCD, aborted SCD, history of SCD, non-sustained ventricular tachycardia and unexplained syncope were defined as recommended [5]. New-onset ventricular tachycardia was defined as at least three consecutive ventricular beats at a rate of $\geq$ 120 beats/min and < 30 seconds in duration on Holter monitoring (minimum duration 24 hours) at or before evaluation, regardless of symptoms [5]. Accordingly, the European Society of Cardiology HCM risk score assessing the 5-year risk of SCD was calculated for each patient.

Follow-up

The composite endpoint was occurrence of adverse cardiac events, encompassing SCD, appropriate defibrillator therapy, hospitalisation for heart failure, new onset of ventricular tachycardia, need for implanted cardioverter defibrillator (ICD) or pacemaker implantation, AF ablation, alcohol septal ablation, myomectomy and heart transplantation. Occurrence and dates of death were retrieved from the patients' medical records and by telephone calls to all patients and family members. As per routine clinical practice, therapeutic management was decided by the patients' personal physicians.

Statistical analysis

Categorical variables are presented as numbers (percentages) and quantitative variables as means ± standard deviations. An overall description of the study population,

Please cite this article in press as: Essayagh B, et al. Left atrial dysfunction as marker of poor outcome in patients with hypertrophic cardiomyopathy. Arch Cardiovasc Dis (2020), https://doi.org/10.1016/j.acvd.2020.06.004

