Valeur pronostique de nouveaux paramètres d'imagerie dans la cardiomyopathie hypertrophique : étude prospective

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T H E S E

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Par

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Je donnerai gratuitement mes soins à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail ; je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intérieur des maisons, mes yeux ne verront pas ce qui se passe, ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses,

Que je sois déshonoré et méprisé de mes Confrères si j'y manque.

***Abbreviations*:** HCM, hypertrophic cardiomyopathy ; SCD, sudden cardiac death ; MRI, magnetic resonance imaging; LGE, late gadolinium enhancement; BNP, brain natriuretic peptide ; LV, left ventricle; LA, left atrial; ECG, electrocardiography; TTE, transthoracic echocardiography; PALS, peak atrial longitudinal strain; PACS, peak atrial contraction strain; LASR, left atrial strain rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricle ejection fraction; MR, mitral regurgitation; NSVT, non-sustain ventricular tachycardia; GLS, left ventricle global longitudinal strain; AF, atrial fibrillation; PISA, proximal isovelocity surface area; RV, regurgitant volume; ROI, region of interest; TPLS, ttime to peak longitudinal strain; TPCS, time to peak contraction strain; ED, end-diastolic; ES, end-systolic.

TABLE DES MATIERES

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Valeur pronostique de nouveaux paramètres d'imagerie dans la cardiomyopathie hypertrophique : étude prospective

Résumé – *Accepté au congrès ESC 2018*

Contexte : La cardiomyopathie hypertrophique (CMH) est une maladie cardiaque héréditaire fréquente (1/500) et une cause majeure de mort subite chez le jeune. Bien que le score de risque ESC soit très utile dans la pratique clinique, sa valeur prédictive a été remise en question puisqu'il était rétrospectif et n'incluait pas les paramètres d'imagerie par résonnance magnétique (IRM) et les nouveaux marqueurs échocardiographiques.

Objectif : Évaluer la valeur additionnelle des nouveaux paramètres échocardiographiques et IRM dans la prédiction de la mort subite et le pronostic des patients atteints de CMH.

Méthodes : Entre 2007 et 2017, 307 patients atteints de CMH ont été inclus prospectivement dans le centre de cardiomyopathie de la Timone et suivis pendant 1.64 ans. En plus des facteurs pronostiques classiques, tous les patients ont subi une IRM cardiaque avec étude du réhaussement tardif après injection de gadolinium, une mesure échocardiographique transthoracique (ETT) des volumes du ventricule gauche (VG) et de l'oreillette gauche (OG), ainsi que du strain VG et OG, comprenant le strain longitudinal de l'OG nommé PALS (« Peak Atrial Longitudinal Strain ») évaluant la fonction « réservoir » de l'OG, le PACS (« Peak Atrial Contraction Strain ») évaluant la fonction « contraction » de l'OG et le LASR (« Left Atrial Strain Rate ») évaluant la déformation radiale de l'OG. Le critère principal d'évaluation était la mort subite ou le choc approprié par le défibrillateur automatique implantable (DAI). Le critère secondaire d'évaluation était un critère composite comprenant la mort subite, le choc approprié, le décès toutes causes, l'hospitalisation pour insuffisance cardiaque, l'apparition d'une nouvelle tachycardie ventriculaire, l'indication d'implantation d'un DAI ou pacemaker, l'ablation de fibrillation auriculaire, l'alcoolisation septale, la myomectomie et la transplantation cardiaque.

Résultats : Parmi les 307 patients, 6 patients (2%) sont décédés et le critère secondaire d'évaluation est survenu chez 65 patients (21%). Les facteurs associés à la mort subite par analyse univariée étaient une baisse de la fraction d'éjection VG (FEVG) (HR 0.91 [0.83-0.99]), une altération du PALS (HR 0.86 [0.72-0.97]), une augmentation de la surface (HR 1.13 [1.04-1.22]) et du volume de l'oreillette gauche (HR 1.02 [1.01-1.03]), des pressions de remplissage VG élevées et une insuffisance mitrale (IM) modérée, en plus de la tachycardie ventriculaire non soutenue (TVNS) (HR 7.00 [1.48-32.88]), de la syncope (HR 6.3 [1.09-28.31]) et de l'épaisseur maximale de la paroi du VG (HR 1.29 [1.11-1.54]). En revanche, le strain global longitudinal VG, le BNP, l'identification d'un gène responsable de CMH et un réhaussement tardif du gadolinium en IRM n'étaient pas associés à la survenue de mort subite.
Les facteurs associés au critère d'évaluation secondaire étaient les suivants : altération du strain VG (HR 1.23 [1.13-1.35]), altération du PALS (HR 0.94 [0.91-0.97]) et PACS (HR 0.91 [0.86-0.95]) en coupe 4 cavités, altération du PALS (HR 0.93 [0.89-0.96]) et PACS (HR 0.86 [0.83-0.94]) en coupe 2 cavités, ainsi qu'une insuffisance mitrale en ETT et IRM, des pressions de remplissage VG élevées et la présence d'un rehaussement tardif du gadolinium en IRM. Le PALS en coupe 4 cavités apparaissait comme facteur prédictif indépendant pour le critère composite (HR 0.92 [0.87-0.97]), après ajustement sur l'âge, le BNP, l'épaisseur maximale de la paroi VG, le volume de l'OG, le strain VG, la présence d'une IM en ETT et le rehaussement tardif du gadolinium en IRM. De même, la corrélation avec la morbidité cardiovasculaire a été établie de façon significative avec les facteurs de risque habituels de mort subite, tels que l'épaisseur maximale du VG en ETT et IRM, le diamètre de l'OG, la TVNS et la syncope.

Conclusions :

1 - Cette étude suggère une valeur pronostique additionnelle de l'altération du strain VG et OG, de la présence d'une IM et d'un rehaussement tardif du gadolinium en IRM, aux 7 facteurs de risque classiques recommandés par l'ESC.

2 - Une étude multicentrique supplémentaire doit être réalisée pour proposer une modification du score de risque de l'ESC.

Prognostic value of new imaging parameters in patients with hypertrophic cardiomyopathy: a prospective study

Abstract – *Accepted ESC Congress 2018*

Background: Hypertrophic cardiomyopathy (HCM) is a frequent hereditary cardiac disease (1/500) and a major cause of sudden cardiac death (SCD) in youth. Although the ESC risk score is very useful in clinical practice, its predictive value has been interrogated since it was retrospective and did not include magnetic resonance imaging (MRI) parameters and new echocardiographic markers.

Purpose: To assess the additional value of new echocardiographic and MRI parameters in predicting sudden death and outcome in patients with HCM.

Methods: Between 2007 and 2017, 307 patients with HCM were prospectively included in our cardiomyopathy center and followed for 1.64 years. In addition to conventional prognostic factors, all patients underwent cardiac MRI evaluation of late gadolinium enhancement (LGE), and transthoracic echocardiographic (TTE) measurements of left ventricle (LV) and left atrium (LA) volumes, and LV and LA strains, including left atrial peak longitudinal strain (PALS), left atrial peak contraction strain (PACS), and left atrial strain rate (LASR). The primary end-point was sudden death or appropriate implantable cardioverter defibrillator (ICD) therapy. The secondary end-point was a composite end-point including death, hospitalization for heart failure, new onset of ventricular tachycardia, need for ICD and pacemaker implant, atrial fibrillation ablation, alcohol septal ablation, myomectomy, or heart transplantation.

Results: Among the 307 patients, 6 patients (2%) died and the secondary end point occurred in 65 patients (21%). Factors associated with sudden death by univariate analysis were low LV ejection fraction (LVEF) (HR 0.91 [0.83-0.99]), impaired PALS (HR 0.86 [0.72-0.97]), increased LA area (HR 1.13 [1.04-1.22]), and volume (HR 1.02 [1.01-1.03]), high LV filling pressures and moderate mitral regurgitation (MR), in addition to non-sustain ventricular tachycardia (NSVT) (HR 7.00 [1.48-32.88]),

syncope (HR 6.25 [1.09-28.31]), and maximal LV wall thickness (HR 1.29 [1.11-1.54]), while LV global longitudinal strain (GLS), BNP, genetic result and LGE were not.

