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DOCTORAL SCHOOL
GENERAL MEDICINE

COMPLEX ELECTROCARDIOGRAPHIC AND IMAGING ANALYSIS TO IDENTIFY PREDICTORS FOR ATRIAL FIBRILLATION AND MALIGNANT VENTRICULAR ARRHYTHMIAS IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY

PhD THESIS SUMMARY

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SUMMARY

ABBREVIATIONS

HCM = hypertrophic cardiomyopathy

SCD = sudden cardiac death

IC = heart failure

AF = atrial fibrillation

CMR = cardiac magnetic resonance

Na = sodium

K = potasium

Ca = calcium

SVT = sustained ventricular tachycardia

NSVT = non-sustained ventricular tachycardia

LV = left ventricle

LA = left atrium

ECG = electrocardiogram

NYHA = New York Heart Association

ICD = internal cardioverter-defibrillator

HR = hazard ratio

QTc= corrected QT interval

QTcd = QTc interval dispersion

Tpe = T Wave peak to end interval

Tped= Tpe interval dispersion

LVH = left ventricular hypertrophy

LGE = late gadolinium enhancement

QRSdur= QRS duration

QRSd = dispersion of QRS duration

EF = ejection fraction

RV = right ventricle

MD = mechanical dispersion

STE= speckle-tracking

GLS = global longitudinal strain

RA = right atrium

Pd = P wave dispersion

Pdur max/min = maximal/minimum duration of the P wave

Pamp = P wave amplitude as defined in the methods section

HT = systemic hypertension

DM= diabetes mellitus

LAD(i) = left atrial anteroposterior diameter (indexed)

LAV(i) = left atrial maximal volume (indexed)

LAε = left atrial global longitudinal strain

SSr = left atrial systolic strain rate

ESr= left atrial protodiastolic strain rate

ASr= left atrial telediastolic strain rate

VTI = velocity-time integral

NNT = number needed to treat

TA = arterial tension

LV/RV MWT = maximal wall thickness of the left/right ventricle

BNP = brain natriuretic peptide

BSA = body surface area

BMI = body mass index

FPS = frame per second

FELA = global ejection fraction of the left atrium (%)

LAPI = left atrium performance index

LVOT = left ventricular outflow tract

ROI = region of interest

TAPSE = tricuspid annulus plane systolic excursion

FAC = fractional area change (%)

MR = mitral regurgitation

LVTDVi = indexed left ventricular telediastolic volume

LVTSVi = indexed left ventricular systolic volume

PAPs = pulmonary artery systolic pressure

Sb = sensibility

Sp = specificity

VPN = positive predictive value

VPP = negative predictive value

LBBB = left bundle branch block

RBBB = right bundle branch block

IVS = interventricular septum

PW = posterior wall of the left ventricle

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common pathology with genetic substrate involving the myocardium, determined by polygenic, autosomal dominant transmission, and is characterized by heterogeneous phenotypic expression as a common result of the multitude of genetic mutations and incomplete penetrance, having as a final pathophysiological element the presence of ventricular hypertrophy in the absence of obvious secondary causes (defined as a wall thickness of 15 mm or 13-14 mm but with positive genotype or a history of HCM in first-degree relatives) [1].

The current concept of the disease regards HCM as a primary impairment of the sarcomere/Z disk/calcium-regulating proteins – with over 1400 described genetic mutations [2,3], having as final pathophysiological elements myocytic disorganization, ventricular hypertrophy, myocardial fibrosis and thickening of the media of the small intramural arteries, leading to reduced flow reserve [4]. The consequence of these changes is the increased morbidity and mortality compared to the general population though evolution towards heart failure (HF), thromboembolism, cardiac arrhythmias and sudden death, secondary to the myopathic process involving the ventricular and atrial myocardium [4-6].

Of the possible complications, sudden cardiac death (SCD) – defined as unexpected, nonviolent and non-traumatic death (within 1 hours from the onset of symptoms) due to cardiac causes – is the most formidable, with an annual incidence of 1-2% – among the main causes being thromboembolism (consequence of atrial fibrillation), HF (asystole/electromechanical dissociation) and fatal arrhythmias (most commonly ventricular fibrillation, rarely supraventricular tachyarrhythmias with circulatory collapse) [7-9]. In addition, most cases of SCD are found in young patients, and HCM remains the leading cause of death among athletes [10]. With the advent of the internal defibrillator as an effective therapeutic method in the prevention of sudden death, there is also a pressing need to identify as accurately as possible the patients at risk who could benefit from this therapy.

The estimation of the risk of sudden death in primary prevention in patients with HCM is based mainly on the use of a prediction model recommended by the European Guide (HCM risk-SCD) based on the use of 7 parameters, estimating and stratifying the risk over a period of 5 years [11-12]. Although the performance of this prediction algorithm is superior to previous

models [11], there are a number of drawbacks of this model derived from the way data was collected in the study that validated the algorithm and from omitting clear predictors of sudden death. In addition, even in the intermediate-low-risk subgroup, the probability of SCD remains significantly higher than in the general population (4%/5 years vs. 0,5%/5 years), especially if we take into account that these events mainly affect young patients [11,13,14].

The prevalence of atrial fibrillation (AF) is significantly higher in patients with HCM versus the general population (and is possibly underrated) – up to 20-30% versus 1% [14], with negative implications through worsening of HF and thromboembolic events [12,13].

In these circumstances, it is necessary to assess additional electrical and imaging parameters that allow for a better stratification of the risk of atrial fibrillation (through its negative impact on morbidity and mortality) and of SCD/ventricular arrhythmias (VA) in patients with HCM, especially those at intermediate or intermediate-low risk, where the additional benefit of these parameters could be greatest in the closer follow-up of these patients and in the optimal therapeutic decision-making.

PREMISES

ECG and echocardiographic parameters associated with the risk of atrial fibrillation in patients with CMH

There is a close link between structural, functional and electrical remodeling of the left atrium (LA) and risk of AF, and patients with HCM have an increased risk of AF through the direct atrial myopathy process and also through the negative impact that diastolic dysfunction has on the LA [15-17].

Most studies have assessed the link between structural remodeling of LA and the risk of AF, but a significant percentage of patients with HCM without significant as dilation (LAD<45 mm), however, develop lifelong AF, suggesting that LAD (although easy to measure and reproducible) is not sensitive enough to detect early atrial remodeling and, implicitly, to detect patients at risk of AF [11, 18].

Regarding the study of the LA function, there are currently data on the alteration of the reservoir function and the pump function and the increase in the risk of AF. The link between the conduct function and AF or the pump function estimated by the STE method (which has

the advantage of independence from hemodynamic conditions compared to volumetric methods) and AF [18-20] has not been evaluated.

The electrical remodeling of LA analyzed by simple parameters on surface ECG is less studied. There are limited data from small, retrospective studies that showed a correlation between P-wave parameters (Pd, Pdur max) and AF risk, but patients who developed persistent AF/permanent AF were excluded and the link between electrical and functional/structural remodeling was not analyzed [21,22]. Also, the role of the right atrium (RA) in the genesis of AF is insufficiently studied [23,24].

Given the adverse clinical impact of AF (thromboembolic risk, risk of IC), especially if it remains undetected [25,26], it is important to identify new predictive parameters of AF with increased sensitivity, especially in patients with HCM considered at intermediate-low risk (those with LAD<45 mm), which still poses a significantly higher risk than the general population.

ECG and echocardiographic parameters associated with the risk of ventricular arrhythmia and sudden death in patients with CMH

The substrate of ventricular arrhythmias in CMH patients is represented by both anatomical changes [27,28] and functional and electrical changes (alteration of intracellular Ca/Na currents) [29,30]. Most studies focused on the detection of clinical and structural risk factors associated with ventricular arrhythmias (age, history of sudden death/syncope, MWT LV, presence of LGE in MRI/apical aneurysm of LV, LAD, LVOT gradient) [10-13,31], while the link between the parameters revealing electrical remodeling and ventricular arrhythmias is less studied.

There are a number of simple and reproducible ECG parameters that are influenced by proarrhythmic potential electrical remodeling (QTc interval, QTcd, TpTe, TpTed, QRSdur interval, QRSd)[32-36]. There are small, retrospective studies for some of them that have shown a correlation with ventricular arrhythmias, while the link to arrhythmia risk in CMH patients has not been studied for the majority.

The mechanical dispersion measured by the STE reflects contractile heterogeneity, and in patients with HCM is influenced by both anatomical remodeling and electrical remodeling [37]. There are studies that have shown the link between increased LV MD (left ventricular

mechanical dispersion) and risk of NSVT (non-sustained ventricular tachycardia), but the direct relationship between LV MD and risk of SVT (sustained ventricular tachycardia)/SCD remains under-studied [38,39]. At the same time, there is no data in the literature on the link between DMVS and the electrical remodeling detected by the ECG parameters.

Whereas the risk of SCD due to malignant ventricular arrhythmias is increased compared to the general population even in patients with HCM who are classified as intermediate-low or low risk according to the current guidelines, and classical risk factors have a reduced individual positive predictive value, the detection of new independent predictors of ventricular arrhythmias could refine the arrhythmia risk analysis and, implicitly, improve the prognosis of these patients.

HYPOTHESIS

Based on the above assumptions, the hypothesis of the first study was that structural, electrical and functional remodeling of LA is common in patients with HCM compared to the general population and patients with HCM and AF show a more pronounced remodeling of LA and, as in the first study, ventricular structural and electrical remodeling is common in patients with HCM compared to the general population, and patients with HCM and ventricular arrhythmias have greater ventricular electrical and structural remodeling than those without VAs.