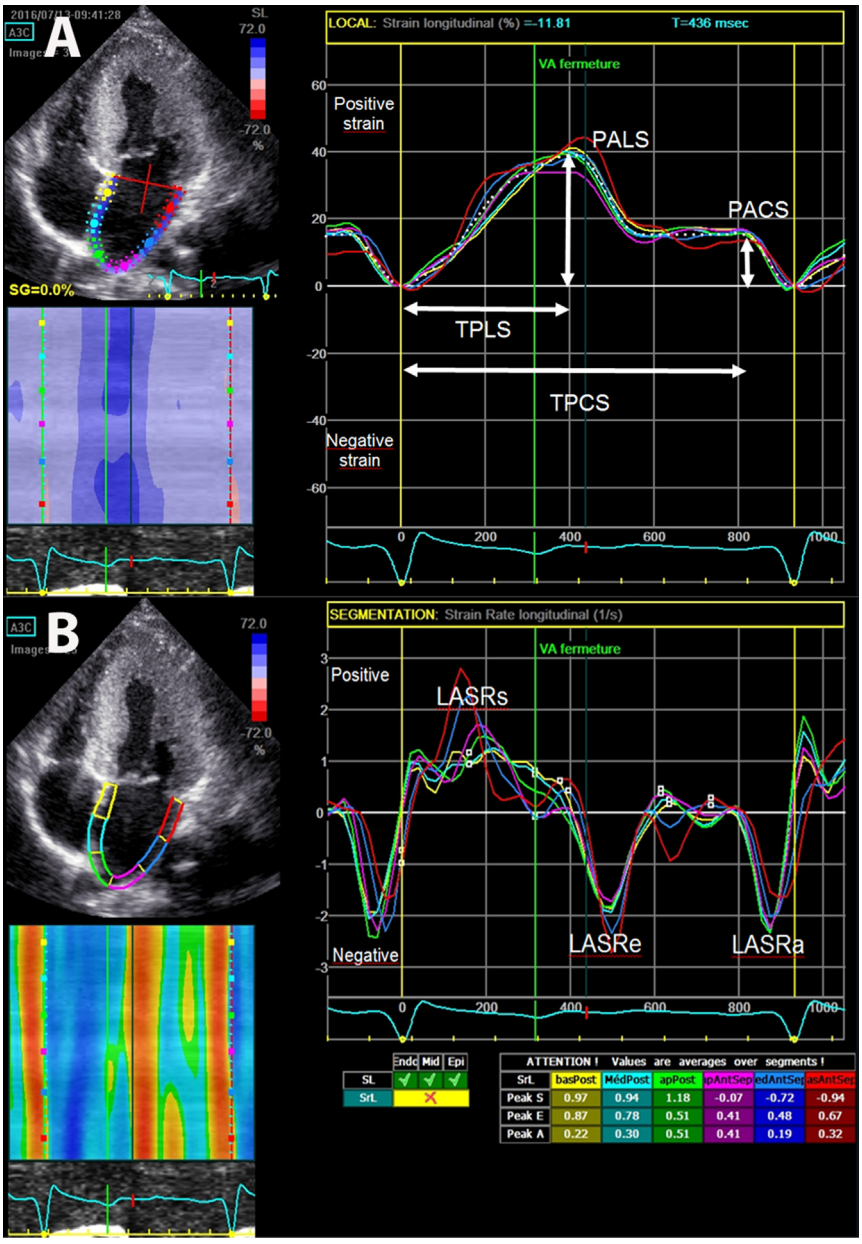

Figure 1. Left atrial function assessed by two-dimensional speckle tracking in hypertrophic cardiomyopathy. A. Four-chamber view showing measurement (double white arrow) of peak atrial longitudinal strain (PALS), time to peak longitudinal strain (TPLS), peak atrial contraction strain (PACS) and time to peak contraction strain (TPCS). PALS results from maximal stretching of the left atrium during the reservoir phase and PACS results from contraction of the left atrium during the contraction phase. PALS and PACS are expressed in %; TPLS and TPCS in ms. B. Four-chamber view showing left atrial strain waves. The positive left atrial peak strain rate S-wave (LASRs) determines LA reservoir function, and the negative left atrial peak strain rate E-wave (LASRe) and A-wave (LASRa) determine LA contractile function, all expressed in s^{-1}.

including imaging measurements, was performed. Quantitative data were compared using Student's *t*-test when appropriate (or the non-parametric Mann—Whitney U test otherwise), and categorical data were compared using the χ^2 test (or the non-parametric Fisher's exact test, accordingly). Characteristics associated with the main independent variable of interest defined by PALS as a continuous variable or categories (< 17%, 17% to < 30% and ≥ 30%, according to cohort tertiles), were assessed by logistic regression using patient and HCM characteristics: age, AF, B-type natriuretic peptide (BNP), LVEF and LV thickness. Odds ratios (ORs) of impaired PALS (versus preserved PALS, stratified by cohort average) were reported for each independent determinant, unadjusted and in multivariable analysis. To avoid overfitting in the model predicting impaired PALS, a limited number of potential determinants were allowed. Overall fitting of models was summarised through the C-statistic. Spline curves were elaborated to show the relationship between global PALS and BNP and the occurrence of cardiovascular events in the whole study population. To assess the impact

Please cite this article in press as: Essayagh B, et al. Left atrial dysfunction as marker of poor outcome in patients with hypertrophic cardiomyopathy. Arch Cardiovasc Dis (2020), https://doi.org/10.1016/j.acvd.2020.06.004

of potential prognostic factors on the time-to-event occurrence, time-to-event analysis was performed. Univariate Cox regression models were established to estimate hazard ratios (HRs) with their 95% confidence intervals (CIs). Covariates with a P value < 0.05 according to univariate analysis were entered into a multivariable Cox regression model to identify potential independent prognostic factors. No statistical selection was performed at this step. Adjusted HRs with their 95% CIs were estimated. Bland–Altman analysis was performed to assess intraobserver agreement regarding measures of LA strain, and intraclass correlation coefficients were calculated. All tests were two-sided and a P value < 0.05 was considered significant.