Factors associated with the secondary endpoint were impaired LV GLS (HR 1.23 [1.13-1.35]), impaired LA 4 chamber PALS (HR 0.94 [0.91-0.97]) and PACS (HR 0.91 [0.86-0.95]), LA 2 chamber PALS (HR 0.93 [0.89-0.96]) and PACS (HR 0.86 [0.83-0.94]), as well as TTE and MRI MR, high LV filling pressures and presence of MRI LGE. Impaired LA 4 chamber PALS remained as an independent predictor for the composite end-point (HR 0.92 [0.87; 0.97]), after adjustment for age, BNP, maximal LV wall thickness, LA volume, LV GLS, TTE MR et MRI LGE. Similarly, the correlation with cardiovascular morbidity was significantly established with usual SCD risk factors such as maximum TTE and MRI wall thickness, LA diameter, NSVT and syncope.

Conclusions:

1 - This study suggests an additive prognostic value of an impaired LV and LA TTE strain, the presence of MR, and MRI LGE, to the classical ESC 7 recommended risk factors.

2 - Additional multicenter studies should be performed to propose modifications in ESC criteria.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a complex genetically transmitted cardiac disease, present in 1 of 500 people in general population[1-2]. Since the first description by Tear in 1958[3], HCM is known as the most common cause of sudden cardiac death (SCD) in the young.

Implantable cardioverter defibrillator (ICD) remains the only available treatment option capable of definitely prolonging life in HCM[2], with a primary prevention rate of 4%/year[4]. After > 50 years of recognition and study, the HCM SCD risk prediction model has merged as an accurate prognostic tool regarding SCD[5]. It has the potential to improve the management of our HCM patients by guiding ICD therapy and protecting low risk patients from the relatively high lifetime risk of device related complications[6]. However, the challenge remains to select more precisely those patients who will benefit from this therapy, including the small but important subset in which conventional risk markers are not predictive but in whom sudden-death events may nevertheless occur[2,7].

In addition to SCD, and paradoxically more likely in patients < 60 years of age[8], HCM can lead to functional disability from congestive heart failure and stroke due to atrial fibrillation (AF). However, sever heart failure and functional disability due to left ventricular outflow obstruction are potentially reversible; myomectomy operation extends longevity with survival similar to that expected in the general population[9] and alcohol ablation is effective in reducing outflow gradient and symptoms, although adding a risk of arrhythmogenic alcohol-induced transmural myocardial infarction[2,10-14]. In case of irreversible heart failure associated with systolic dysfunction and left ventricular remodelling, heart transplantation is the only definitive treatment option[2,15], with post-transplant survival of 70% at 5 years[16]. Also, AF described as the most common sustain arrhythmia in HCM (20% of patients), has been reported occasionally as a trigger for ventricular arrhythmias, causing ICD intervention[17]. AF radiofrequency catheter ablation appears successful in restoring sinus rhythm and improving symptomatic status in short term in > 50% of patients[18] but there is no compelling evidence yet that paroxysmal AF is specially a predictor of SCD in cohort analyses[7].

These major therapeutic interventions available for HCM patients are capable of changing the natural history of the disease but much work remains in the area of risk stratification. Identifying more at-risk patients with novel markers continues to be an important goal for which contrast-cardiovascular magnetic resonance imaging (MRI) with extensive late-gadolinium enhancement (LGE) (presumably myocardial scarring) shows significant promise[2,19] in addition to left ventricle (LV) global longitudinal

strain (GLS)[20,21]. Similarly, elevated B-type natriuretic peptide (BNP)[22] as well as left atrial (LA) remodelling assessed by echocardiographic strain[23] showed independent correlation to HCM prognosis.

Despite its contribution, the predictive value of the HCM-risk SCD prediction model[5] has been interrogated since it was retrospective and did not include MRI parameters and new bio- and echocardiographic markers. Thus, the aim of our study was to assess the additional value of new echocardiographic and MRI parameters in predicting sudden death and outcome in patients with HCM.

METHODS

Study design and data collection

We considered for this study 436 consecutive HCM patients, prospectively evaluated in the cardiomyopathy center of la Timone Hospital, Marseille, between 2007 and 2017. The diagnosis of HCM was on the basis of demonstration by two-dimensional echography and/or cardiac MRI of a hypertrophied and non-dilatated LV (wall thickness ≥ 13 mm), in the absence of another cardiac or systemic disease capable of producing a similar degree of hypertrophy[24]. Excluded from the study were patients aged ≤ 16 years old, and patients with known metabolic disease (e.g. Anderson-Fabry disease) or syndromic causes of HCM (e.g. Noonan syndrome)[5]. The study was conducted in accordance with institutional policies, national legislation, and the revised Helsinki declaration.

All patients had planned clinical reviews every 6-12 months or earlier if there was a change in symptoms. Patients underwent clinical assessment, pedigree analysis, physical examination, electrocardiography (ECG), transthoracic echocardiography (TTE), mutation screening of 4 genes implicated in HCM (MYH7, MYBPC3, TNNT2, and TNNI3) in genomic DNA isolated from blood samples[25], serum BNP measurement (normal value < 100 pg/mL) and MRI evaluation of LGE. The HCM Risk-SCD score, which estimates the risk of sudden cardiac death at 5 years in patients with hypertrophic cardiomyopathy, was assessed for each patient[5]. Risk factors in the HCM Risk-SCD score were: 1) age; 2) family history of SCD due to HCM; 3) unexplained recent syncope; 4) multiple repetitive non-sustained ventricular tachycardia (NSVT) on ambulatory ECG monitoring; 5) LV hypertrophy; 6) LA diameter; 7) LV ventricular outflow gradient. According to ESC Guidelines, in patients with a 5-year risk of SCD < 4%, an ICD is generally not indicated, in patients with a risk of 4 to less than 6%, an ICD may be considered and in patients with a 5-year risk ≥ 6%, an ICD should be considered[5].

Clinical outcomes

SCD was defined as witnessed sudden death with or without documented ventricular fibrillation or death within 1h of new symptoms or nocturnal deaths with no antecedent history of worsening symptoms[26]. Aborted SCD during follow-up and appropriate implantable cardioverter defibrillator (ICD) shocks were considered equivalent to SCD. Expert electrophysiologists from our center analyzed stored intracardiac electrocardiograms for arrhythmias responsible for defibrillator discharges (shocks or antitachycardia pacing), according to prior definitions in HCM studies[27]. ICD shocks were considered appropriate when triggered by ventricular fibrillation or rapid sustained ventricular tachycardia (rate > 180/min), in an identical manner to previous studies[5,28-34].

History of SCD was defined as SCD in ≥ 1 first degree relatives under 40 years of age or SCD in a first degree relative with confirmed HCM at any age (post or ante-mortem diagnosis)[5,33,35-37], and unexplained syncope as history of unexplained syncope at or prior to evaluation[5,33-34,36,38-39].

Single- or dual-chamber ICDs capable of antitachycardia and antibradycardia pacing were implanted for primary prevention, according to the risk stratification model advanced for HCM in guidelines and consensus panels[5]. Rate cutoffs for arrhythmia detection were programmed and antitachycardia pacing activated at the electrophysiologist's discretion[28]. Other major interventions included hospitalization for heart failure, pacemaker implantation, AF ablation, need for alcohol septal ablation, myomectomy, or heart transplantation.

Echocardiography

All patients underwent a comprehensive two-dimensional echocardiographic study, with conventional Doppler and tissue Doppler, using commercially available high quality ultrasound system (Vivid 7, GE Healthcare, USA).

Conventional echocardiography

Measurements of LV and LA dimensions were made in accordance with current American Society of Echography and European Association of Cardiovascular Imaging recommendations[40] and indexed by body surface area (DuBois method). LA diameter was determined by M-mode or 2D echocardiographic mode in the parasternal long axis plane[5,41]. Maximal wall thickness was defined as the greatest thickness in anterior septum, posterior septum, lateral wall and posterior wall of LV, measured at level of the mitral valve, papillary muscles, and apex using parasternal short axis plane at time of evaluation[5,30,34,41-43]. LV ejection fraction (LVEF) was measured using the modified biplane

Simpson's rule. LV outflow tract gradient was measured at rest (in the left lateral decubitus position) and with Valsalva provocation with continuous wave Doppler interrogation directly parallel to the outflow tract in the apical views under direct visualization[44]. Care was taken to differentiate Doppler waveform signals from LV outflow tract and mitral regurgitation[24,44-45].