STUDY OBJECTIVES

The relationship between electrical, structural and functional remodeling of LA and AF

Primary objectives

•Study of electrical, structural and functional LA remodeling (by evaluating the ECG parameters of the P-wave, LA diameter and volume, LA function parameters through volumetric and STE-type techniques) inn patients with HCM

• Study of the relationship between LA remodeling and the presence of AF in HCM patients – determination of independent electrical and echographic predictors of AF in these patients

Secondary objectives

• Determination of independent predictors of AF in HCM patients with low/intermediate risk of AF (with LAD<45 mm)

• Correlation between the parameters of LA electrical remodeling and the LA parameters of structure and function

The relationship between electrical, structural and functional ventricular remodeling and VAs (SVT/NSVT)

Primary objectives

•Study of parameters reflecting HCM electrical/structural remodeling associated with risk of ventricular arrhythmias and SCD – ECG parameters (PD, QT interval, QTcd, TPE, Tped, QRSdur, QRSd) and echographic parameters (LV MD, RV MD)

• Study of the relationship between these parameters and the risk of ventricular arrhythmias/SCD – determination of new AV correlates in HCM patients

Secondary objectives

• Determination of new independent correlates of ventricular arrhythmias in patients <60 years

• The correlation between ECG and echographic parameters reflecting ventricular remodeling

METHODS

Patients aged 18 years and older who presented themselves at the Emergency Institute for Cardiovascular diseases "Prof. Dr. C. C. Iliescu" Bucharest diagnosed with HCM according to the current guidelines, were enrolled consecutively if they met the eligibility criteria for inclusion in the study. They were investigated clinically, biologically, ECG/Holter ECG and by echocardiography according to study protocol. The control group consisted of subjects who were free from cardiovascular pathology following clinical, biological, electrocardiographic and echocardiographic evaluation and who were not undergoing cardiological treatment. I have excluded patients with a history of documented myocardial infarction/unstable angina, cardiac surgery/valvular prosthesis/plasty, moderate/severe renal/hepatic impairment, uncontrolled dysthyroidias, active neoplastic disease, permanent atrial fibrillation, Grade II or III

atrioventricular block, preexcitation, permanent paced rhythm, ECG/echocardiography not suitable for the analysis of the studied parameters, significant valvular stenoses, significant valvular regurgitation (except mitral regurgitation due to characteristic valvular apparatus abnormalities found in HCM), wall motion abnormalities/systolic LV dysfunction, severe pulmonary hypertension of a cause other than that secondary to left heart disease.

A follow-up record was made for each patient, including relevant medical and personal history, anthropometric data (age, height, weight, body surface area –BSA, body mass index – BMI), cardiovascular risk factors, symptoms at enrollment and symptom progression at each assessment, clinical cardiovascular examination data, cardiac treatment.

Of the 234 patients with HCM initially evaluated, 126 patients were included in the first study, who were then prospectively followed for a median duration of 56 months (7-124 months). Of these, 39 patients had an incident AF. Subgroup analysis was also performed for patients with LAD<45 mm (72 patients), with 16 patients in this subgroup developing incident AF during follow-up.

The final population of the second study was comprised from 131 patients with HCM. Ventricular arrhythmias (SVT, NSVT) were observed during a median follow-up of 56 months (7-124 months). Thirty patients had NSVT and 6 patients had SVT. Subgroup analysis was performed in 75 patients under 60 years of age. Of these, 25 had ventricular arrhythmias during follow-up.

The control group consisted of subjects who were free from cardiovascular pathology following clinical, biological, electrocardiographic and echocardiographic evaluation and who were not undergoing cardiological treatment.

The comparative analysis of the two groups was carried out in terms of the followed electrocardiographic and echocardiographic parameters – the parameters related to electrical remodeling as well as those of left atrium and ventricular structure and function. In the group of patients with HCM, the relationship between these parameters and the risk of AF, ventricular arrhythmias and HF was studied, according to the methodology described for each sub study within the doctoral paper.

Electrocardiographic study

All patients were evaluated by standard 12-lead electrocardiogram (0.5-150 Hz filter, 50 Hz AC filter), synchronously recorded, performed at 25 mm/s scroll speed, in supine position at rest for at least 15 minutes before recording (changes to decubitus may influence Pb) - on which we analyzed the rhythm, morphology of QRS complexes (presence of criteria of ventricular hypertrophy, fragmentation of QRS complex, exclusion of hypo voltage leads) and the presence of atrio-ventricular or intraventricular conduction abnormalities.

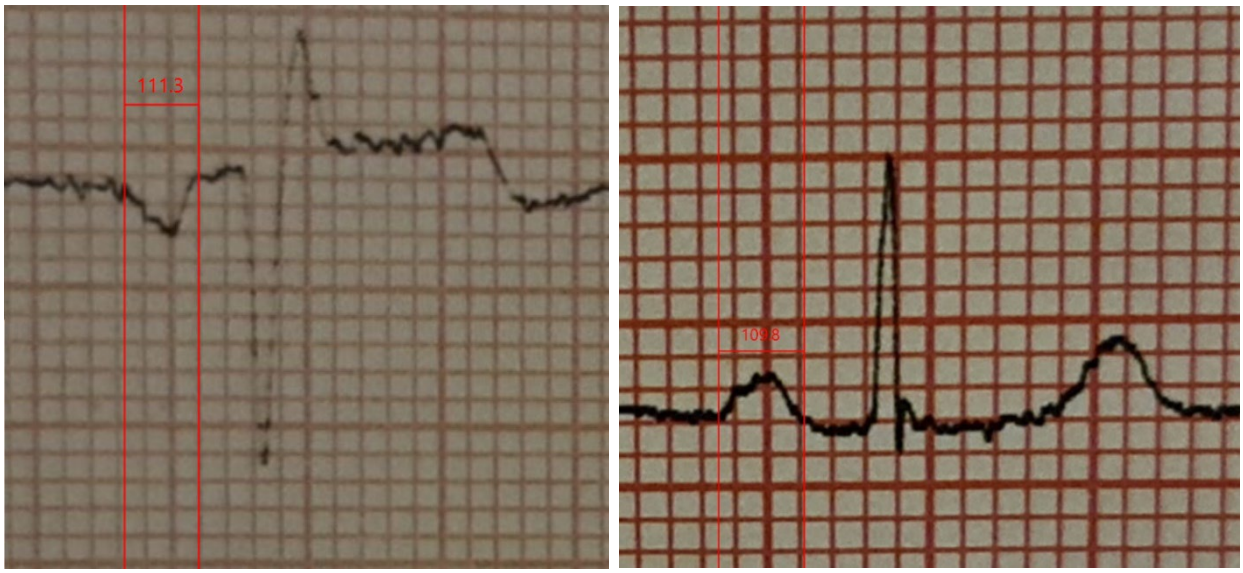

Figure 1. Calculation of the P-wave duration in the aVR lead (left) – approximate value 110 ms, respectively in the DII lead (right) – approximate value also 110 ms.

The acquired waveforms were scanned and stored digitally to facilitate manual analysis of P-wave, QRS complex and QT interval parameters. The measurements were made electronically on the magnified waveforms using a digital compass/ruler (EP caliper, version 2.6, EP Studios). The duration of the P-wave was calculated in each lead – represented by the time expressed in milliseconds (ms) from the beginning to the end of the P-wave (defined by the junction between the isoelectric line and the deflection corresponding to the P-wave – Fig. 1) [40,41]. The calculated values were expressed approximately from 5 ms to 5 ms (with extra rounding for values greater than 2,5 ms and less for values less than 2,5 ms). Pd was defined as the absolute difference between P dur max and P durum min of the measured values,

expressed in ms [40,41]. The maximum P-wave amplitude in the DII was calculated (for bifid P-waves encountered in atrial blocks or atrial conduction delays the highest amplitude component was used) and the absolute maximum amplitude of the respective negative component of the positive component of the P-wave in V1, all relative to the baseline. The Pamp parameter was defined as the sum of the maximum absolute values of the P-wave components in V1 and the maximum amplitude of the P-wave in DII, expressed in mV.

The duration of the QRS complex was measured from the onset of the q/Q or R/R wave to the end of the s/S wave in each lead [42]. We determined the q/R/s wave from the baseline if there was a difference of amplitude >50% from the variations in the amplitude of the baseline. QRSmax is the maximum value of the QRS complex duration between the measured values. We defined QRSd as the difference between QRSmax and the minimum QRS complex time value in the 12-lead, expressed in ms [43,44].].

The tangent method was used to measure the end of the T-wave, which is currently the most widely used method for the calculation of the QT interval [32,45]. Thus, the end of the T-wave is defined as the intersection of the tangent to the descending slope of the T-wave and the isoelectric line. The QT interval was calculated as the time elapsed from the start of the QRS complex to the end of the T-wave QT interval correction based on heart rate was made using the Bazett method. Tpe is the time from the peak of the T-wave (defined as the maximum of positive or negative deflection of the T-wave) to the end of the T-wave and corresponds electrically to the vulnerable period of ventricular repolarization. QTc was measured in all 12 leads and Tpe was measured in the precordial leads. Both QT dispersion and Tpe dispersion were calculated as the difference between the maximum and minimum value obtained from the heart rate-corrected interval measurements [32,45].

Echocardiographic study

Patients enrolled in the study were comprehensively evaluated by echocardiography at the EUROECOLAB Laboratory. The standard echocardiographic evaluation protocol recommended by the European Association of Echocardiography (AEE) was used, with image optimization for optimal acquisition by adjusting the frequency of the ultrasound probe, and gain, focus, size and depth of the sector of interest [46]. In addition, separate ECG-guided acquisitions (three consecutive cardiac cycles) were made in expiratory apnea for the proper

analysis of STE longitudinal deformation using the second harmonic for an optimal two-dimensional image with a frame rate of at least 50 FPS (ideal 60-100 FPS) [47]. In order to achieve optimum frame speed, the sector size and depth have been reduced to the minimum necessary to cover the area of interest [47].