Results

Baseline characteristics

Baseline characteristics of the overall cohort, comprising 307 patients (105 women; mean age 54 ± 17 years), are presented in Table 1. Clinically, AF was present in 13%, NYHA functional class II–III in 54%, and the BNP concentration was 199 ± 278 pg/mL. By echocardiography, LVEF was 67 ± 10%, LV thickness was 21 ± 5 mm and the European Society of Cardiology HCM risk score was 3 ± 3%, with 109 patients (36%) presenting obstructive HCM, with LV outflow gradient 21 ± 32 mmHg. Overall, 7% presented with at least moderate mitral regurgitation. LA diameter was 41 ± 8 mm [with 109 (36%) presenting LA diameter ≥ 40 mm], LA volume index was 50 ± 26 mL/m^2, PALS was 24 ± 13%, PACS was 11 ± 7% and LASRs was 1.7 ± 0.6 s^{-1}. Table A.1 shows baseline characteristics compared by PALS subsets (PALS ≥ 30%, PALS 17% to < 30% and PALS < 17%). Differences reaching a clinically relevant magnitude were noted in the patients in the lowest PALS group, with more frequent dyspnoea, non-sustained ventricular tachycardia and AF. Associated with higher BNP was a trend for older age with impaired PALS. With lower PALS, LVEF was lower, but with similar LV diameters between groups. Whereas differences in LV outflow gradient were minimal, LV thickness, LA volume index and LV filling pressures were higher with lower PALS. LV global longitudinal strain was more impaired with lower PALS, and moderate-to-severe mitral regurgitation was more frequent with more frequent fibrosis by MRI assessment. Hence, lower PALS was not isolated, but compounded many differences in baseline characteristics.

Patients without adverse cardiac events (n = 242) were similar to patients with adverse cardiac events (n = 65) regarding age, sex, mutated gene identification, hypertension and AF (P ≥ 0.09; Table 1). However, patients with adverse cardiac events more often had a family history of SCD, non-sustained ventricular tachycardia, dyspnoea and unexplained syncope (P < 0.0001). Also, these patients presented with significantly greater LV hypertrophy (25 ± 5 vs 20 ± 5 mm), higher ESC HCM risk scores (5 ± 4 vs. 2 ± 2%), impaired LV global longitudinal strain (−13 ± 3 vs. −16 ± 4), lower PALS (17 ± 11 vs. 27 ± 13%), lower PACS (7 ± 5 vs. 12 ± 7%) and more frequent MRI late gadolinium enhancement (93 vs. 76%); all P < 0.01.

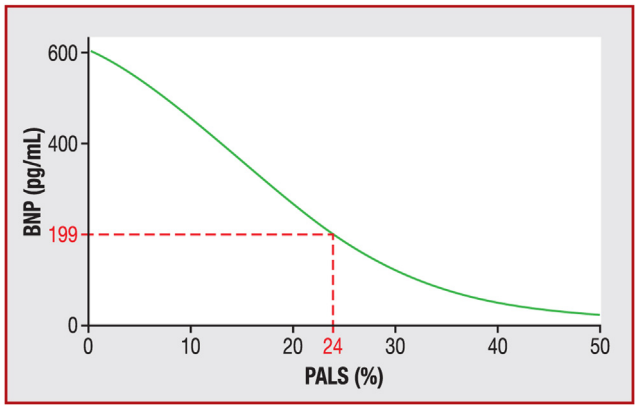

Figure 2. Peak atrial longitudinal strain (PALS) distribution according to B-type natriuretic peptide (BNP) increment by logistic regression. Note the linear correlation between impaired PALS and higher BNP; PALS < 24% is associated with BNP > 199 pg/mL.

Characteristics associated with atrial dysfunction

Clinical/echocardiographic characteristics associated with impaired PALS are presented in Table 2. Univariate analysis showed AF, but also BNP and LV thickness, emerging as the strongest predictors of atrial dysfunction, all remaining independently associated with impaired PALS: adjusted ORs versus preserved PALS were 4.71 (95% CI 1.60–13.85) for AF, 1.27 (95% CI 1.06–1.53) for BNP per 100 pg/mL increment and 1.14 (95% CI 1.05–1.24) for LV thickness (all P ≤ 0.004; Table 2). Other independent predictors of lower PALS were age and LVEF, whereas sex, index LV end diastolic diameter, severe mitral regurgitation and fibrosis were not (model C-statistic 0.84). Distribution of PALS, according to BNP concentration assessed by logistic regression, showed linear correlation between impaired PALS and higher BNP, with PALS < 24% associated with > 199 pg/mL BNP (Fig. 2). BNP and LVEF did not appear to be independent determinants of LA enlargement: adjusted ORs versus preserved LA diameter were 1.06 (95% CI 0.94–1.19) for BNP per 100 pg/mL increment and 0.98 (95% CI 0.95–1.01) for LVEF (all P ≥ 0.1), reinforcing the additional value of LA function over LA diameter in predicting HCM outcome (Table A.2).