Evaluation of LV diastolic function by standard Doppler imaging was based on two factors: (i) LV filling, determining maximum early (E-wave) and late (A-wave) diastolic velocities, the relationship between both (E/A) and E-wave deceleration time: (ii) tissue Doppler peak diastolic velocities of the mitral annulus (E' and A')[46].

Echocardiographic data for mitral regurgitation (MR) grading were acquired according to a standardized protocol with multiple 2D incidences. The Proximal Isovelocity Surface Area (PISA) radius was measured in midsystole, in either apical or parasternal views, as appropriate, with the lower Nyquist limit set to 30 to 40 cm/s and zoomed in on the area of flow convergence. Mitral regurgitant volume (RV PISA) was calculated using the PISA technique as previously described[47] and RV PISA was categorized as recommended by American Heart Association/American college of Cardiology[48]: mild, < 30ml; mild to moderate, 30 to 44ml; moderate to severe, 45 to 59ml; and severe, ≥ 60ml.

Speckle tracking echocardiography

Two-dimensional echocardiography using dedicated software (2D strain, EchoPAC™, GE Healthcare, USA) was used to assess LA and LV myocardial deformation. Apical four- and two- chamber views images were obtained, during breath hold with a stable ECG recording. Particular attention was given to obtain an adequate gray scale image, allowing reliable delineation of myocardial tissue and extracardiac structures[49]. The frame rate was set between 60 and 80 frames per second.

LV GLS strain was quantified and the values for six myocardial LV segments in apical four-chamber view, two-chamber view and three-chamber view were averaged.

The LA deformation was quantified and averaged for six LA segments from the apical four- and the two-chamber view, with initial onset in the ECG before P-wave (aortic valve closure), in order to isolate LA contractile function[50]. Strain represents myocardial deformation, whereas strain rate represents the speed at which myocardial deformation occurs (expressed in s^{-1})[51]. Briefly, LA endocardial surface was manually traced by a three point-and-click approach. An epicardial surface tracing was then automatically generated by the system, thus creating a region of interest (ROI). After manual adjustment of ROI width and shape, the software divided the ROI into 6 segments, and the

resulting tracking quality for each segment was automatically scored as either acceptable or non-acceptable, with the possibility of further manual correction. Segments in which no adequate image quality could be obtained were rejected by the software and excluded from the analysis. Lastly, the software generated strain curves for each atrial segment (***Figure 1***). In subject with adequate image quality, a total of 6 segments were then analyzed to trace the ROI in the discontinuity of LA wall corresponding to pulmonary veins and LA appendage; the direction of LA endocardial and epicardial surfaces at the junction with these structures were extrapolated[49].

Peak atrial longitudinal strain (PALS) resulted of maximal stretching of LA (LA end diastole), during the reservoir phase, and was expressed in percentage. Time to peak longitudinal strain (TPLS) was the time between beginning of QRS and PALS, expressed in milliseconds. Peak atrial contraction strain (PACS) resulted of contraction of LA, during the contraction phase, and was expressed in percentage. Time to peak contraction strain (TPCS) was the time between beginning of QRS and PACS, expressed in milliseconds (***Figure 2***).

PALS, PACS, TPLS and TPCS were calculated in 4- and 2-chamber views. In patients in whom some of the 6 segments were excluded because of the impossibility of achieving adequate tracking, those were calculated by averaging values measured in the remaining segments.

We determined LA peak strain rate (S-wave, LASRs) 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 (***Figure 3***). Strain rate values during the reservoir phase (LA diastole) are positive (due to LA chamber dilatation and wall stretch)[51]. Alternatively, myocardial shortening during LA contractile phase (LA systole) results in strain rate values that are negative.

Cardiovascular MRI technique

Cardiovascular MRI studies were performed with a 1.5-Tesla MR scanner (Symphony TIM, Siemens, Erlangen, Germany with a 12-element phased array cardiac coil, Achieva, Philips Medical System, Best, The Netherlands). Assessment of cardiac function was performed with a cine steady-state free precession pulse sequence, with retrospective gating, in end-expiration breath-hold. The following projections were acquired: 2-chamber, 4-chamber and parallel contiguous short axis (to cover the entire LV from the mitral plane to the apex). All examinations were transferred to a dedicated workstation and flow was quantified using Siemens Argus^{TM} Flow software (Siemens, Erlangen, Germany). Maximal MRI LV wall thickness was defined as the greatest thickness in anterior septum,

posterior septum, lateral wall and posterior wall of the LV, measured at level of the mitral valve, papillary muscles, and apex using parasternal short axis plane. On the cine images, LVEF, end-diastolic (ED) and end-systolic (ES) volumes were calculated using the standard formula. Aortic phase contrast was performed 10 mm above the tip of the aortic valve perpendicular to the aorta. Aortic outflow volume was derived from quantitative flow measurements. Mitral regurgitation was assessed by MRI regurgitant volume (RV MRI) method. RV MRI was calculated as the difference between LV total stroke volume obtained from MRI acquisition and aortic forward flow volume (obtained from phase contrast analysis). Gadolinium administration and delayed enhancement were used according to the standard protocol. Briefly, LGE images were acquired using a high-resolution 3 dimensional electrocardiographic-gated free breathing and respiratory navigator gated inversion recovery spoiled gradient echo sequence, in the short axis orientation, 20 minutes after intra venous administration of 0.2 mmol/kg Gd-DOTA (DOTAREM, Guerbet, France).

Arrhythmias

AF were diagnosed by the cardiologist in charge of the patient, during clinical review at our center or during hospital stay where ECG was continuously monitored and recorded, on a 12 lead-ECG. NVST was defined as 3 consecutive ventricular beats at a rate of ≥ 120 beats per min and < 30s in duration on Holter monitoring (minimum duration 24 hours) at or prior to evaluation, as recommended[5,30,33,36,37].

Statistical analysis

The primary end-point was SCD or appropriate defibrillator therapy. The secondary end-point was a composite end-point including SCD, appropriate defibrillator therapy, hospitalization for heart failure, new onset of ventricular tachycardia, need for ICD and pacemaker implantation, AF ablation, alcohol septal ablation, myomectomy, or heart transplantation.

Data for study population and imaging measurements are presented as number (percent) for categorical variables and mean ± standard deviation for continuous variables. Unpaired continuous variables were compared using the Student's test or Mann-Whitney rank-sum test. Comparison of categorical variables was performed with a Chi^2 test or Fisher's exact test.

Clinical parameters were tested as univariate predictors of SCD or cardiovascular morbimortality. A p value of < 0.05 was considered significant. Covariates with a p value of < 0.05 for univariate associations were entered into a stepwise multivariate Cox proportional hazards model to

identify independent predictors. These covariates were age, BNP, maximal TTE LV wall thickness, LA volume, LV GLS, TTE MR et MRI LGE. All statistical analyses were performed using commercially available software (R, version 3.4.1, Vienna, Austria).

RESULTS

Patient demographics and characteristics

One hundred and twenty-nine patients (30%) were excluded because they did not show up to clinical reviews. Thus, the final study group consisted of 307 patients (202 men; mean age 50±17). Baseline demographic and clinical characteristics of the 307 patients are displayed in Table 1. Most patients were asymptomatic or mildly symptomatic and demonstrated New York heart Association (NYHA) functional class I and II (226/307, 74%). Mean LVEF was 67±10%, maximal TTE LV thickness 21±5 mm, LA diameter 41±8mm, left ventricular outflow gradient 21±32 mmHg and mean LV global longitudinal strain (performed in 172 patients) -15±4%. Mean BNP concentration (measured in 283 patients) was 199 ng/mL. LA strain was performed in 235 (77%) patients. Mean PALS were similar in both four-chamber and two-chamber view (25±14% and 23±12%, p=0.021) as well as mean PACS (11±7% and 12±7%, p=0.020). HCM genetic study was performed in 174 (57%) patients. Among the 230 (75%) patients who underwent MRI examination, 215/230 (93%) had gadolinium administration.