Thus, for the analysis of the longitudinal deformation of the LV and LV MD, we acquired apical images centered on the LV (4, 3 and 2 chambers respectively) and the acquisition from apical section (4 chambers modified section, LA-centered) was used for longitudinal deformation of the LA. For the analysis of longitudinal deformation of the right ventricle (RV) and MD RV, the 4 chambers modified apical section (as recommended by the European guide for RV measurement) centered on RV [48] was used.

Echocardiographic acquisitions were analyzed off-line using special software (EchoPAC PC version 201; GE Medical systems, Milwaukee, Wi).

The echocardiographic protocol used was identical for HCM patients and control subjects.

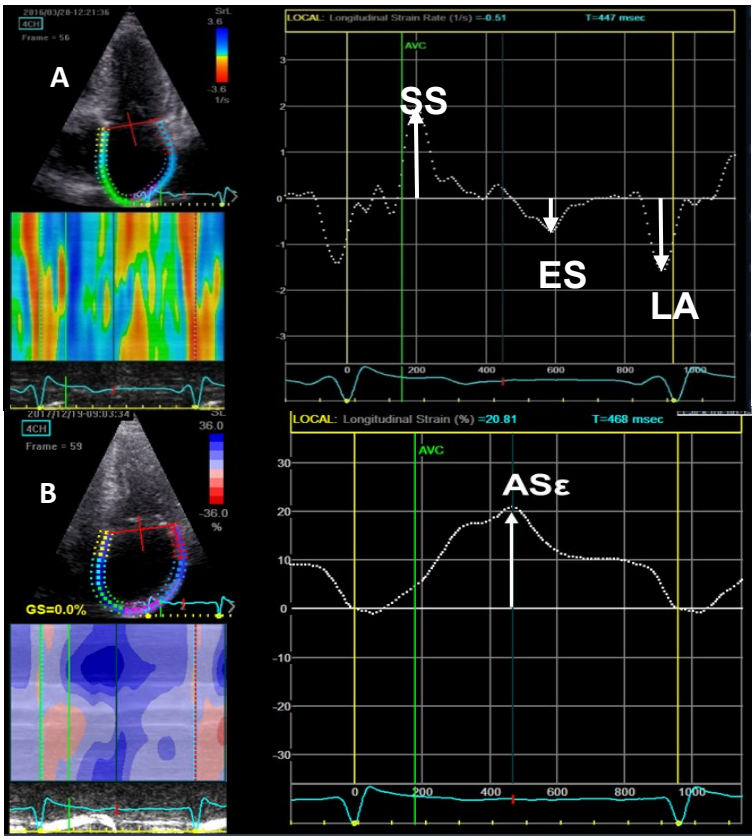

Figure 2. Analysis of longitudinal deformation of LA by the STE method - apical section 4 chambers. A. The mean myocardial deformation rate curve allows the assessment of the reservoir, conduct and pump function of the LA. **B.** The ASε calculation allows the assessment of the LA reservoir function.

Longitudinal deformation analysis of LA using the STE method was used to assess the phasic functions of LA. Image acquisition was performed in 4-chamber apical section, evaluating only part of the atrial wall. The measured parameters were expressed as the mean of the deformation/ deformation rate of 6 atrial segments. The reservoir function was expressed through LAε (LA strain) and SSr, the conduit function through ESr and the booster pump function through ASr.

For all patients for whom the image acquisition was suitable for STE, analysis of longitudinal systolic LV deformation for each myocardial segment was performed [49]. Similar to the assessment of the LV, the overall longitudinal deformation of the RV was analyzed by STE.

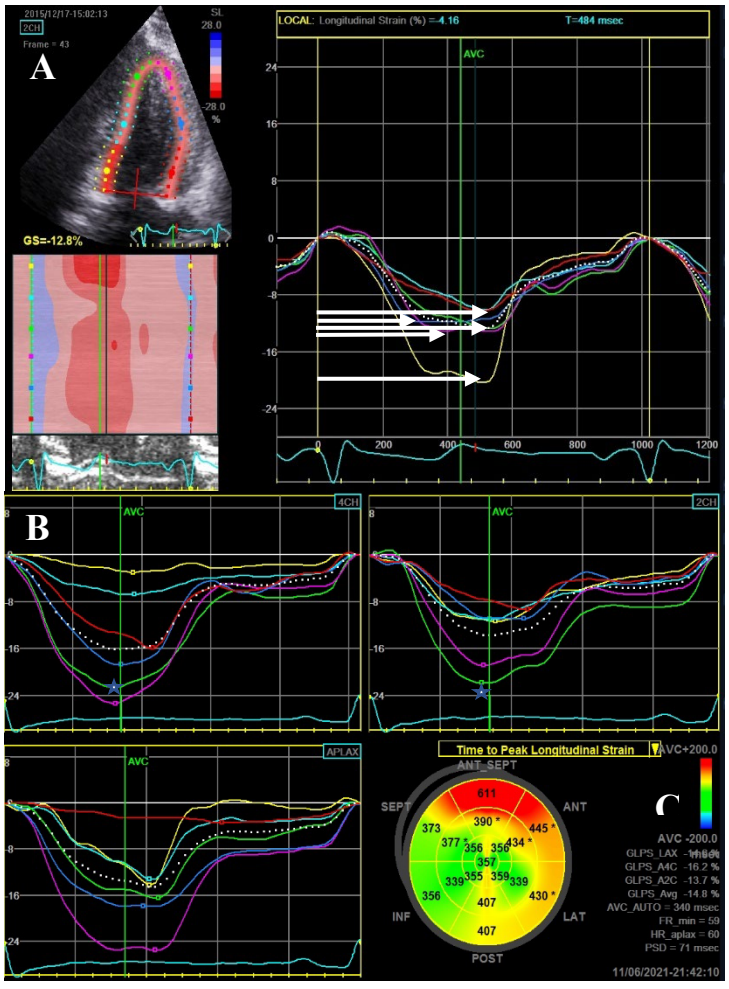

Figure 3 — calculation of mechanical dispersion of LV (MD LV). A. Method of calculating the time from the onset of the QRS complex (yellow line) to the peak of the negative maximal longitudinal deformation of each myocardial segment (represented by the white arrow). **B.** Automatic calculation of MD LV – the peak of the maximum negative longitudinal deformation is represented by a square in the analysis program (blue star) at the level of each deformation curve – it can be adjusted manually if its automatic placement is erroneous. The Bull's eye (**C**) image shows the time from the start of the QRS complex to this peak. The LV MD value calculated in this case is 71 Ms.

For the calculation of MD, the time from the onset of the QRS complex (onset of q/R wave) to the maximum negative peak of longitudinal deformation for each myocardial segment was measured, whether it is post systolic or not [39]. Segments that did not show an obvious negative peak on the longitudinal deformation curve were excluded from the analysis. MD has been defined as the standard deviation of these times in all myocardial segments analyzed by the classical (fixed ROI) analysis of GLS (Fig. 3). No MD was calculated if deformation times for more than 3 myocardial segments could not be calculated [39].

RESULTS

1. Study of the relationship between left atrial remodeling and the presence of atrial fibrillation in patients with HCM

General population

Patients who developed AF during follow-up were older (p=0,002), with more HF symptoms (p=0,008) and more likely to have HF worsening (p=0,001) and an increase in BNP (p=0,004). The severity of HT has also been linked to the risk of AF (p=0,007). Patients who developed AF during follow-up had higher Pd and Pdur max values, with reduced Pamp values (P<0,001 for all). Also, echographic parameters evaluating structural remodeling showed a significant increase in the size of LA (p=0,009 for LADi and p<0,001 for LAVi)

with a significant impairment of LA function in patients with AF (p<0,001 for ASR, LA strain, p=0,001 for LA emptying fraction and LA performance Index) — Table 1.

Table 1. ECG and echocardiographic characteristics in patients with HCM, and in patients with and without atrial fibrillation (AF)

	Study group (N=126)	**HCM patients with AF (N=39)**	**HCM patients without AF (N=87)**	**p**
ECG parameters				
PD (ms)	**42±16,4**	**57±17,4**	**35,1±10,1**	**<0,001**
Pdur max (ms)	**107,3±16**	**118,4±18,7**	**102,3±11,7**	**<0,001**
Pamp (mV)	**0,24±0,11**	**0,19±0,05**	**0,26±0,13**	**<0,001**
Echocardiographic parameters				
LV parameters				
LV MWT (mm)	20,9±5,1	20±4	21,3±5,6	0,186
LV indexed mass(g/m^2)	170,6±63,2	182,8±62,2	165,1±63,3	0,137
LV EF (%)	67,5±6,8	67,1±6	67,7±7,2	0,671
Mean E/e'	18,4±8,2	19,6±8,7	17,8±8	0,258
LV GLS (%)	-14±3,5	-13,7±3,8	-14,2±3,3	0,513
LVTDVi (ml/m^2)	42,8±12,3	44,2±16,7	42,2±9,8	0,486
LVTSVi (ml/m^2)	13,9±5,4	14,6±6,5	13,6±4,7	0,293
Diastolic dysfunction (Grade 1/2/3) n(%)	40/70/16 31,7/55,5/12,7%	9/22/8 23/56,4/20, 5%	31/48/8 35,6/55,17/9,1%	0,281
LA parameters				
LADi (mm/m^2)	**24,1±3,5**	**25,3±3,1**	**23,6±3,5**	**0,009**
LAVi (ml/m^2)	**62,2±25,6**	**77,6±31,9**	**55,2±18,5**	**<0,001**
LA strain (%)	**16,6±7,2**	**12,6±6**	**18,4±6,9**	**<0,001**