Outcome after diagnosis

During a mean follow-up of 21 (range 18–23) months, six patients (2%) died or underwent appropriate ICD therapy, 14 (5%) underwent alcohol septal ablation, four (1%) septal myomectomy, one (0.3%) new ventricular tachycardia, five (2%) AF ablation, 25 (8%) primary prevention ICD implantation, two (0.7%) pacemaker implantation, five (2%) hospitalisation for heart failure and three (1%) heart transplantation. During the overall study period, a total of 57 patients (19%) were treated with an ICD (32 before their enrolment).

Adverse cardiovascular events

Univariate Cox regression found impaired LA reservoir function (by PALS and LASRs) and impaired LA contractile

Please cite this article in press as: Essayagh B, et al. Left atrial dysfunction as marker of poor outcome in patients with hypertrophic cardiomyopathy. Arch Cardiovasc Dis (2020), https://doi.org/10.1016/j.acvd.2020.06.004

Table 1 Demographic and clinical features, and echocardiographic and magnetic resonance imaging variables in 307 patients with hypertrophic cardiomyopathy stratified by outcome.

	Overall cohort ($n = 307$)	Adverse cardiac events ($n = 65$)	No adverse cardiac events ($n = 242$)	*P*
Baseline characteristics				
Age (years)	54 ± 17	53 ± 16	54 ± 17	0.5
Female sex	105 (34)	27 (42)	78 (32)	0.2
Family history of SCD	19 (6)	10 (15)	9 (4)	0.00
NYHA functional class II–III	142 (54)	40 (28)	102 (49)	0.00
NSVT	35 (11)	19 (29)	16 (7)	0.00
Unexplained syncope	32 (10)	16 (25)	16 (7)	0.00
AF	36 (13)	11 (20)	25 (11)	0.09
HCM-associated gene identified	63 (21)	13 (20)	50 (21)	0.50
BNP (pg/mL)	199 ± 278	406 ± 436	147 ± 190	0.00
Hypertension	72 (25)	12 (21)	60 (26)	0.5
Diabetes	21 (7)	3 (5)	18 (8)	0.9
Dyslipidaemia	43 (15)	11 (20)	32 (14)	0.2
ESC HCM risk score (%)	3 ± 3	5 ± 4	2 ± 2	0.00
Echocardiographic variables				
Maximal LV thickness (mm)	21 ± 5	25 ± 5	20 ± 5	0.00
LVEF (%)	67 ± 10	64 ± 12	68 ± 10	0.00
LV outflow gradient (mmHg)	21 ± 32	34 ± 36	18 ± 30	0.00
HOCM	109 (36)	37 (57)	72 (30)	0.00
LA diameter (mm)	41 ± 8	45 ± 7	40 ± 8	0.00
LA area (cm^2)	25 ± 8	28 ± 3	25 ± 8	0.00
LA volume index (mL/m^2)	50 ± 26	61 ± 28	47 ± 24	0.00
Interventricular septum (mm)	19 ± 6	22 ± 7	18 ± 5	0.00
LV EDD index (mL/m^2)	62 ± 21	62 ± 27	61 ± 19	0.8
LV ESD index (mL/m^2)	21 ± 14	24 ± 19	21 ± 12	0.2
LV global longitudinal strain (%)	−15 ± 4	−13 ± 3	−16 ± 4	0.00
Mitral E/A ratio	1.3 ± 0.7	1.4 ± 6	1.3 ± 0.7	0.3
E/e'	13 ± 7	17 ± 10	12 ± 5	0.00
Elevated LV filling pressure	39 (15)	15 (27)	24 (11)	0.00
MR				0.02
No-to-mild MR	244 (93)	43 (84)	201 (95)	
Moderate-to-severe MR	17 (7)	8 (16)	11 (5)	
LA strain				
LA PALS (%)	24 ± 13	17 ± 11	27 ± 13	0.00
LA TPLS (ms)	434 ± 60	457 ± 68	428 ± 57	0.00
LA PACS (%)	11 ± 7	7 ± 5	12 ± 7	0.00
LA TPCS (ms)	868 ± 165	872 ± 132	867 ± 173	0.9
LASRs[a] (s^{-1})	1.7 ± 0.6	1.4 ± 0.1	1.8 ± 0.05	0.00
LASRe[a] (s^{-1})	−1.7 ± 0.9	−1.2 ± 0.6	−1.8 ± 0.9	0.00
LASRa[a] (s^{-1})	−1.7 ± 0.8	−1.3 ± 0.7	−1.9 ± 0.8	0.00
MRI variables				
Maximal LV thickness (mm)	21 ± 6	25 ± 6	20 ± 5	0.00
LVEF (%)	67 ± 11	65 ± 14	67 ± 10	0.01
LV aneurysm	4 (2)	1 (2)	3 (2)	0.8
Presence of LGE	171 (80)	41 (93)	130 (76)	0.00