Study endpoints

Patients were followed for a median duration of 598 days (1.64 years). During this time, 6 patients (2%) died or underwent appropriate ICD therapy. 14 (5%) patients underwent alcohol septal ablation, 4 (1%) septal myomectomy (1 patients (0.3%) had both procedures), 1 (0.3%) new ventricular tachycardia, 5 (2%) atrial fibrillation ablation, 25 (8%) primary prevention ICD implantation, 2 (0.7%) pacemaker implantation, 5 (2%) hospitalization for heart failure and 3 (1%) heart transplantation. During the study period, a total of 57 patients (19%) were treated with an ICD.

<u>SCD or appropriate defibrillator therapy</u>

In 3 patients (1%), SCD events occurred at 48±28 years of age (range 16 to 70); 1.38±1.29 years after initial evaluation (and risk scoring). Of the 3 patients, no one was judged to be at high-risk with an ESC score > 6%/5 years, sufficient to recommend an ICD. In 1 (33%) patient, risk score was intermediate (4-6%/5 years), but the majority, i.e., 2 patients (67%), were judged at lowest risk (< 4%/5

years), inconsistent with an ICD recommendation. Also, 2 of these 3 patients had 2 or 3 conventional risk factors (each with massive LV hypertrophy (22±6 mm, range 18 to 29)), and would be regarded at high-risk independent of the calculated risk score[52]. MRI examination was performed on 2 patients, and both of them had LGE.

3 patients experienced appropriate ICD intervention at age 39±20 years (range 16 to 52). 2 of them (67%) received a risk score > 6%/5 years, consistent with the strongest "*ICD should be considered*". Similarly, MRI examination was performed on 2 patients, and both of them had LGE.

In the 6 patients where the primary end point occurred, all had important LV hypertrophy (25±6 mm by TTE examination and 31±8 by MRI) and LV outflow gradient (29±27 mmHg). They had lower LVEF 59±17%, p< 0.0001, increased LV filling pressures (with E/A septal 17±4, p<0.0001). Median BNP was 606±422 ng/mL. Patients had no or moderate MR (3/6, 50%) and genetic testing was available for only 2 of them (1 positive for MYBPC3 and 1 negative). In those patients, LA was dilated (LA area 34±13 cm2 and LA volume 142±75 ml) and LA four-chamber strain impaired (PALS 11±6%, PACS 6±4%, LASRs 1±4s^{-1}, LASRe -0.7±0.3$s^{-1}$and LSREa -1±0.7s^{-1}).

Univariable Cox regression found low LVEF (HR 0.91; 95% CI [0.83-0.99], p=0.022), impaired PALS (HR 0.86; 95% CI [0.72-0.97], p=0.007), increased LA area (HR 1.13; 95% CI [1.04-1.22], p=0.004) and LA volume (HR 1.02; 95% CI [1.01-1.03], p=0.003), high LV filling pressures (HR 7.01; 95% CI [1.48-33.23], p=0.016) and moderate MR (HR 9.29; 95% CI [1.95-44.31], p=0.007) were significant predictors of death or appropriate ICD therapy (***Table 2***). Impaired LV global longitudinal strain (HR 1.33; 95% CI [0.85-2.42], p=0.20, elevated BNP concentration (HR 1; 95% CI [1.00-1.00], p=0.010) and MRI LGE (HR 3.74; 95% CI [0.39-498], p=0.30) were not.

Conventional prognostic markers of SCD were found to be significantly associated with SCD or appropriate ICD therapy (***Table 2***). Indeed, patients with NSVT had seven-fold increased risk of death or appropriate ICD shock (HR 6.97; 95% CI [1.48-32.88], p=0.017) compared to those without ventricular arrhythmias. Also, patients with syncope (HR 6; 95% CI [1.09-28.31], p=0.042) and thick LV wall by MRI examination (HR 1.29; 95% CI [1.11-1.54], p= 0.001) had an increased risk of sudden death. No association with positive genetic result was found (HR 0.65; 95% CI [0.05-7.97], p= 0.71).

The event rate did not allow further multivariable analysis.

Cardiovascular morbimortality

Cardiovascular morbimortality related events occurred in 65 (21%) patients, which is 10 times more than the incidence of SCD, with significant correlation to NYHA symptoms (HR 5.31; 95% CI [2.55-11.36], p<0.001 for NYHA functional class III vs HR 2.18; 95% CI [1.125-4.46], p=0.020 for NYHA functional class II) (***Table 3***). Low LVEF (HR 0.96; 95% CI [0.93-0.98], p=0.001), impaired LV global longitudinal strain (HR 1.23; 95% CI [1.13-1.35], p<0.001) and LV diastolic dysfunction expressed through elevated LV filling pressures (HR 2.70; 95% CI [1.44-4.84], p=0.003), elevated lateral E/E' (HR 1.07; 95% CI [1.04-1.10], p <0.001) and elevated septal E/E' (HR 1.05; 95% CI [1.03-1.07], p<0.001), were significantly associated to the secondary end-point on a univariable Cox regression.

LA area (HR 1.05; 95% CI [1.02-1.08], p <0.001), and LA volume (HR 1.01; 95% CI [1.01-1.01], p<0.001) as a surrogate for LA dilatation and more precisely impaired LA reservoir function (measured by the PALS and the LASRs) and impaired LA contractile function (measured by the PACS and the LASRe / LASRa) were also significantly associated to adverse cardiovascular events in HCM patients, by univariate analysis. This association was found on four-chamber view measurements of LA strain with HR of 0.94 (95% CI [0.91-0.97], p<0.001) for PALS, 0.91 (95% CI [0.86-0.95], p<0.001) for PACS, 0.46 (95% CI [0.28-0.72], p<0.001) for LASRs, 2.85 (95% CI [1.78-4.79], p<0.001) for LASRe and 2.08 (95% CI [1.48-2.98], p<0.001) for LASRa. Equally, the analysis on two-chamber view measurements showed HR of 0.93 (95% CI [0.89-0.96], p<0.001) for PALS, 0.89 (95% CI [0.83-0.94], p<0.001) for PACS, 0.43 (95% CI [0.22-0.79], p=0.007) for LASRs, 1.88 (95% CI [1.25-2.89], p=0.002) for LASRe and 2.42 (95% CI [1.21-5.44], p=0.01) for LASRa.

Also, significant association to adverse cardiovascular events was found with the presence of MR on TTE examination (HR 1.96; 95% CI [1.12-3.53], p= 0.017), MR on MRI examination (HR 2.42; 95% CI [1.21-4.09], p= 0.011) and MRI LGE (HR 4.83; 95% CI [1.83-17.84], p< 0.001). No association was found with the presence of LV aneurysm on MRI (HR 0.82; 95% CI [0.09-3.13], p=0.80) but only 4/230 (2%) patients had one.

Finally, conventional prognostic markers of SCD were found to be significantly associated with cardiovascular morbimortality. Patients had an increased risk of adverse cardiovascular events with family history of SCD (relative risk 2.93, 95% CI [1.43-5.54], p=0.005), increased TTE LV wall thickness (HR 1.12; 95% CI [1.08-1.17], p<0.001) and MRI LV wall thickness (HR 1.12; 95% CI [1.07-1.17],

p<0.001), increased LA diameter (HR 1.06; 95% CI [1.03-1.09], p<0.001), NSVT (HR 2.99; 95% CI [1.72-4.99], p<0.001), and syncope (HR 3.72; 95% CI [2.07-6.37], p<0.001).

The multivariate independent predictor of HCM mortality and cardiovascular events (n= 65) was impaired LA four-chamber PALS (HR 0.92; 95% CI [0.87-0.97], p=0.001) (***Table 4***).

DISCUSSION

The main findings of the current study can be summarized as follows: (1) in a significant cohort of HCM patients, LA strain is associated with the primary end-point of SCD (and appropriate ICD therapy) but longer follow-up and a larger cohort is needed; (2) LV GLS, LA strain, the presence of MR and MRI LGE are significantly associated with the secondary end-point; (3) LA strain is independently associated with HCM-related events.