LA SSR (s^{-1})	**0,84±0,43**	**0.65±0.47**	**0.92±0.37**	**<0,001**
LA ESr (s^{-1})	-0,67±0,33	-0,58±0,29	-0,71±0,34	0,053
LA ASr (s^{-1})	**-0,96±0,52**	**0,65±0,47**	**0,92±0,37**	**<0,001**
LA emptying fraction (%)	**0,44±0,15**	**0,36±0,12**	**0,48±0,14**	**0,001**
LA performance index (%)	**0,11±0,16**	**0,03±0,07**	**0,14±0,18**	**0,001**
RV parameters				
MWT (mm)	6,2±1,7	6,2±1,8	6,2±1,6	0,906
TAPSE (mm)	23,3±3,6	22,9±3,9	23,4±3,5	0,437
RV strain (%)	-20,1±4,9	-19,1±5	-20,4±4,8	0,211
FAC (%)	51±8,1	51,2±7,1	50,9±8,4	0,865
RA parameters				
RA mediolateral diameter (mm)	36,4±6,1	37,1±7,8	36±5,1	0,426
sPAP (mmHG)	36,7±11,4	38,29±9,1	36±12,2	0,339
Resting LVOT gradient (mmHg)	**45±42,5**	**58,6±45,9**	**38,8±39,6**	**0,013**
Maximal LVOT gradient (mmHg)	**57,2±45,5**	**72,9±44,2**	**50,3±44,6**	**0,01**
MR severity (degree 1/2/3/4,%)	**54/40/28/1 42,8/31,7/22,2/0,8%**	**9/14/15/0 23/35/38,5 /0%**	**45/26/13/1 51,7/29,9/14,9/1,1%**	**0,023**

Pd= P-wave dispersion; Pdur max= maximum P-wave duration; Pamp= sum of the maximum P-wave amplitude in lead V1 and DII; LV=left ventricle, MWT=maximum wall thickness; EF=ejection fraction; GLS=global longitudinal deformation; LADI=indexed anteroposterior diameter of the left atrium; LVTDVI= left ventricular indexed telediastolic volume; LVTSVi = left ventricular indexed telesystolic volume; LAVi=the maximal indexed volume of the left atrium; LA strain= left atrial systolic longitudinal deformation (%); LA= left atrium; ; LA SSR= the rate of left atrial systolic longitudinal deformation; LA ESR= the rate of left atrium protodiastolic longitudinal deformation; AS ASR, the rate of telediastolic longitudinal deformation of the left atrium during atrial contraction; VD= right ventricle; TAPSE, systolic excursion of the tricuspid ring plane; FAC=fractional area change; sPAP=estimated pulmonary arterial systolic pressure; LVOT=left ventricular outflow tract; MR= mitral regurgitation.

Patients with LAD<45 mm

The prevalence of AF in this group was 22,2% (16 patients had an incident AF episode during follow-up, accounting for about 41% of all AF events in the general population with CMH) – significantly higher compared to the general population. This suggests the need for better predictors for AF in patients who are supposed to be at low risk, where active AF screening is not recommended. In the LAD < 45 mm group, those who had AF during follow-up were older (p=0,024) with a higher degree of hypertension severity (p=0,041) and were more likely to have a worsening in HF symptoms (p=0,001) compared to those without AF. All ECG parameters were changed in patients who experienced an incident AF episode during follow-up with Pd and P max prolongation (p<0,001 and p=0,001, respectively) and Pamp reduction (p=0,028). Of the LA structure and function parameters the only ones that were statistically different between patients with and without AF were LA dimensions (LADi, p=0,009 and LAVi, p<0,001), LA strain (p=0,004) and LA SSR (p=0,009). At the same time, the prevalence of rest/exercise obstruction in LVOT was higher in patients who developed AF (p=0,024) – Table 2.

Table 2. ECG and echocardiographic characteristics in patients with LAD<45 mm with and without atrial fibrillation (AF)

	HCM patients with LAD<45 mm and AF (N=16)	**HCM patients with LAD<45 mm without AF (N=56)**	**p**
ECG characteristics			
PD (ms)	**58,2±16,2**	**34,4±10,5**	**<0,001**
Pdur MAX (ms)	**114,4±11,1**	**101,5±11,6**	**0,001**
Pamp (mV)	**0,19±0,06**	**0,25±0,10**	**0,028**
Echographic parameters			

LV parameters			
LV MWT (mm)	18,8±3,3	21,2±5,2	0,075
LV mass index (g/m2)	169,9±42	157,6±52,5	0,380
LV EF (%)	68,9±4,9	69±7,4	0,990
Mean E/e'	21,7±8,5	18,6±9	0,226
LV GLS (%)	-14,8±3,3	-14,3±3,1	0,608
LVTDVi (ml/m2)	38,4±7	40,4±9,7	0,442
LVTSVi (ml/m2)	12±2,5	12,4±4,4	0,750
Diastolic dysfunction	4/9/3	23/26/6	0,453
(Degree 1/2/3) n(%)	25/56,2/18,7%	41/46,4/10,7%	
LA parameters			
LADi (mm/m2)	**24±2,4**	**22,5±2,7**	**0,040**
LAVi (ml/m2)	**65,3±12,8**	**49,6±15,5**	**0,001**
LA Strain (%)	**13,2±7,2**	**19,3±7,4**	**0,004**
LA SSR (s-1)	**0,68±0,52**	**1±0,38**	**0,009**
LA ESr (s-1)	-0,58±0,32	-0,71±0,34	0,170
LA ASr (s-1)	-0,85±0,35	-1,15±0,57	0,059
La emptying fraction (%)	**0,39±0,12**	**0,49±0,15**	**0,011**
LA performance index (%)	**0,05±0,09**	**0,16±0,19**	**0,003**
RV parameters			
MWT (mm)	6,2±2,1	5,9±1,5	0,604
TAPSE (mm)	22,5±3,4	23±3,6	0,588

RV strain (%)	-20,3±5,6	-20,7±4,6	0,774
FAC (%)	52,5±7,07	51,7±8,8	0,737
RA parameters			
RA mediolateral diameter (mm)	35,3±6,4	34,5±4,3	0,623
sPAP (mmHg)	34,5±4,3	36±13,7	0,989
Resting LVOT gradient (mmHg)	**62,4±44,4**	**36,8±39,6**	**0,026**
Maximal LVOT gradient (mmHg)	**78±45,4**	**47,5±46,9**	**0,024**
MR severity (Degree 1/2/3/4, n,%)	7/3/6 43,7/18,7/37,5%	31/16/6 55,3/28,5/10,7%	0,113

Pd= P-wave dispersion; Pdur max= maximum P-wave duration; Pamp= sum of the maximum P-wave amplitude in lead V1 and DII; LV=left ventricle, MWT=maximum wall thickness; EF=ejection fraction; GLS=global longitudinal deformation; LADI=indexed anteroposterior diameter of the left atrium; LVTDVI= left ventricular indexed telediastolic volume; LVTSVi = left ventricular indexed telesystolic volume; LAVi=the maximal indexed volume of the left atrium; LA strain= left atrial systolic longitudinal deformation (%); LA= left atrium; ; LA SSR= the rate of left atrial systolic longitudinal deformation; LA ESR= the rate of left atrium protodiastolic longitudinal deformation; AS ASR, the rate of telediastolic longitudinal deformation of the left atrium during atrial contraction; VD= right ventricle; TAPSE, systolic excursion of the tricuspid ring plane; FAC=fractional area change; sPAP=estimated pulmonary arterial systolic pressure; LVOT=left ventricular outflow tract; MR= mitral regurgitation.

AF predictors in the general HCM population

After performing univariate Cox regression, age, severity of hypertension, Pd, Pdur max, Pamp, LADI, LADi, ASr, LA strain, LVOT resting gradient and the severity of mitral regurgitation resulted as independent predictors for incident AF – Table 3.

Table 3. Independent predictors for incident AF in the general study population with HCM

	Univariate Cox regression			Multivariate Cox regression
	HR	**95% CI**	**p**	**p value**
Age	**1,032**	**1,010-1,055**	**0,003**	
HT (1/2/3)	**1,585**	**1,233-2,054**	**<0,001**	
Nyha Class			0,110	
Pd*	**1,044**	**1,029-1,058**	**<0,001**	**0,001**
Pdur MAX*	**1,037**	**1,021-1,053**	**<0,001**	
Pamp **	10^{-4}	10^{-4}-0,025	**<0,001**	
LADi	**1,122**	**1,032-1,220**	**0,011**	
LAVi	**1,024**	**1,013-1,036**	**<0,001**	0,287
LA Strain	**0,897**	**0,853-0,944**	**<0,001**	
LA ASr (s-1)	**4,244**	**1,847-9,751**	**<0,001**	**0,038**
Resting LVOT gradient	**1,009**	**1,001-1,016**	**0,022**	
Maximal LVOT gradient	*1,007*	*1-1,014*	**0,050**	
MR severity (Grad 1/2/3/4)	**1,604**	**1,131-2,277**	**0,008**	

*HT= Systemic hypertension; PD= P-wave dispersion; Pdur max=P-wave maximum duration; Pamp=sum of maximum amplitudes in DII, V1 leads; LADi—indexed anteroposterior diameter; LAVi = LA indexed maximal volume; LA = left atrium; ASR=telediastolic longitudinal myocardial deformation rate during left atrium contraction; LVOT – left ventricular outflow tract; MR – mitral regurgitation; *HR for each 1 Ms increase. ** HR for each increase in amplitude by 1 mV*

In order to compare the accuracy of the different independent LA parameters in patients with HCM, the ROC analysis was performed and the corresponding AUC values were calculated (Fig. 4).