Data are expressed as mean ± standard deviation or number (%). AF: atrial fibrillation; BNP: B-type natriuretic peptide; EDD: end-diastolic diameter; ESC: European Society of Cardiology; ESD: end systolic diameter; HCM: hypertrophic cardiomyopathy; HOCM: hypertrophic obstructive cardiomyopathy; LA: left atrial; LASR: left atrial strain rate; LASRa: left atrial peak strain rate (A-wave); LASRe: left atrial peak strain rate (E-wave); LASRs: left atrial peak strain rate (S-wave); LGE: late gadolinium enhancement; LV: left ventricular; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; MRI: magnetic resonance imaging; NSVT: non-sustained ventricular tachycardia; NYHA: New York Heart Association; PACS: peak atrial contraction strain; PALS: peak atrial longitudinal strain; SCD: sudden cardiac death; TPCS: time to peak contraction strain; TPLS: time to peak longitudinal strain.

[a] Using the P-wave as the onset for deformation analysis, the positive LASRs determines LA reservoir function, and the negative LASRe and LASRa determine LA contractile function, all expressed in s^{-1}.

Please cite this article in press as: Essayagh B, et al. Left atrial dysfunction as marker of poor outcome in patients with hypertrophic cardiomyopathy. Arch Cardiovasc Dis (2020), https://doi.org/10.1016/j.acvd.2020.06.004

Table 2 Univariate and multivariable analysis of atrial dysfunction determinants.

	Univariate analysis		Multivariable analysis[a]	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Determinants of impaired PALS				
Age (per 10 years)	1.20 (1.02—1.43)	0.03	1.45 (1.12—1.89)	0.003
AF	8.10 (3.23—20.34)	< 0.0001	4.71 (1.60—13.85)	0.004
BNP (per 100 pg/mL increment)	1.59 (1.35—1.87)	< 0.0001	1.27 (1.06—1.53)	0.004
LVEF	0.94 (0.91—0.97)	< 0.0001	0.94 (0.90—0.98)	0.001
LV thickness	1.09 (1.04—1.15)	0.0004	1.14 (1.05—1.24)	0.002

AF: atrial fibrillation; BNP: B-type natriuretic peptide; CI: confidence interval; LV: left ventricular; LVEF: left ventricular ejection fraction; OR: odds ratio; PALS: peak atrial longitudinal strain.
[a] Adjusted for age, AF, BNP, LVEF and LV thickness.

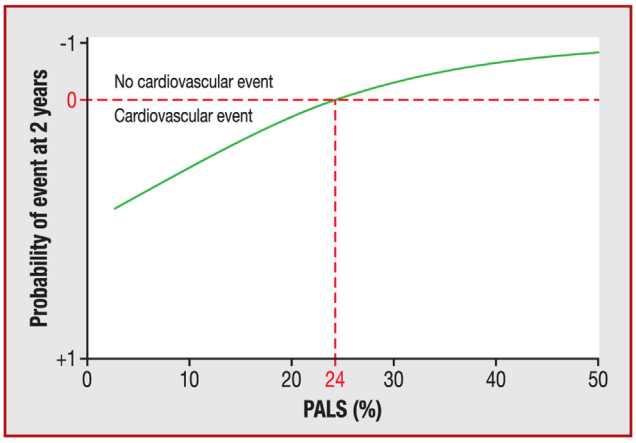

Figure 3. Hypertrophic cardiomyopathy-related events at 2 years according to peak atrial longitudinal strain (PALS). Note the linear increase in cardiovascular event occurrence with lower PALS within the first 2 years of follow-up.