Accuracy of the ESC prediction model

The risk prediction model developed by O'Mahony et al[5] to predict SCD in patients with HCM showed its limits in our study. Indeed, 2 of the 6 patients who encountered SCD had a 5-year risk of SCD < 4%, where ICD is generally not indicated according to the ESC prediction model. Despite important LV hypertrophy, elevated LV outflow gradient and enlarged LA diameter, those patients' score was not high enough to indicate ICD implantation.

As previously demonstrated by Maron et al[52] in a large cohort of > 1600 consecutive patients during a follow up period of > 20 years, where the ESC SCD risk model strengths and limitations were retrospectively tested, 60% of the 35/1629 (2%) patients where SCD occurred had the lowest risk scores of < 4%/5 years which excluded prophylactic ICDs that would have prevented SCD. Indeed, the ESC model arbitrary incorporated 2 new risk markers, i.e., dynamic LV outflow obstruction and left atrial size that have not proved to be independent predictors of SCD risk, and also are not included as risk markers in the international HCM literature[52]. Still, the ESC model appears to identify many patients at low SCD risk who may not require primary prevention ICD as 91% of surviving patients without events in our study were in the lowest ESC risk category (< 4%/5 years), demonstrating high specificity.

We should underline that HCM is a complex genetic heart disease with relatively low prevalence of SCD 2% reported here (between 2-5% by others[53]). Therefore, as Maron et al[52] suggested, we would not expect that management decisions for individual HCM patients could be reliably translated from a complex mathematical formula, based on statistical analyses, which minimize clinician judgment so

important in this context. Thus, new imaging prognostic factors found particular interest in “grey zone” clinical circumstances when the conventional risk factors assessment proves ambiguous. They are useful to guide the physician decision in prophylactic ICD therapy but also to deliver additional objective elements to involve the patient in the physician’s decision, reinforcing the patient-physician relation in this pathology.

MRI late gadolinium enhancement

Extensive LGE by quantitative contrast-cardiovascular magnetic resonance is probably one of those independent SCD risk marker and decision arbitrator in HCM, including in patients without conventional risk factors[19,54], forgotten in the ESC model[52]. In our study, both 2/6 (33%) patients with SCD and a 5-year risk of SCD < 4% had MRI LGE which could have help reconsidering ICD implantation.

Indeed, MRI with gadolinium affords the unique capability for in vivo myocardial tissue characterization. LGE is frequent (between 40-80%) in HCM[55-58] as found in our cohort (171/215 (80%) of patients with contrast enhancement study had LGE) and is often the evidence of myocardial fibrosis and replacement scarring[19,58-62]. It is a source of ventricular tachyarrhythmias[62] and an independent prognostic marker for SCD or appropriate ICD discharges[19]. As Chan RH and al[19] demonstrated, LGE ≥ 15% of LV mass conveys a 2-fold increase in risk and raises consideration for the primary prevention of sudden death with implantable defibrillator in young patients with, as well as without, other conventional risk markers. Absence of LGE is associated with lower risk.

Moreover, diffuse transmural high signal intensity LGE is characteristic of end-stage heart failure and systolic dysfunction as presence of LGE was significantly correlated with HCM-related events and mortality (HR of 4.83 (95% CI [1.83-17.85], p<0.001)). The risk of HCM-related events seemed proportional to the importance of LGE (HR 4.31 95% CI [1.46-16.80], p<0.007 for mild LGE vs HR 7.43 95% CI [2.62-28.42], p<0.011 for severe LGE). Whether extensive LGE can be regarded as an indisputable risk factor in HCM ultimately requires adequately powered studies in large populations with sufficient numbers of events accrued over many years[63]. A recent meta analysis[64] added to the evidence that extensive LGE may be potentially considered a novel risk marker to help identify high-risk patients who are candidates for life-saving therapy with ICD.

GLS strain

GLS strain showed a possibility of providing useful information on myocardial fibrosis and prognosis in patients with HCM. It appears as a clinically promising parameter for risk stratification[21]. In their study involving 48 patients, Saito et al[21] showed that LV GLS in patients with LGE (36/48, 75%) was significantly lower than without LGE (-11.8±2.8 vs -15.0±1.7%, p<0.001), that GLS was an independent predictor of %LGE and that all 5 events occurred in the worse GLS group (p= 0.018). Our study confirmed those previous observations on a larger cohort of 173 patients with MRI contrast enhancement study and LV GLS measurement. Our patients with GLS measurement and LGE (131/173, 75%) had significantly lower GLS than patients without LGE (-15±4 vs -16±4, p<0.001) and regardless LGE, patients with cardiovascular events had worse GLS (-13±4 vs -15±4, p< 0.001). Similarly, impaired GLS was significantly associated to HCM cardiac events (HR 1.23 95% CI [1.13-1.35], p<0.001) and tented to be associated to SCD (HR 1.33 CI [0.85-2.42], p<0.21). Hiemstra et al[65] recently demonstrated on a larger cohort of 427 patients with HCM that a cut-off value of GLS <-15% was significantly associated with better survival for patients. The small number of SCD events and the compensation of impaired basal strain by normal apical strain probably explains the absence of significance of impaired GLS on our primary end-point[66].

LA strain

LA reservoir and contractile function are known to be reduced and closely related to LV longitudinal myocardial deformation on small cohorts of patients with HCM (25 to 50 patients)[23,67,68]. In patients with normal LA, both increased LA volume and altered LA strain (≤ 23 %) improve prediction of new-onset AF in HCM patients and may therefore be preferred over LA diameter for risk stratification[69]. LA function correlated significantly with NYHA class and the severity of heart failure symptoms increased with the severity of LA dysfunction[67].

The LA plays an important role in maintaining LV filling and consequently LV stroke volume, especially when the LV is dysfunctional[70]. The enlargement of the LA and the increase in LA emptying fraction are adapatative responses to impaired LV diastolic function to maintain normal LV filling pressures[71]. LA remodeling predicts exercise capacity[72] and development of severe symptoms in HCM patients[73].

Our study adds to the evidence that impaired LA strain correlates with mortality (HR 0.86 CI [0.72-0.97], p=0.007) and is, in addition to LA enlargement[74,75] an independent predictor of HCM long term prognosis (HR 0.92 CI [0.87-0.97], p=0.001). The non-invasive assessment of LA deformation may add incremental information to predict HCM prognosis.

Limitations

This study has several limitations that should be mentioned. A larger cohort with longer follow-up is necessary to conclude with statistical significance on the primary end-point. In this single-center study, only echocardiographic equipment of GE was used; therefore, the results should be interpreted with caution when compared with other vendors as suggested previously[65]. The European Association of Cardiovascular Imaging and the American Society of Echocardiography recently set up a task force to evaluate the intervendor variability. From this evaluation, LV GLS showed a variability < 10% between different vendors, which is comparable to standard echocardiographic measurements currently used[76]. Standardization remains an issue dampening enthusiasm to the widespread clinical applicability of this technique[65]. Moreover, LA strain measurement was derived from the LV GLS 3-chamber point-and-click method which was not initially made for LA myocardial deformation study. Finally, data on LA strain validation is missing and as Maron M.S.[77] recently reported, strain measurement is not in place consistently in all echocardiographic laboratories. Validation and standardization are particularly important issues if we are going to promote cutoff values of LA and LV strain that could ultimately justify changes in HCM patient management, such as recommendations for primary prevention ICD.

Conclusions

This study suggests an additive prognostic value of an impaired LV GLS and LA strain, the presence of MR, and MRI LGE, to the classical ESC 7 recommended risk factors. Additional multicenter studies should be performed to propose modifications in ESC criteria.