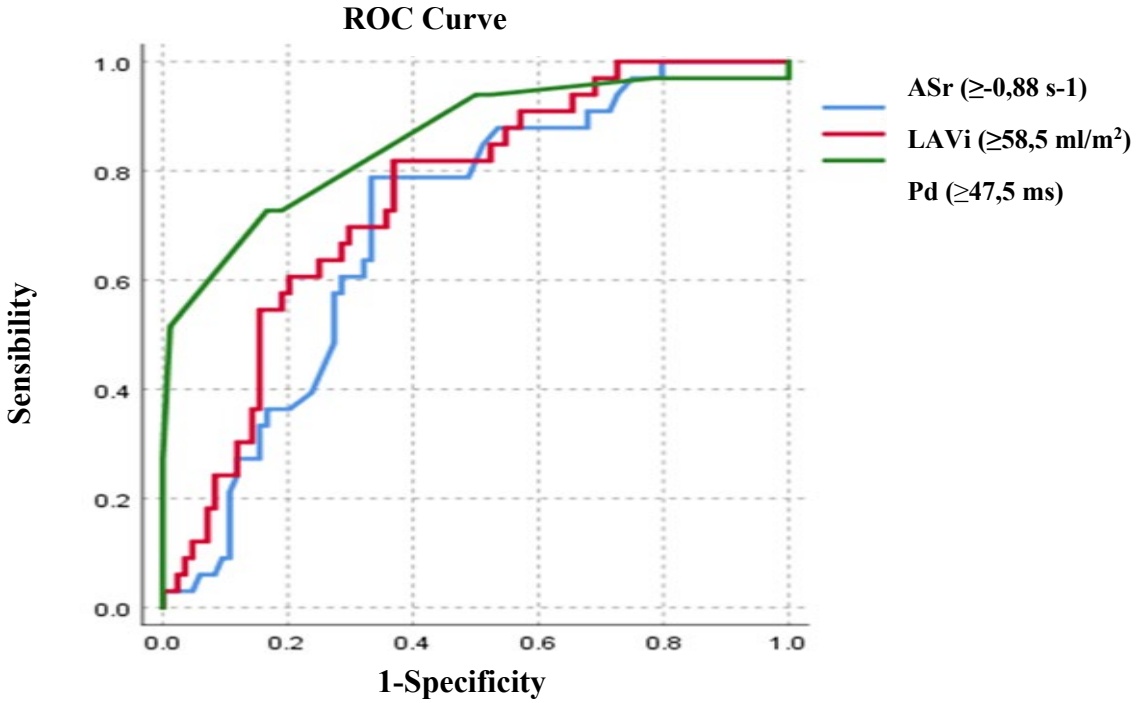

Figure 4 – ROC analysis and area under the curve (AUC) for incident AF in the overall study population: Best accuracy is observed for PD (AUC=0.86), LAVi (AUC=0.76) and ASR (AUC=0.7), respectively, and threshold values for optimal sensitivity and specificity.

Atrial fibrillation predictors in patients with LAD<45 mm

After performing univariate Cox regression, age, severity of hypertension, Pd, Pdur max, LADI, LAVi, LA strain and resting LVOT gradient resulted as independent predictors for incident AF in this subgroup of patients (Table 4). Age, PD, LAVi, LVOT resting gradient and degree of hypertension (categorical variable) were included in the multivariate analysis. Following the multivariate Cox analysis, the only predictor of incident AF in patients with LAD<45 mm was Pd (HR=1.105, 95% CI 1,059-1,154, p=0,002), independent of age, LAVi, LA strain or LVOT rest gradient (Table 4), with good predictive accuracy following ROC analysis, with a similar threshold value greater than 47,5 ms (Fig. 5).

Table 4. Independent predictors for incident AF in patients with HCM and LAD<45 mm

	Univariate Cox regression			**Multivariate Cox regression**	
	HR	**95% CI**	**p**	**P value**	

Age	**1,041**	**1,004-1,079**	**0,031**	
HT (1/2/3)	**1,772**	**1,153-2,725**	**0,009**	
PD*	**1,105**	**1,059-1,154**	**<0,001**	**0,002**
Pdur MAX*	**1,061**	**1,012-1,112**	**0,013**	
Pamp			*0,054*	
LADi	**1,211**	**1,019-1,439**	**0,030**	
LAVi	**1,047**	**1,018-1,077**	**0,001**	
LA Strain	**0.910**	**0.845-0.981**	**0,013**	
Resting LVOT gradient	**1.000**	**1.000-1.022**	**0,051**	
Maximal LVOT gradient			0,061	

*HT= Systemic hypertension; PD= P-wave dispersion; Pdur max=maximum P-wave duration; Pamp=sum of maximum amplitudes in DII, V1 leads; LADI—indexed anteroposterior diameter; LAVi = LA maximum indexed volume; LA= left atrium; LVOT—left ventricular outflow tract; *HR for each increase by 1 Ms.*

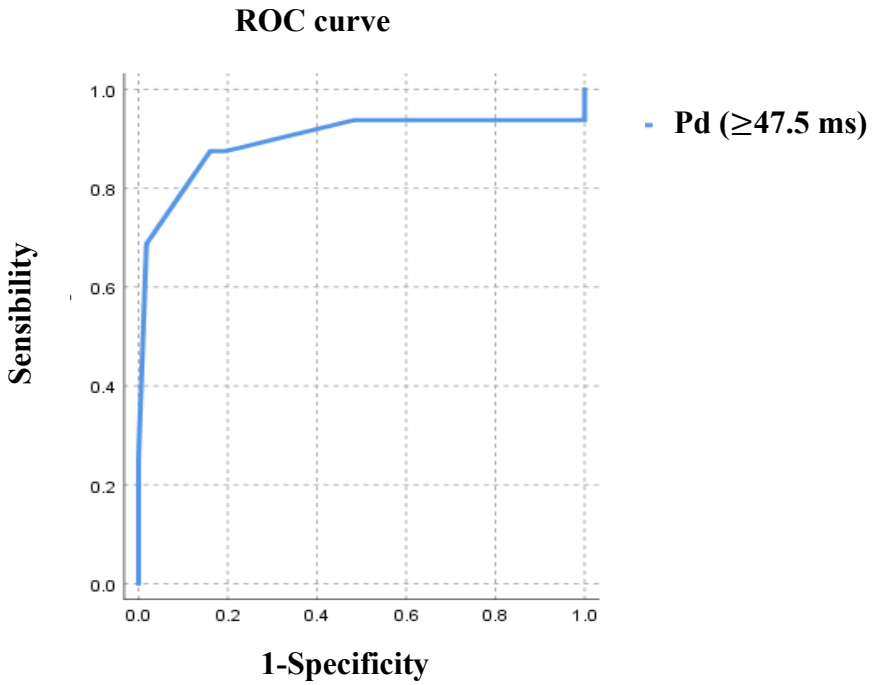

Figure 5. ROC analysis for predictive PD accuracy in patients with HCM and anteroposterior LA diameter<45 mm (AUC=0.89).

2. Study of the relationship between electrical and structural remodeling of the ventricles and the presence of ventricular arrhythmias in HCM patients

General population

Patients with ventricular arrhythmias (VAs) were younger (p=0,026) – similar to other studies, had a higher SCD risk score (p=0,001) and consequently were more likely to carry an internal defibrillator (p=0,001).

Patients without ventricular arrhythmias had more frequent cardiovascular risk factors – hypertension (p=0,012), dyslipidemia (p=0,017), diabetes mellitus (p=0,042), probably because their age was significantly higher than those with ventricular arrhythmias. VAs patients had higher TPE, Tped and TPE/QTc ratio (p=0,001 for all), longer QRS complex duration (p=0,037) and greater QRS complex dispersion (p=0,001) than patients without VAs during follow-up -Table 5.

Table 5. Electrocardiographic characteristics in HCM patients with and without VAs

	HCM population (N=131)	**HCM pts without VAs (N=95)**	**HCM pts with VAs (N=36)**	**p**
QTc (ms)	455,35±32,29	452,37±31,11	463,22±34,42	0,086
QTcd (ms)	57,89±23,7	56,74±22,73	60,94±26,18	0,366
Tpe (ms)	**104,16±20,59**	**99,74±17,66**	**115,83±23,34**	**0,001**
Tped (ms)	**29,58±17,77**	**24,04±12,68**	**44,03±20,97**	**0,001**
Tpe/QTc	**0,228±0,038**	**0,22±0,034**	**0,24±0,041**	**0,001**
QRSdur (ms)	**107,13±21,46**	**104,71±20,85**	**113,44±22,03**	**0,037**
QRSd* (ms)	**21,39±10,5**	**18,75±8,99**	**29,03±10,98**	**0,001**
Wide QRS, n(%)	21(16,2%)	13(13,8%)	8(22,2%)	0,245
LBBB, n(%)	9(6,9%)	6(6,3%)	3(8,3%)	0,684
RBBB, n(%)	11(8,4%)	6(6,3%)	5(13,9%)	0,163

VAs=ventricular arrhythmias; QTc= corrected QT interval; QTcd = corrected QT interval dispersion; TPE = time of the end portion of the T-wave (T-wave peak-end); Tped = dispersion of the end portion of the T-wave;

TPE/QTc = ratio of the end portion of the T-wave to the corrected QT interval; QRSdur = QRS complex duration; QRSd = QRS complex dispersion; LBBB = left bundle branch block; RBBB = right bundle branch block.*

** - Were calculated/reported only in patients with narrow QRS complex (no intraventricular conduction disorders).*

Echocardiographic parameters evaluating LV global longitudinal deformation and LV MD were different between VA and non-VA patients – thus VA patients had greater LV longitudinal dysfunction (p=0,001) and higher LV MD (p=0,044). The presence of RV free-wall hypertrophy, RV free-wall maximal thickness, RV global longitudinal deformation and RV MD were significantly different between VA and VA-free patients, the former having higher RV free-wall thickness (p=0,003), the alteration of RV global longitudinal deformation (p=0,008 for GLS RV and p=0,011 for RV free wall GLS) and higher RV free wall MD values (p=0,016) - Table 6.