function (by PACS, LASRe and LASRa) to be significant predictors of adverse cardiac events, with linear correlation between lower PALS < 24% and a higher probability of an event at 2-year follow-up (Fig. 3). The univariate HRs attached to impaired LA reservoir function were 0.94 (95% CI 0.92—0.97) for PALS and 0.42 (95% CI 0.25—0.69) for LASRs (all $P \leq 0.0004$; Table A.3). The univariate HRs attached to impaired LA contractile function were 0.91 (95% CI 0.88—0.95) for PACS, 2.70 (95% CI 1.71—4.38) for LASRe and 2.21 (95% CI 1.51—3.34) for LASRa (all $P < 0.0001$).

Other significant determinants of HCM adverse cardiac events were impaired LV global longitudinal strain (univariate HR 1.23, 95% CI 1.13—1.35; $P < 0.01$), at least moderate mitral regurgitation (univariate HR 2.45, 95% CI 1.13—5.34; $P = 0.02$) and MRI late gadolinium enhancement (univariate HR 4.83, 95% CI 1.83—17.85; $P < 0.01$).

After adjustment for age, BNP, LA volume index, LV wall thickness, LV global longitudinal strain, mitral regurgitation and MRI late gadolinium enhancement, PALS remained as a strong and independent predictor of adverse cardiac events (adjusted HR 0.86, 95% CI 0.79—0.94; $P = 0.0008$; Table 3).

Interobserver intraclass correlation coefficients were 0.97 and 0.95 for PALS and PACS, respectively; the coefficients of variation were 4.3% (95% CI 2.7—6.4%) for PALS and 15.4% (95% CI 10.1—23.6%) for PACS. Bland—Altman analysis showed acceptable limits of agreement.

Discussion

The present study, by gathering for the first time an important cohort of more than 300 patients with HCM and comprehensive echocardiographic examination, including LA function by strain measurement, irrespective of rhythm at baseline, has demonstrated that LA strain is feasible in patients with HCM. LA dysfunction by speckle tracking appears to be correlated with HCM-associated adverse cardiac events during the first 2 years of diagnosis, in addition to validated and experimental HCM predictors. Thus, further study is needed to include PALS as a potential marker of poor outcome.

LA function impairment in HCM

LA reservoir and contractile function impairment had long been considered a passive response to LV myocardial deformation [19,20], maintaining LV filling pressures [21] and, consequently, LV stroke volume [22]. However, a pilot study suggested that LA strain might be linked to worse outcome in HCM [8,9,23]. The mechanism modulating LA response to LV diastolic dysfunction is not well understood. Experimental [24] and clinical studies [25,26] have potentially linked variable LA fibrosis to LA impairment. Presumed mechanisms warrant clarification, as evidence is mounting that the left atrium is not a passive bystander, but that its dysfunction is independently linked to worse outcome, not just in HCM, but also in heart failure [27] and severe mitral regurgitation [28]. Irrespective of LA strain impairment mechanism, its link to outcome and sudden cardiac death might have considerable implications for HCM management.

Study strengths and limitations

Our study strength relies on LA strain measurement in a cohort of consecutively enrolled patients presenting with HCM. Echocardiographic characterisation was done prospectively, and although LA strain was performed retrospectively by an experienced board-certified echocardiographer, this

Please cite this article in press as: Essayagh B, et al. Left atrial dysfunction as marker of poor outcome in patients with hypertrophic cardiomyopathy. Arch Cardiovasc Dis (2020), https://doi.org/10.1016/j.acvd.2020.06.004

Table 3 Multivariable predictors of hypertrophic cardiomyopathy-related events and mortality.