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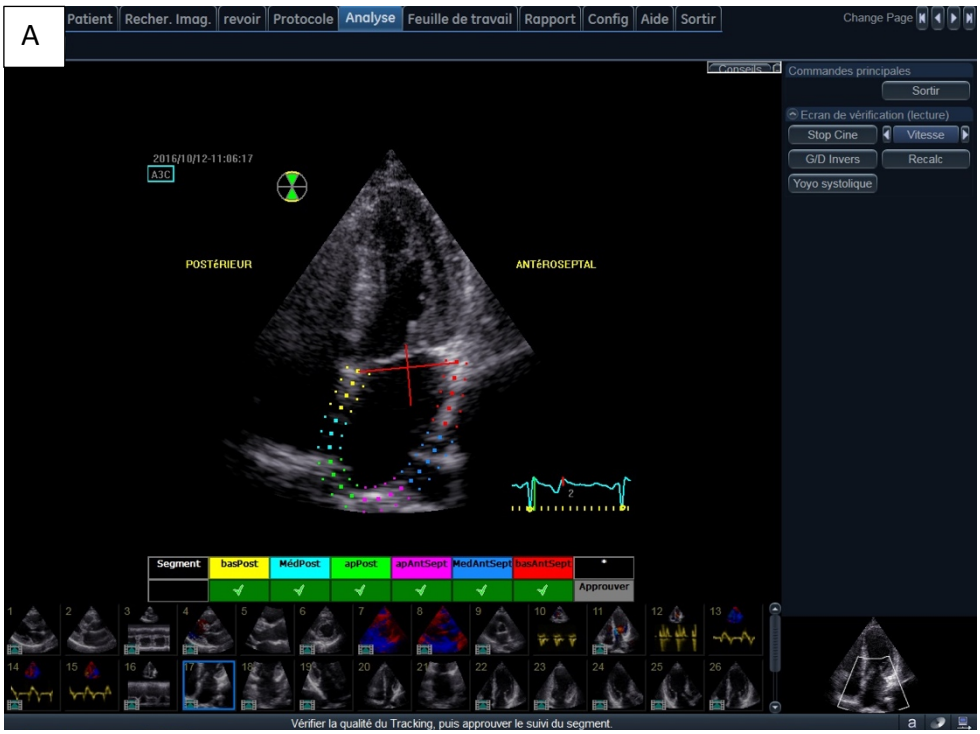
Figure 1. Two-dimensional echocardiographic assessment of left atrial myocardial deformation.
(A) On an apical four-chamber view, with initial onset in the ECG before P-wave the atrial endocardial border was manually traced by a point and-click approach. After automatic creation of a region of interest (ROI) divided in 6 subdivisions, segmental tracking quality was analyzed.
(B) After approval by the user, segmental longitudinal strain curves were generated. The dashed curve represented the average strain.



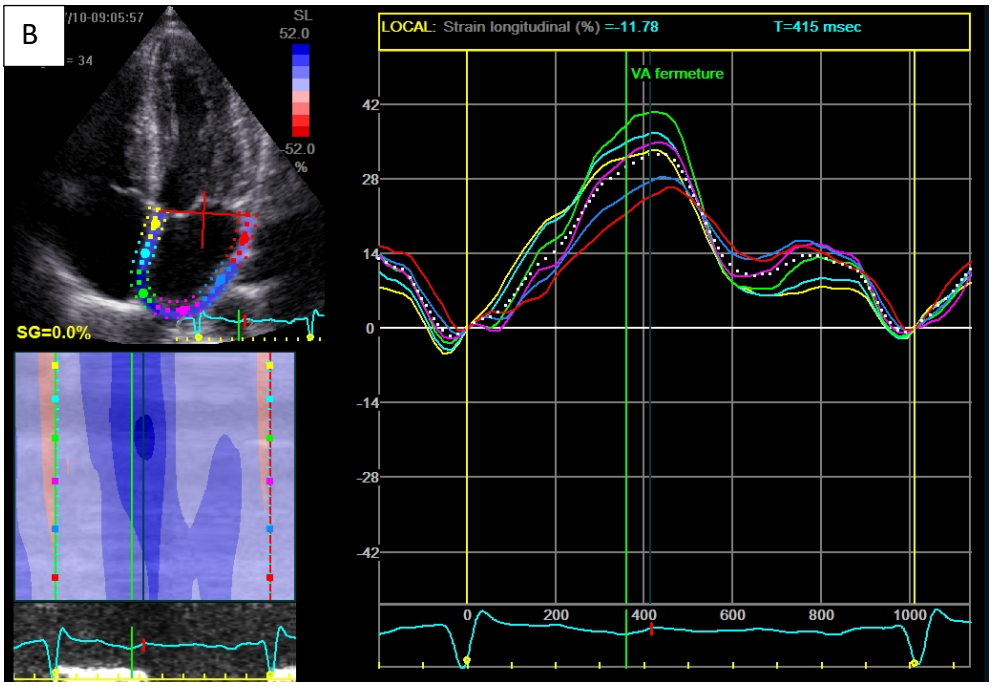


Figure 2. Four-chamber view showing measurement of Peak atrial longitudinal strain (PALS), Time to peak longitudinal strain (TPLS), Peak atrial contraction strain (PACS) and Time to peak contraction strain (TPCS). PALS resulted of maximal stretching of the left atrial during the reservoir phase and PACS resulted of contraction of the left atrial during the contraction phase. PALS and PACS are expressed in %, TPLS and TPCS in milliseconds.

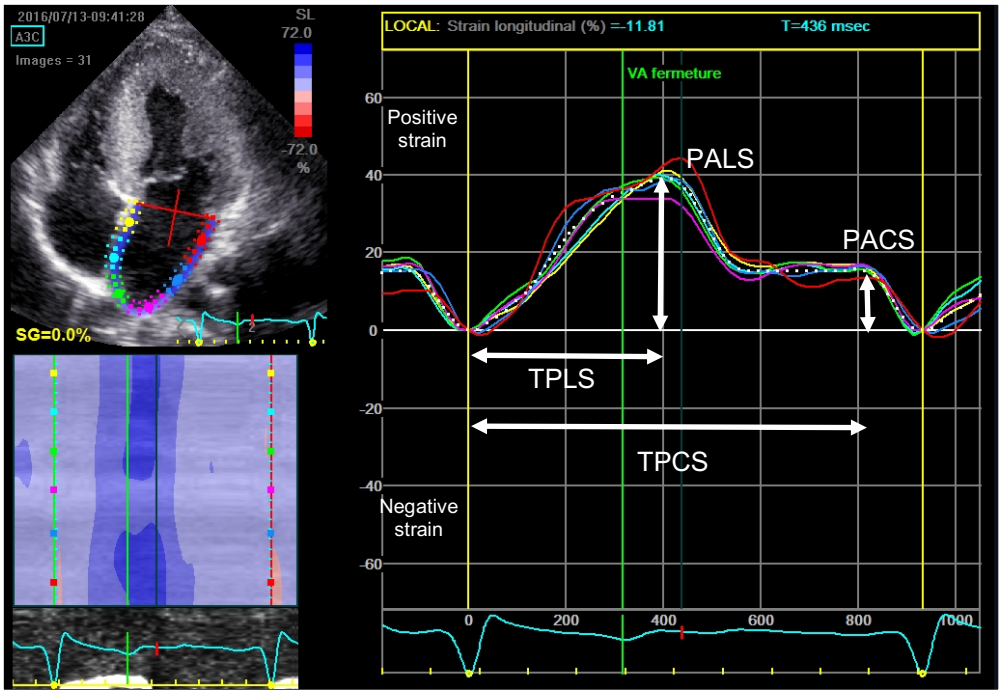


Figure 3. Four-chamber view showing left atrial strain waves. The positive left atrial peak strain rate S-wave (LASRs) evaluates left atrial reservoir function and the negative left atrial peak strain rate E-wave (LASRe) and A-wave (LASRa) the left atrial contractile function.