Table 6. Echocardiographic features in HCM patients with and without AV

	HCM study group (N=131)	**HCM pts without VAs (N=95)**	**HCM pts with VAs (N=36)**	**p**
LV parameters				
LV MWT (mm)	**20,7±4,6**	**20±4,3**	**22,3±4,8**	**0,02**
LV mass index (g/m^2)	170,7±63,3	167,2±66,3	179,8±54,1	0,310
LV EF (%)	67,5±6,9	67,8±6,9	66,7±6,6	0,393
Septal S (cm/s)	5,7±1,5	5,8±1,5	5,3±1,4	0,062
Lateral S(cm/s)	5,5±2,4	5,6±2,6	5,1±1,6	0,334
Mean E/E'	18,4±8,3	18,6±8,3	18±8,3	0,743
LV MD (ms) *	**73,9±31,3**	**70,3±26,9**	**84,1±40,2**	**0,044**
LVTDVi (ml/m^2)	42,9±12,4	42,6±12,6	43,4±11,9	0,736
LVTSVi (ml/m^2)	13,9±5,4	13,6±5,3	14,7±5,6	0,291
LV GLS (%)	**-14,2±3,6**	**-14,9±3,5**	**-12,5±3,3**	**0,001**

Diastolic dysfunction (degree 1/2/3, %)	41/71/17 31,3/54,2/13%	33/53/8 34,7/55,8/8,4%	8/18/9 22,2/50/25%	0,057
LA parameters				
LADi (mm/m^2)	43,9±5,4	43,5±5,2	45,3±5,7	0,085
LAVi (ml/m^2)	24,2±3,5	24±3,5	24,5±3,5	0,504
LA Strain (%)	16,6±7,2	17,2±7,2	15±7	0,132
RV parameters				
RV MWT (mm)	**6,2±1,7**	**5,9±1,5**	**6,9±2,1**	**0,003**
RV S (cm/s)	13,2±2,7	13,5±2,9	12,8±2,4	0,210
TAPSE (mm)	23,3±3,7	23,5±3,5	22,9±4,1	0,439
RV GLS (%)	**-20,1±4,9**	**-20,9±5,1**	**-18,2±3,9**	**0,008**
RV free wall GLS (%)	**-26±6,5**	**-27,1±6,1**	**-23,7±7**	**0,011**
RV-RA Gradient (mmHg)	31±11	31,3±12	30,3±8,1	0,675
FAC (%)	51±8,1	51±8,6	51±6,8	0,974
RV diameter (mm)	30,5±4	30,2±4	31,2±4,1	0,213
RV MD (ms) *	30,5±4,0	30,2±4	31,2±4,1	0,213
Free wall MD (ms) *	**36,8±28**	**32,8±23,7**	**47,5±25,8**	**0,016**
RV free wall hypertrophy (%)	**14,3±16**	**11,2±9,9**	**23,4±24,9**	**0,001**
RA parameters				
RAD (mm)	36,4±6,2	37,2±7,9	36,1±5,2	0,426
sPAP (mmHg)	36,7±11,4	36,9±12,3	36,4±9,3	0,834
Resting LVOT gradient (mmHg)	45,1±42,5	49,1±44,2	34,5±36,4	0,080

Maximal LVOT gradient (mmHg)	57,2±45,6	61,6±46,9	45,1±39,7	0,074
MR severity (Degree 1/2/3/4) (%)	56/40/28/1 42,7/30,5/21,4/0,8 %	42/28/20/1 44,2/29,5/21,1/1,1%	14/12/8/0 38,9/33,3/22,2/0%	0,939

VA = ventricular arrhythmias; LV EF = left ventricular ejection fraction (Simpson biplane); LV MD = left ventricular mechanical dispersion; LV GLS = left ventricular overall longitudinal deformation; LVTDVi = left ventricular telediastolic indexed volume; LVTSVi = left ventricular telesyistolic indexed volume; LADi = indexed anteroposterior diameter of the left atrium; LAVi = indexed maximal volume of the left atrium; LA strain = global longitudinal deformation of the left atrium; RV = right ventricle; RV MWT =right ventricular maximum free wall thickness ; TAPSE = systolic excursion of the tricuspid annulus plane; RV GLS = global longitudinal deformation of the right ventricle; RV free wall GLS = global longitudinal deformation of the free wall of the right ventricle; FAC = fractional area change; RV MD = mechanical dispersion of the right ventricle; Free wall MD = mechanical dispersion of the free wall of the right ventricle; RAD = mediolateral diameter of the right atrium; sPAP = estimated pulmonary arterial systolic pressure; LVOT = left ventricular outflow tract; SAM = anterior systolic movement of the mitral valve

** only for patients with narrow QRS*

Patients under 60 years of age

As with patients in the general group, VA patients had a higher SCD risk score (0,001) and were therefore more likely to carry an internal defibrillator (p=0,001).

Patients without ventricular arrhythmias had more frequent cardiovascular risk factors – hypertension (p=0,033), dyslipidemia (p=0,008), smoking (p=0,030).

VA patients had longer QTc (p=0,005), TPE, Tped and TPE/QTc ratio (p=0,001 for all), longer QRS complex duration (p=0,011) and greater QRS complex dispersion (p=0,004) than patients without VAs during follow-up. Patients with a history of VA also had a wider QRS complex more frequently (p=0,001) and the presence of LBBB was more common in patients with VA (p=0,001) – Table 7.

Table 7. Electrocardiographic characteristics in CMH patients < 60 years of age with and without AV

	HCM patients, age<60 years, without VAs (N=50)	**HCM patients, age<60 years, with VAs (N=25)**	**p**
QTc (ms)	443,37±25,88	458,6±32,04	0,051
QTcd (ms)	**51,1±20,9**	**69,75±28,77**	**0,005**
Tpe (ms)	**95,61±16,78**	**113,25±21,54**	**<0,001**
Tped (ms)	**20,61±8,82**	**47,75±17,95**	**<0,001**
Tpe/QTc	0,22±0,04	0,25±0,04	**0,004**
QRSdur (ms)	96,78±10,19	101,8±10,29	0,077
QRSd* (ms)	**17,32±6,36**	**31,15±10,14**	**0,004**
Wide QRS, (%)	8(16%)	5(20%)	0,754

VA=ventricular arrhythmias; QTc= corrected QT interval; QTcd = corrected QT interval dispersion; TPE = duration of the end portion of the T-wave (T-wave peak-end); Tped = dispersion of the end portion of the T-wave; TPE/QTc = ratio of the end portion of the T-wave to the corrected QT interval; QRSdur = QRS complex duration; QRSd = QRS complex dispersion;*

** Were calculated/reported only in patients with narrow QRS complex (no intraventricular conduction disorders).*

Of the echocardiographic parameters evaluating myocardial LV deformation, only LV MD was different between the two groups, with higher values in VA patients (p=0,029). RV global longitudinal deformation and RV MD were significantly different between VA and non-VA patients, the former having significant alteration in RV global longitudinal deformation (p=0,009 for GLS RV and p=0,014 for free wall GLS RV) and higher values of RV MD and free wall VD MD (p=0,037 and p=0,01 respectively) - Table 8.

Table 8. Echocardiographic characteristics in patients with HCM, with and without VA and age<60 years

	HCM patients, age<60 years, without VAs (N=50)	**HCM patients, age<60 years, with VAs (N=25)**	**p**
LV parameters			
LV MWT (mm)	20,8±4,8	23±5,1	0,130
LV mass index (g/m2)	165,1±72,1	176,9±54,1	0,518
LV EF (%)	68,7±7,2	68,2±6,4	0,825
Septal S (cm/s)	6,2±1,5	5,6±1,5	0,126
Lateral S(cm/s)	5,8±2,8	5,4±1,8	0,591
Mean E/E'	17,1±7,5	15,2±7,4	0,375
LV MD (ms) *	**65,4±23,8**	**85,2±45,7**	**0,029**
LVTDVi (ml/m^2)	44,8±12,6	45,2±13,5	0,898
LVTSVi (ml/m^2)	14,3±6,2	14,9±6,1	0,704
LV GLS (%)	-14,9±3,3	-13.7±3.1	0,086
Diastolic dysfunction (degree 1/2/3, %)	13/30/7 26%/60%/14%	3/11/11 12%/44%/44%	0,091
LA parameters			
LADi (mm/m2)	43,3±5,3	44,1±6,2	0,588
LAVi (ml/m2)	23,2±2,8	24,7±4,1	0,110
LA Strain (%)	20,2±6,9	17,4±6,5	0,139
RV parameters			
RV MWT (mm)	5,8±1,5	6,3±1,8	0,283
RV S (cm/s)	13,5±2,7	13,1±2,5	0,576
TAPSE (mm)	24,5±3,4	24,8±3,7	0,757
RV GLS (%)	**-22,3±4,8**	**-18,9±3,8**	**0,009**
RV free wall GLS (%)	**-29,1±6,1**	**-24,1±8,2**	**0,014**
RV-RA Gradient (mmHg)	29,5±8,3	29±9,1	0,850