	Univariate analysis		Multivariable analysis[a]	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Echocardiographic variables				
Maximal LV thickness	1.12 (1.09—1.13)	< 0.0001	1.13 (1.00—2.28)	0.04
LV global longitudinal strain	1.24 (1.12—1.37)	< 0.0001	1.06 (0.88—1.28)	0.5
MR	2.10 (1.18—3.74)	0.02	1.45 (0.40—5.26)	0.6
PALS	0.94 (0.92—0.97)	< 0.0001	0.86 (0.79—0.94)	0.0008

CI: confidence interval; HR: hazard ratio; LV: left ventricular; MR: mitral regurgitation; PALS: peak atrial longitudinal strain.
[a] Adjusted for age, B-type natriuretic peptide, left atrial volume index, LV thickness, LV global longitudinal strain, MR presence and magnetic resonance imaging fibrosis.

study provides additional evidence that LA strain (which is not part of routine practice) is feasible in the vast majority of patients with HCM. Moreover, it suggests that further assessment of PALS may provide additional prognostic information to help physicians in the management of patients with HCM. One could argue that AF alone is associated with worse outcome in HCM [29], thus introducing a bias by including patients with AF. However, AF — despite its association with SCD [30] — is not part of the HCM SCD risk score, and its occurrence is not a trigger for prophylactic ICD therapy. Moreover, AF is not the only independent determinant of LA dysfunction. Therefore, including patients with AF and HCM to assess PALS determinants and the independent impact of lower PALS on outcome was essential. Another limitation is the relative low number of events (particularly SCD in combination with more benign events) and the short follow-up, even though we present the largest HCM cohort with LA strain measurement and outcome ever assembled on this issue. However, further studies should focus on severe events only, including new-onset AF and ischaemic stroke, with long-term follow-up. Modelling by moderate/severe mitral regurgitation, instead of mitral regurgitation presence, showed that impaired PALS (adjusted HR 0.89, 95% CI 0.82—0.95; $P < 0.001$) remained highly predictive of worse outcome. Also, additional adjustment on LV outflow tract gradient did not change the association of PALS with worse outcome (adjusted HR 0.86, 95% CI 0.79—0.94; $P = 0.0009$). Finally, LA strain (derived from the LV global longitudinal strain three-chamber point-and-click approach) is not a standardised measurement. This issue is particularly important to consider if we are going to promote cut-off values of LA strain that could ultimately justify changes in the management of patients with HCM management.

Conclusions

This study suggests additive prognostic value of LA dysfunction by two-dimensional speckle tracking in assessing HCM outcome, with PALS as a potential target for future prospective studies of large magnitude to integrate LA dysfunction into the clinical decision-making process.

Sources of funding

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.acvd.2020.06.004.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE. Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA study. Coronary artery risk development in (young) adults. Circulation 1995;92:785—9.
[2] Zheng ZJ, Croft JB, Giles WH, Mensah GA. Sudden cardiac death in the United States, 1989 to 1998. Circulation 2001;104:2158—63.
[3] Winkel BG, Holst AG, Theilade J, et al. Nationwide study of sudden cardiac death in persons aged 1—35 years. Eur Heart J 2011;32:983—90.
[4] Hayashi M, Shimizu W, Albert CM. The spectrum of epidemiology underlying sudden cardiac death. Circ Res 2015;116:1887—906.
[5] O'Mahony C, Jichi F, Pavlou M, et al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). Eur Heart J 2014;35:2010—20.
[6] Mills H, Espersen K, Jurlander R, Iversen K, Bundgaard H, Raja AA. Prevention of sudden cardiac death in hypertrophic cardiomyopathy: risk assessment using left atrial diameter predicted from left atrial volume. Clin Cardiol 2020;43:581—6.
[7] Maron BJ. Contemporary insights and strategies for risk stratification and prevention of sudden death in hypertrophic cardiomyopathy. Circulation 2010;121:445—56.
[8] Paraskevaidis IA, Panou F, Papadopoulos C, et al. Evaluation of left atrial longitudinal function in patients with hypertrophic