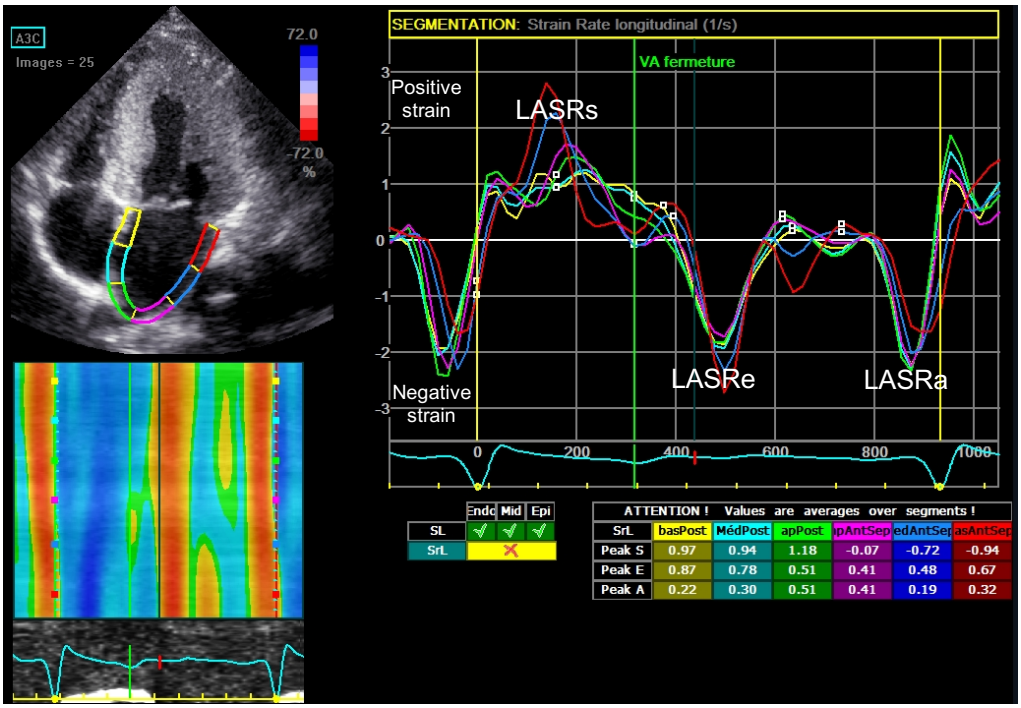


Table 1. Demographic, clinical features, echocardiographic and MRI parameters in 307 HCM patients.

Predictor variable	**Followed patients (n= 307)[a]**
Baseline characteristics	
Age, yrs	50 ± 17
Male, n (%)	202 (66)
Family History of SCD, n (%)	19 (6)
NYHA functional class, n (%)	
I	119 (39)
II	107 (35)
III	35 (11)
IV	0 (0)
Maximal LV thickness, mm	21 ± 5
LVEF, n (%)	67 ± 10
LA diameter, mm	41 ± 8
Left ventricular outflow gradient, mmHg	21 ± 32
Non-sustain ventricular tachycardia, n (%)	35 (11)
Unexplained syncope, n (%)	32 (10)
Atrial fibrillation, n (%)	36 (13)
HCM-associated gene identified, n (%)	63 (21)
BNP, ng/l	199 ± 278
BP ≥ 140/ 90mmHg, n (%)	72 (25)
Diabetes, n (%)	21 (7)
Dyslipidemia, n (%)	43 (15)
Tobacco, n (%)	67 (23)
Myocardial infarction, n (%)	2 (0.7)
ESC HCM risk score ≥ 4, n (%)	50 (16)
Echocardiographic parameters	
LA area, cm2	25 ± 8
LA volume, ml	94 ± 48
Interventricular septum, mm	19 ± 6
LV end-diastolic volume, ml	116 ± 43
LV end-systolic volume, ml	40 ± 26
LV global longitudinal strain, n (%)	-15 ± 4
Mitral E/A ratio	1.3 ± 0.7
Lateral E/E’	11 ± 6
Septal E/E’	16 ± 8
Elevated LV filling pressure, n (%)	39 (13)
Mitral regurgitation, n (%)	123 (47)
No MR	140 (45)
Mild MR	104 (33)
Moderate MR	16 (5)
Severe MR	3 (1)

LA strain four-chamber, n (%)	235 (77)
LA PALS*, n (%)	25 ± 14
LA TPLS‡, ms	434 ± 63
LA PACS^, n (%)	11 ± 7
LA TPCS◦, ms	867 ± 170
LASRs└, s^{-1}	1.7 ± 0.7
LASRe, s^{-1}	-1.5 ± 0.9
LASRa, s^{-1}	-1.9 ± 1
LA strain two-chamber, n (%)	235 (77)
LA PALS*, n (%)	23 ± 12
LA TPLS‡, ms	431 ± 67
LA PACS^, n (%)	12 ± 7
LA TPCS◦, ms	864 ± 171
LASRs└, s^{-1}	1.6 ± 0.6
LASRe, s^{-1}	-2 ± 1
LASRa, s^{-1}	-1.3 ± 0.7
MRI parameters, n (%)	230 (75)
Maximal LV thickness, mm	21 ± 6
LVEF, n (%)	67 ± 11
LV aneurysm, n (%)	4 (2)
LGE, n (%)	215 (93)
Presence of LGE	171 (80)
Mitral regurgitation, n (%)	50 (22)

Values are mean ± SD or n(%) as appropriate.

[a] Missing data in followed patients group: NYHA: 15%, genetic: 43%, BNP: 8%, LA area: 8%, LA volume:12%, blood pressure: 12%, LV diastolic function 28%, 4-chamber LA strain 23%, 2-chamber LA strain 56%, MRI examination 25%.

*PALS means Peak Atrial Longitudinal Strain and is a positive value measured in %

‡TPLS is the Time to Peak Longitudinal Strain, measured in ms

^PACS means Peak Atrial Contraction Strain, measured in %

◦TPCS means Time to Peak Contraction Strain, measured in ms

└LASR refers to the Left Atrial Strain Rate waves. Using the P-wave as the onset for deformation analysis, the S-wave (LASRs) referred as LA peak systolic strain rate determines the LA reservoir function and the A-wave (LASRa) and E-wave (LASRe) the LA contractile function.

LVEF indicates left ventricle ejection fraction; LA, left atrial; BP, blood pressure; LV, left ventricle; MR, mitral regurgitation; LGE, late gadolinium enhancement.

Table 2. Univariate predictors of HCM-mortality.

Predictor variable	SCD group characteristics (n= 6)[a]	Hazard ratio	95% confidence interval		p value
Baseline characteristics					
LVEF, n (%)	59 ± 17	0.91	0.83	0.99	0.0220
Non-sustain ventricular tachycardia, n (%)	3 (50)	6.97	1.48	32.88	0.0165
Unexplained syncope, n (%)	2 (33)	6.25	1.09	28.31	0.0415
Echocardiographic parameters					
LA area, cm2	34 ± 13	1.13	1.04	1.22	0.0040
LA volume, ml	142 ± 75	1.02	1.01	1.03	0.0026
Septal E/E'	17 ± 4	1.08	1.03	1.12	0.0069
Elevated LV filling pressure, n (%)	3 (50)	7.01	1.48	33.23	0.0164
Mitral regurgitation, n (%)	3 (50)				
Moderate MR	3 (100)	9.29	1.95	44.31	0.0071
LA strain four-chamber, n (%)	5 (83)				
LA PALS*, n (%)	11 ± 6	0.86	0.72	0.97	0.0073
MRI parameters, n (%)	4 (67)				
Maximal LV thickness, mm	31 ± 8	1.29	1.11	1.54	0.0011

Values are mean ± SD or n (%) as appropriate.
[a] Missing data in SCD group (LVEF: 15%, LA strain: 15%, Septal E/E': 15%and MRI examination: 30%)
*PALS means Peak Atrial Longitudinal Strain and is a positive value measured in %
LVEF indicates left ventricle ejection fraction; LA, left atrial; LV, left ventricle; MR, mitral regurgitation; LGE, late gadolinium enhancement.

Table 3. Univariate predictors of HCM-related events and mortality.