FAC (%)	52,8±8,8	52,9±6,3	0,954
RV diameter (mm)	31,3±4,1	31,7±4	0,730
RV MD (ms) *	**34,1±23,5**	**51,4±3,9**	**0,037**
Free wall MD (ms) *	**11,2±9,2**	**22,8±24,5**	**0,010**
RV free wall hypertrophy (%)	23(46,3%)	13(52%)	0,525
RA parameters			
RAD (mm)	37,8±5,3	37,1±5,5	0,647
sPAP (mmHg)	35,1±8,5	34,9±10,1	0,942
Resting LVOT gradient (mmHg)	45,8±41,6	33,6±38	0,273
Maximal LVOT gradient (mmHg)	61,1±45,8	43,8±42,3	0,166
MR severity (Degree 1/2/3/4) (%)	24/12/9/1 48%/24%/18/2%	13/5/3/0 52%/20%/12%/0%	0,845

VA = ventricular arrhythmias; LV EF = left ventricular ejection fraction (Simpson biplane); LV MD = left ventricular mechanical dispersion; LV GLS = left ventricular overall longitudinal deformation; LVTDVi = left ventricular telediastolic indexed volume; LVTSVi = left ventricular telesyistolic indexed volume; LADi = indexed anteroposterior diameter of the left atrium; LAVi = indexed maximal volume of the left atrium; LA strain = global longitudinal deformation of the left atrium; RV = right ventricle; RV MWT =right ventricular maximum free wall thickness ; TAPSE = systolic excursion of the tricuspid annulus plane; RV GLS = global longitudinal deformation of the right ventricle; RV free wall GLS = global longitudinal deformation of the free wall of the right ventricle; FAC = fractional area change; RV MD = mechanical dispersion of the right ventricle; Free wall MD = mechanical dispersion of the free wall of the right ventricle; RAD = mediolateral diameter of the right atrium; sPAP = estimated pulmonary arterial systolic pressure; LVOT = left ventricular outflow tract; SAM = anterior systolic movement of the mitral valve

** only for patients with narrow QRS*

Ventricular arrhythmias correlates in the general population

After univariate logistic regression, the correlates for VA in the overall study population were age, TPE, Tped, TPE/QTc, QRSdur, QRSd, RV MD of free wall, GLS LV, GLS RV, GLS free wall VD, RV MWT and LV MWT — Table 9.

Table 9. Independent correlates for VA in the overall study population with CMH

	Univariate logistic analysis			Multivariable analysis
	HR	95% CI	p	P value
Age	**0,968**	**0,922-0,997**	**0,029**	
Tpe	**1,032**	**1,013-1,051**	**<0,001**	
Tped	**1,078**	**1,015-1,144**	**<0,001**	**<0,001**
Tpe/QTc	**1,673**	**1,75-1,59**	**<0,001**	
QRSdur	**1,018**	**1,001-1,036**	**0,018**	
QRSd*	**1,105**	**1,052-1,161**	**<0,001**	**0,002**
*LV MD**			*0,194*	
RV free wall MD*	**1,044**	**1,013-1,077**	**0,006**	
RV MD*	**1,018**	**1,003-1,034**	**0,022**	
LV GLS	**1,227**	**1,086-1,386**	**0,001**	
RV GLS	**1,129**	**1,030-1,238**	**0,010**	**0,021**
RV free wall GLS	**1,089**	**1,015-1,169**	**0,018**	
LV MWT	**1,109**	**1,019-1,206**	**0,016**	
RV MWT	**1,399**	**1,114-1,756**	**0,008**	

VA=ventricular arrhythmias; TPE= duration of the end portion of the T-wave (T-wave peak-end); Tped = dispersion of the end portion of the T-wave; TPE/QTc = ratio of the end portion of the T-wave to the corrected QT interval; QRSdur = duration of the QRS complex; QRSd = dispersion of the QRS complex; LV MD= mechanical dispersion of the left ventricle; MD of the RV free wall = mechanical dispersion of the free wall of the right ventricle; LV GLS = global longitudinal deformation of the left ventricle; RV GLS = global longitudinal deformation of the right ventricle; RV free wall GLS = global longitudinal deformation of the free wall of the right*

*ventricle; RV MWT = maximum right ventricular free wall thickness ; LV MWT = left ventricular maximum wall thickness..*Calculated only for patients with narrow QRS complex*

In order to compare the accuracy of different independent VA correlates in HCM patients, the ROC analysis was performed and the corresponding AUC values were calculated (Fig. 6). The following parameters were included in the multivariate analysis (binary logistics regression) - Tped, QRSdur, QRSd, MD of the RV free wall, LV GLS, RV GLS and RV MWT (parameters with AUC>0,6 were included; If two parameters correlated - r>0,5 - the parameter with better AUC was chosen to compensate for collinearity). The only independent VA correlates in the overall HCM patient population were Tped (HR=1,078, IC=1,015-1,144, p<0,001), QRSd (HR=1.079, IC=1,018-1,144, p=0,003) and RV GLS(HR=1,129, IC=1,030-1,238, p=0,024), with good diagnostic accuracy, sensitivity and specificity.

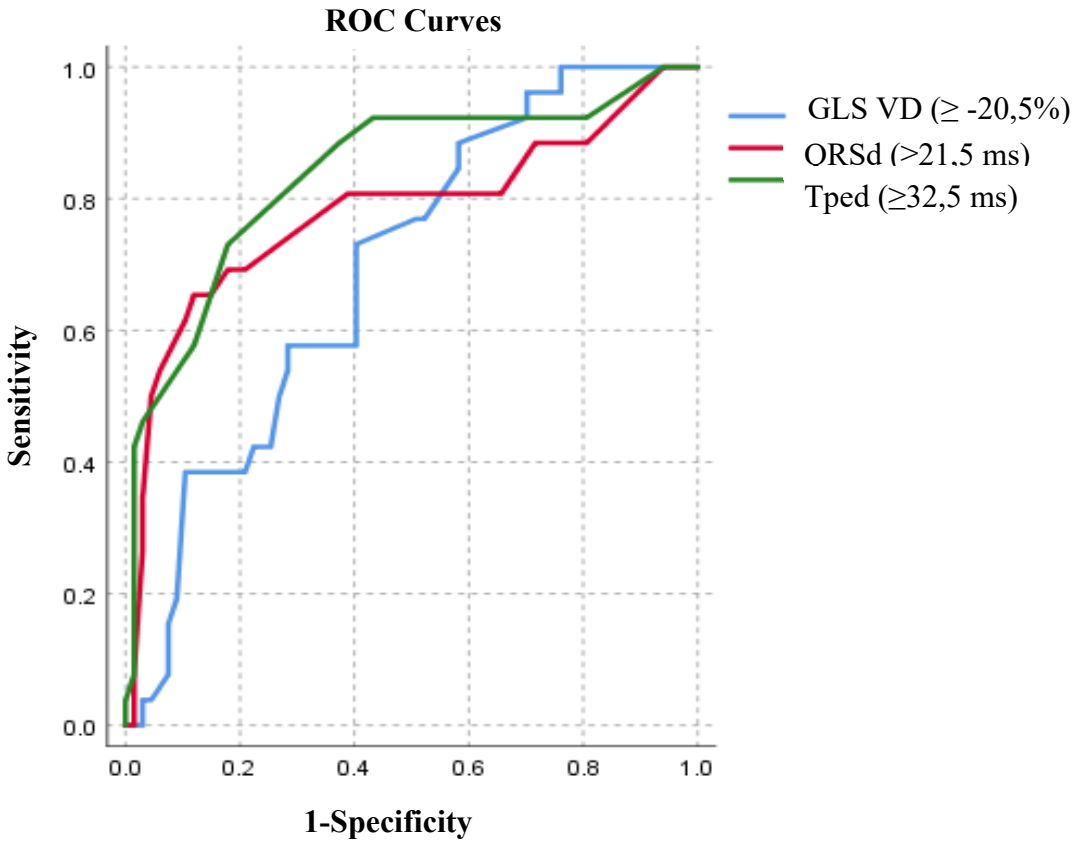

Figure 6 – ROC analysis and area under the curve (AUC) for AV in the overall study population: Best accuracy is observed in descending order for Tped (AUC=0.837), QRSd (AUC=0.780) and GLS VD (AUC=0.694), respectively.

Ventricular arrhythmias correlates in HCM patients <60 years

After performing univariate logistic regression, age (inversely proportional), Tped, TPE/QTc, QRSd, RV MD, RV Free wall MD and RV GLS correlated with VA risk in this patient subgroup (Table 10). The following parameters were included in the multivariate analysis - Tped, QRSd, RV free wall MD and RV GLS.

Following the multivariate logistic analysis, independent correlates for VAs in patients under 60 years of age were Tped (HR=1.113, 95% CI 1,056-1,172, p=0,048) and QRSd (HR=1.198, 95% CI 1,099-1,307, p=0,025) (Table 10) with good predictive accuracy following the ROC analysis, with a similar threshold value equal to or greater than 21,5 Ms, respectively greater than or equal to 32,5 ms (Fig 7).