cardiomyopathy: a tissue Doppler imaging and two-dimensional strain study. Heart 2009;95:483—9.
[9] Kobayashi Y, Moneghetti KJ, Bouajila S, et al. Time based versus strain based myocardial performance indices in hypertrophic cardiomyopathy, the merging role of left atrial strain. Eur Heart J Cardiovasc Imaging 2018;20:334—42.
[10] Iio C, Inoue K, Nishimura K, et al. Characteristics of left atrial deformation parameters and their prognostic impact in patients with pathological left ventricular hypertrophy: analysis by speckle tracking echocardiography. Echocardiography 2015;32:1821—30.
[11] Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233—70.
[12] Lancellotti P, Moura L, Pierard LA, et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). Eur J Echocardiog 2010;11: 307—32.
[13] Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009;22:107—33.
[14] Elliott PM, Anastasakis A, Borger MA, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2733—79.
[15] Cameli M, Caputo M, Mondillo S, et al. Feasibility and reference values of left atrial longitudinal strain imaging by two-dimensional speckle tracking. Cardiovasc Ultrasound 2009;7:6.
[16] Vianna-Pinton R, Moreno CA, Baxter CM, Lee KS, Tsang TS, Appleton CP. Two-dimensional speckle-tracking echocardiography of the left atrium: feasibility and regional contraction and relaxation differences in normal subjects. J Am Soc Echocardiogr 2009;22:299—305.
[17] Todaro MC, Choudhuri I, Belohlavek M, et al. New echocardiographic techniques for evaluation of left atrial mechanics. Eur Heart J Cardiovasc Imaging 2012;13:973—84.
[18] Kramer CM, Barkhausen J, Flamm SD, Kim RJ, Nagel E. Standardised cardiovascular magnetic resonance (CMR) protocols 2013 update. J Cardiovasc Magn Reson 2013;15:91.
[19] Anwar AM, Soliman OI, Nemes A, Geleijnse ML, ten Cate FJ. An integrated approach to determine left atrial volume, mass and function in hypertrophic cardiomyopathy by two-dimensional echocardiography. Int J Cardiovasc Imaging 2008;24:45—52.
[20] Rosca M, Popescu BA, Beladan CC, et al. Left atrial dysfunction as a correlate of heart failure symptoms in hypertrophic cardiomyopathy. J Am Soc Echocardiogr 2010;23:1090—8.
[21] Leung DY, Boyd A, Ng AA, Chi C, Thomas L. Echocardiographic evaluation of left atrial size and function: current understanding, pathophysiologic correlates, and prognostic implications. Am Heart J 2008;156:1056—64.
[22] Matsuda Y, Toma Y, Ogawa H, et al. Importance of left atrial function in patients with myocardial infarction. Circulation 1983;67:566—71.
[23] Fujimoto K, Inoue K, Saito M, et al. Incremental value of left atrial active function measured by speckle tracking echocardiography in patients with hypertrophic cardiomyopathy. Echocardiography 2018;35:1138—48.
[24] Everett 4th TH, Wilson EE, Verheule S, Guerra JM, Foreman S, Olgin JE. Structural atrial remodeling alters the substrate and spatiotemporal organisation of atrial fibrillation: a comparison in canine models of structural and electrical atrial remodeling. Am J Physiol Heart Circ Physiol 2006;291:H2911—23.
[25] Kottkamp H. Human atrial fibrillation substrate: towards a specific fibrotic atrial cardiomyopathy. Eur Heart J 2013;34:2731—8.
[26] Bouazizi K, Rahhal A, Kusmia S, et al. Differentiation and quantification of fibrosis, fat and fatty fibrosis in human left atrial myocardium using ex vivo MRI. Plos One 2018;13:e0205104.
[27] Freed BH, Daruwalla V, Cheng JY, et al. Prognostic utility and clinical significance of cardiac mechanics in heart failure with preserved ejection fraction: importance of left atrial strain. Circ Cardiovasc Imaging 2016;9:10.1161.
[28] Yang LT, Tsai WC, Luo CY, Li YH, Tsai LM. Role of left atrial reservoir strain rate in left atrial remodeling in severe mitral regurgitation. J Med Ultrasound 2017;25:16—23.
[29] Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. Circulation 2001;104:2517—24.
[30] Favale S, Pappone C, Nacci F, Fino F, Resta F, Dicandia CD. Sudden death due to atrial fibrillation in hypertrophic cardiomyopathy: a predictable event in a young patient. Pacing Clin Electrophysiol 2003;26:637—9.

Please cite this article in press as: Essayagh B, et al. Left atrial dysfunction as marker of poor outcome in patients with hypertrophic cardiomyopathy. Arch Cardiovasc Dis (2020), https://doi.org/10.1016/j.acvd.2020.06.004