Predictor variable	Hazard ratio	95% confidence interval		p value
Baseline characteristics				
Age, yrs	1.00	0.98	1.01	0.5336
Male	0.70	0.43	1.15	0.1519
Family History of SCD	2.93	1.43	5.45	0.0048
NYHA functional class				
I	1			
II	2.18	1.12	4.46	0.0209
III	5.31	2.55	11.36	0.0001
IV				
Maximal LV thickness, mm	1.12	1.08	1.17	0.0001
LVEF, n (%)	0.96	0.93	0.98	0.0010
LA diameter, mm	1.06	1.03	1.09	0.0003
Left ventricular outflow gradient, mmHg	1.01	1.00	1.02	0.0031
Non-sustain ventricular tachycardia	2.99	1.72	4.99	0.0002
Unexplained syncope	3.72	2.07	6.37	0.0001
Atrial fibrillation	1.84	0.91	3.42	0.0863
HCM-associated gene identified	0.76	0.35	1.71	0.5028
BNP, ng/l	1.00	1.00	1.00	0.0001
BP ≥ 140/ 90mmHg	0.81	0.41	1.46	0.4884
Diabetes	0.92	0.25	2.37	0.8848
Dyslipidemia	1.54	0.77	2.85	0.2132
Tobacco	1.16	0.61	2.05	0.6387
Myocardial infarction	21.90	2.40	88.34	0.0123
ESC HCM risk score ≥ 4	4.90	3.00	7.95	0.0001
Echocardiographic parameters				
LA area, cm2	1.05	1.02	1.08	0.0005
LA volume, ml	1.01	1.01	1.01	0.0001
Interventricular septum, mm	1.08	1.04	1.11	0.0003
LV end-diastolic volume, ml	1.01	1.00	1.01	0.0658
LV end-systolic volume, ml	1.01	1.00	1.02	0.0054
LV global longitudinal strain	1.23	1.13	1.35	0.0001
Mitral E/A ratio	1.21	0.86	1.62	0.2519
Lateral E/E’	1.07	1.04	1.10	0.0003
Septal E/E’	1.05	1.03	1.07	0.0000
Elevated LV filling pressure	2.70	1.44	4.84	0.0026
Mitral regurgitation	1.96	1.12	3.53	0.0174
No MR				
Mild MR	1.71	0.94	3.16	0.0766
Moderate MR	3.16	1.19	7.36	0.0233
Severe MR	15.40	3.03	50.15	0.0033

LA strain four-chamber				
LA PALS*, n (%)	0.94	0.91	0.97	0.0001
LA TPLS‡, ms	1.01	1.00	1.01	0.0148
LA PACS^, n (%)	0.91	0.86	0.95	0.0001
LA TPCS◦, ms	1.00	1.00	1.00	0.7897
LASRs└, s^{-1}	0.46	0.28	0.72	0.0005
LASRe, s^{-1}	2.85	1.78	4.79	0.0001
LASRa, s^{-1}	2.08	1.49	2.98	0.0001
LA strain two-chamber				
LA PALS*, n (%)	0.93	0.89	0.96	0.0001
LA TPLS‡, ms	1.00	1.00	1.01	0.6895
LA PACS^, n (%)	0.89	0.83	0.94	0.0001
LA TPCS◦, ms	1.00	1.00	1.00	0.3708
LASRs└, s^{-1}	0.43	0.22	0.79	0.0065
LASRe, s^{-1}	1.88	1.25	2.89	0.0022
LASRa, s^{-1}	2.42	1.21	5.44	0.0105
MRI parameters				
Maximal LV thickness, mm	1.12	1.07	1.17	0.0001
LVEF	0.96	0.94	0.99	0.0116
LV aneurysm	0.82	0.09	3.13	0.8046
Presence of LGE	4.83	1.83	17.85	0.0006
Mitral regurgitation	2.24	1.21	4.09	0.0113

[a] Missing data in followed patients group: NYHA: 15%, genetic: 43%, BNP: 8%, LA area: 8%, LA volume:12%, blood pressure: 12%, LV diastolic function 28%, 4 chamber LA strain 23%, 2 chamber LA strain 56%, MRI examination 25%.

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‡TPLS is the Time to Peak Longitudinal Strain, measured in ms

^PACS means Peak Atrial Contraction Strain, measured in %

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└LASR refers to the Left Atrial Strain Rate waves. Using the P-wave as the onset for deformation analysis, the S-wave (LASRs) referred as LA peak systolic strain rate determines the LA reservoir function and the A-wave (LASRa) and E-wave (LASRe) the LA contractile function.

LVEF indicates left ventricle ejection fraction; LA, left atrial; BP, blood pressure; LV, left ventricle; MR, mitral regurgitation; LGE, late gadolinium enhancement.

Table 4. Univariate and multivariate predictors of HCM-related events and mortality.

Predictor variable	Univariate					Multivariate	
	Followed patients (n= 307)[a]	Hazard ratio	95% confidence interval		p value	Hazard Ratio (95% CI)	p value
Baseline characteristics							
Family History of SCD, n (%)	19 (6)	2.93	1.43	5.45	0.0048		
NYHA functional class, n (%)							
I	119 (39)	1					
II	107 (35)	2.18	1.12	4.46	0.0209		
III	35 (11)	5.31	2.55	11.36	0.0001		
IV	0 (0)						
Maximal LV thickness, mm	21 ± 5	1.12	1.08	1.17	0.0001	1.07 (0.99-1.16)	0.0886
LVEF, n (%)	67 ± 10	0.96	0.93	0.98	0.0010		
LA diameter, mm	41 ± 8	1.06	1.03	1.09	0.0003		
Left ventricular outflow gradient, mmHg	21 ± 32	1.01	1.00	1.02	0.0031		
Non-sustain ventricular tachycardia, n (%)	35 (11)	2.99	1.72	4.99	0.0002		
Unexplained syncope, n (%)	32 (10)	3.72	2.07	6.37	0.0001		
Myocardial infarction, n (%)	2 (0.7)	21.90	2.40	88.34	0.0123		
Echocardiographic parameters							
LA area, cm2	25 ± 8	1.05	1.02	1.08	0.0005		
LA volume, ml	94 ± 48	1.01	1.01	1.01	0.0001	1.01 (1.00-1.02)	0.2237
Interventricular septum, mm	19 ± 6	1.08	1.04	1.11	0.0003		
LV global longitudinal strain, n (%)	-15 ± 4	1.23	1.13	1.35	0.0001	1.03 (0.90-1.18)	0.6301
Lateral E/E’	11 ± 6	1.07	1.04	1.10	0.0003		
Septal E/E’	16 ± 8	1.05	1.03	1.07	0.0001		
Elevated LV filling pressure, n (%)	39 (13)	2.70	1.44	4.84	0.0026		
Mitral regurgitation, n (%)	123 (47)	1.96	1.12	3.53	0.0174	2.68 (0.91-9.32)	0.0745
Moderate MR	16 (5)	3.16	1.19	7.36	0.0233		
Severe MR	3 (1)	15.40	3.03	50.15	0.0033		

LA strain four-chamber, n (%)	235 (77)						
LA PALS*, n (%)	25 ± 14	0.94	0.91	0.97	0.0001	0.92 (0.87-0.97)	0.0015
LA TPLS+, ms	11 ± 7	0.91	0.86	0.95	0.0001		
LA PACS^, n (%)	1.7 ± 0.7	0.46	0.28	0.72	0.0005		
LA TPCS°, ms	-1.5 ± 0.9	2.85	1.78	4.79	0.0001		
LASRs└, s^{-1}	-1.9 ± 1	2.08	1.49	2.98	0.0001		
LA strain two-chamber, n (%)	135 (44)						
LA PALS*, n (%)	23 ± 12	0.93	0.89	0.96	0.0001		
LA TPLS+, ms	12 ± 7	0.89	0.83	0.94	0.0001		
LA PACS^, n (%)	1.6 ± 0.6	0.43	0.22	0.79	0.0065		
LA TPCS°, ms	-2 ± 1	1.88	1.25	2.89	0.0022		
LASRs└, s^{-1}	-1.3 ± 0.7	2.42	1.21	5.44	0.0105		
MRI parameters							
Maximal LV thickness, mm	21 ± 6	1.12	1.07	1.17	0.0001		
LVEF, n (%)	67 ± 11	0.96	0.94	0.99	0.0116		
Presence of LGE, n (%)	171/215 (80)	4.83	1.83	17.85	0.0006		
Mitral regurgitation, n (%)	50 (15)	2.24	1.21	4.09	0.0113		

Values are mean ± SD or n (%) as appropriate.

[a] Missing data in followed patients group: NYHA: 15%, genetic: 43%, BNP: 8%, LA area: 8%, LA volume:12%, blood pressure: 12%, LV diastolic function 28%, 4 chamber LA strain 23%, 2 chamber LA strain 56%, MRI examination 25%.

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