Table 10. Independent correlates for AV in patients with CMH below 60 years of age

	Univariate logistic analysis			**Multivariable analysis**
	HR	**95% CI**	**p**	**P value**
Age	**0,957**	**0,917-0,999**	**0,044**	
QTcd			*0,071*	
Tpe	**1,044**	**1,016-1,073**	**0,002**	
Tped	**1,113**	**1,056-1,172**	**<0,001**	**0,048**
Tpe/QTc	**1,673**	**1,75-1,59**	**0,002**	
QRSd*	**1,198**	**1,099-1,307**	**<0,001**	**0,025**
*LV MD**	*1,020*	*1-1,039*	*0,119*	
RV MD*	**1,019**	**1,002-1,037**	**0,048**	
RV free wall MD*	**1,043**	**1,004-1,084**	**0,032**	

RV GLS	**1,123**	**1,003-1,256**	**0,044**
RV Free wall GLS			*0,079*
LV MWT			*0,133*

VA=ventricular arrhythmias; QTcd = QT interval dispersion; TPE= duration of the end portion of the T-wave (T-wave peak-end); Tped = dispersion of the end portion of the T-wave; TPE/QTc = ratio of the end portion of the T-wave to the corrected QT interval; QRSd = dispersion of the QRS complex; LV MD= mechanical dispersion of the left ventricle; MD of the RV free wall = mechanical dispersion of the free wall of the right ventricle; RV GLS = global longitudinal deformation of the right ventricle; RV free wall GLS = global longitudinal deformation of the free wall of the right ventricle; LV MWT = left ventricular maximum wall thickness..*Calculated only for patients with narrow QRS complex*

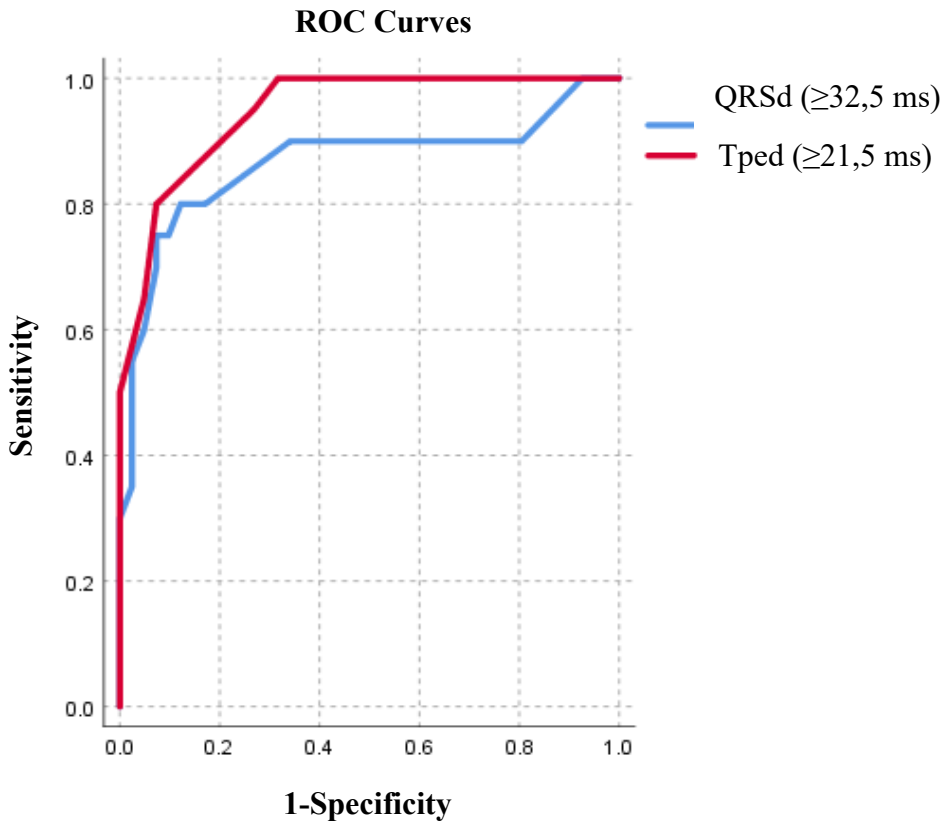

Figure 7 – ROC analysis and area under the curve (AUC) for AV in HCM patients < 60 years of age: The best accuracy is observed in descending order for QRSd (AUC=0.947) and Tped (AUC=0.865), respectively.

Study limits

This study was conducted in a single tertiary center – in this context, some of the results may not apply to a general population with CMH. The second study was transversal, which limited the predictive value of independent correlates in the study group. As the number of patients with sustained ventricular arrhythmias/SCD/persistent AF vs. paroxysmal AF was not high, subgroup analysis of risk factors between patients with SVT and those without SVT and those with persistent AF versus paroxysmal AF could not be performed. In addition, we had no reliable data on the exact cause of death in patients with sudden death, so these events could not be clearly classified as SCD. At the same time, the actual prevalence of VA/AF in the study population was most likely underestimated, as for most patients the diagnosis was made on ECG Holter or ECG examination. The small number of major arrhythmic adverse events (sudden death, SVT) during follow-up can be explained by the fact that enrolled patients were older than the general HCM population, and therefore at lower arrhythmia risk. ECG and echocardiographic measurements were only performed at the study enrollment. In this context, we cannot assess how the risk profile of patients has changed during the follow-up period, nor whether electrical changes in the ventricle/atria precede structural or functional changes.

CONCLUSIONS

Electrical, functional and structural remodeling of the atrial and ventricular myocardium characteristic of HCM (also demonstrated by comparison with the control group) predisposes these patients to the development of atrial fibrillation and ventricular arrhythmias (NSVT, SVTs), with a significantly higher frequency than that found in the general population. In addition, the occurrence of atrial fibrillation aggravates and promotes atrial remodeling, enabling a vicious circle.

Following echographic evaluation, both LA size and function (LAVi, ASR) were related to AF occurrence, but in multivariate analysis only the functional parameter (ASR) was an independent predictor of AF in the general population of patients with HCM. The ECG parameters that evaluated atrial electrical remodeling (PD, Pamp) were superior in predictive accuracy to echographic parameters. In addition, in patients with LAD<45 mm, the only independent predictor of AF was PD, raising the hypothesis that atrial electrical remodeling may precede functional/structural remodeling. There were weak positive correlations between

electrical and echographic parameters. This reinforces the usefulness of their simultaneous use in assessing the risk of AF in patients with HCM. The presence of AF has been associated with a higher risk of HF worsening and BNP increase over the course of follow-up, through its unfavorable effect on diastolic dysfunction, as demonstrated by other studies. Although RA remodeling may also increase the risk of AF, in our group no significant difference in RA size was observed between patients with and without AF. Measurement of functional RA parameters or RA volume may provide additional information for AF risk stratification. Consequently, the results obtained support that analysis of LA function and electrical activity on the surface electrocardiogram can significantly improve the stratification of AF risk in patients with HCM, including those considered at lower risk according to the current guidelines.

In patients with HCM the risk of VAs is related to echographic (GLS, MD, LV and RV wall thickness) and electrical (TPE, Tped, QRSd) parameters, but the only independent VA correlates in the study group were RV GLS, Tped and QRSd. Similar to the results in the atrial fibrillation study, the accuracy of the electrical parameters was superior to that of the echographic parameters. Considering that echographic parameters do not directly reflect electrical remodeling, which is the main arrhythmia substrate, this is not necessarily surprising. In the subgroup of patients < 60 years of age, only electrical parameters (Tped, QRSd) correlated independently with the presence of VAs. Most of the electrical parameters did not correlate with the echographic parameters, and there were weak correlations between those that correlate. Thus, Tped and QRSd correlated poorly with LV MWT and LV/RV GLS. Because electrical dispersion can be influenced by both the severity of ventricular hypertrophy and the severity of longitudinal dysfunction, which correlates with disease progression, these results are not surprising. The results obtained can have clinical utility in refining the stratification of VA risk and, implicitly, in more careful monitoring of patients at high risk.

In conclusion, the implementation of electrical parameters for atrial and ventricular remodeling and functional echographic parameters (ASr, RV GLS) that are reproducible and easy to calculate in current practice can help to stratify the risk of AF/VAs, especially in patients considered at intermediate/low risk.

PERSONAL CONTRIBUTIONS AND CLINICAL IMPLICATIONS

This study was the first to simultaneously evaluate electrical parameters that can be easily measured on the surface electrocardiogram (PD, Pamp, Tped, QRSd) and functional and structural echographic parameters (LAVi, ASr, RV GLS) and their link to the arrhythmic risk (FA, VAs) in patients with CMH, as well as the existence of possible correlations between electrical and structural/functional remodeling.

Electrical parameters showed better predictive accuracy (AUC, Sb, Sp, VPP, VPN) than echographic parameters for AF or AV risk, both in the analysis of the general patient group and in the subgroup analysis (patients with LAD<45 mm for AF risk, Patients < 60 years of age for risk of VAs). At the same time, we have demonstrated that even in the case of manual measurement by using digital instruments, the reproducibility of the electrical parameters is good, and the duration of their measurement on the surface ECG (parameters of the P-wave, QRS complex and T-wave) is less than 10 minutes, which supports their implementation in clinical practice.

In addition, by including PD and ASR in the current predictive model of patient identification at risk for AF, the accuracy of this model was increased incrementally. Measuring RV GLS, Tped, QRSd can further refine the selection of VA-prone patients from the classical risk parameters.

An assessment of the evolution of these parameters during follow-up in a subsequent study could demonstrate whether atrial/ventricular electrical remodeling precedes functional/structural remodeling and to what extent drug treatment may alter the arrhythmia risk profile of patients. The inclusion of a larger number of patients could also allow subgroup analysis of electrical and echographic predictors in patients with paroxysmal versus persistent/permanent AF, respectively in patients with SVT/SCD versus those without SVT (in particular by including young patients, with a higher risk of VA).

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