Title
Electromechanical Relationship in Hypertrophic Cardiomyopathy

Journal
Journal of Cardiovascular Translational Research, 6(4)

ISSN
1937-5387

Authors
Lin, Xiaoping
Liang, Hsin-Yueh
Pinheiro, Aurelio
et al.

Publication Date
2013-08-01

DOI
10.1007/s12265-013-9481-0

Peer reviewed

Published in final edited form as:
J Cardiovasc Transl Res. 2013 August ; 6(4): 604–615. doi:10.1007/s12265-013-9481-0.

Electromechanical Relationship in Hypertrophic Cardiomyopathy

Xiaoping Lin,
Division of Cardiology, Johns Hopkins University School of Medicine, 720 Rutland Ave, Ross 871, Baltimore, MD 21201, USA. Department of Cardiology, the Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China. Key Laboratory of Arrhythmias, Ministry of Education, China (East Hospital, Tongji University School of Medicine), Shanghai, China

Hsin-Yueh Liang,
Division of Cardiology, Johns Hopkins University School of Medicine, 720 Rutland Ave, Ross 871, Baltimore, MD 21201, USA. Graduate Institute of Clinical Medical Science, China Medical University, Taichung, Taiwan. Division of Cardiology, China Medical University Hospital, Taichung, Taiwan

Aurelio Pinheiro,
Division of Cardiology, Johns Hopkins University School of Medicine, 720 Rutland Ave, Ross 871, Baltimore, MD 21201, USA

Veronica Dimaano,
Division of Cardiology, Johns Hopkins University School of Medicine, 720 Rutland Ave, Ross 871, Baltimore, MD 21201, USA

Lars Sorensen,
Division of Cardiology, Johns Hopkins University School of Medicine, 720 Rutland Ave, Ross 871, Baltimore, MD 21201, USA

Miguel Aon,
Division of Cardiology, Johns Hopkins University School of Medicine, 720 Rutland Ave, Ross 871, Baltimore, MD 21201, USA

Larisa G. Tereshchenko,
Division of Cardiology, Johns Hopkins University School of Medicine, 720 Rutland Ave, Ross 871, Baltimore, MD 21201, USA

Yihan Chen,
Key Laboratory of Arrhythmias, Ministry of Education, China (East Hospital, Tongji University School of Medicine), Shanghai, China

Meixiang Xiang,
Department of Cardiology, the Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China

Theodore P. Abraham, and
Division of Cardiology, Johns Hopkins University School of Medicine, 720 Rutland Ave, Ross 871, Baltimore, MD 21201, USA

M. Roselle Abraham

Correspondence to: M. Roselle Abraham, mabraha3@jhmi.edu.

Xiaoping Lin and Hsin-Yueh Liang contributed equally to this work.

Division of Cardiology, Johns Hopkins University School of Medicine, 720 Rutland Ave, Ross 871, Baltimore, MD 21201, USA

M. Roselle Abraham: mabraha3@jhmi.edu

Abstract

We examined whether there is a relationship between repolarization abnormalities on electrocardiography (EKG) and deformation abnormalities by echocardiography. Analysis of baseline EKGs and mechanical (echo-based deformation) changes was performed in 128 patients with a clinical diagnosis of hypertrophic cardiomyopathy (HCM). Patients with left ventricular hypertrophy (LVH) or repolarization abnormalities had higher septal thickness when compared to patients with normal EKG. Patients with EKG evidence of LVH or QT_c prolongation had lower systolic velocity, systolic strain, systolic strain rate, late diastolic velocity, and late diastolic strain rate than patients with a normal EKG. Patients with strain pattern or ST depression/T-wave inversion had lower systolic velocity, systolic strain, systolic strain rate, early diastolic velocity, and late diastolic velocity when compared to patients with normal EKGs. LVH and repolarization abnormalities on surface EKG are markers of impaired systolic and diastolic mechanics in HCM.

Keywords

Strain echocardiography; Electrocardiography; Hypertrophic cardiomyopathy; Repolarization abnormalities

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common (1:500) inherited cardiovascular disorder characterized by ventricular hypertrophy, myocyte disarray, and replacement/interstitial fibrosis which often result in arrhythmias, sudden death, and heart failure [1]. A fair proportion of patients are asymptomatic, and a common and often recognized feature of HCM is the prominent electrocardiography (EKG) abnormalities that range from left ventricular hypertrophy (LVH) to a variety of repolarization abnormalities including QT_c prolongation, strain pattern, and ST and/or T-wave changes.

Deformation mapping by echocardiography has led to several published reports of lower systolic and diastolic strain rates and lower systolic strain in HCM, particularly in the hypertrophied regions [2–4]. There are limited data in the HCM literature (in 41 children), suggesting that the strain pattern on EKG is associated with systolic mechanical changes [5]. But it is not known whether the typical strain pattern has more significant mechanical implications than other ST-T abnormalities. Furthermore, the relationship between various EKG features of cardiac repolarization assessed by routine surface EKG and cardiac mechanics has not been explored in adult HCM patients.

The key pathophysiologic processes in HCM may provide common underlying mechanisms, resulting in electrical and mechanical abnormalities. Figure 1 illustrates the close relationship between electrophysiology and cardiac mechanics. Hypertrophy, ion channel/gap junction remodeling, and fibrosis which commonly occur in HCM can prolong repolarization [6], promote spatial dispersion of repolarization, alteration of the repolarization sequence [7], resulting in ST segment depression and/or T-wave inversion on surface EKG and impairment of diastolic mechanics [8]. Down-regulation of repolarizing K^+ currents reduces cardiac repolarization reserve while alterations in Ca^{2+} handling can influence action potential duration and systolic mechanics. Hence, understanding the electromechanical relationship in HCM may provide insights into the pathologic process and incremental clinical information particularly for individual risk assessment.

Although there are substantial published data separately describing EKG abnormalities and cardiac mechanics in HCM, there are no published data on electromechanical associations in adult HCM patients. We therefore examined EKG and cardiac mechanics by echocardiography, to better understand the electromechanical relationships in adult HCM patients.

Methods

We enrolled patients from the Johns Hopkins HCM registry. We used the following diagnostic criteria outlined by the American College of Cardiology–American Heart Association guidelines for the diagnosis of HCM [9]: (1) septal or apical wall thickness ≥15 mm, in the absence of other causes of LVH such as hypertension and/or valvular disease such as aortic stenosis; (2) LV posterior wall thickness <12 mm; and (3) ratio of septum/apex to posterior wall>1.5. Patients with ventricular pacing, history of myocardial infarction, and alcohol septal ablation or myectomy before echocardiography were excluded. All patients had a 12-lead EKG at rest, and echocardiograms for assessment of cardiac anatomy and mechanics on the same day, and within a week of their clinic visit. All EKGs were evaluated by two independent observers, who were blinded to the clinical information and echocardiography results of the patients. The echocardiography analyses were performed by investigators, who were blinded to the EKG results of the patients.

Electrocardiographic Studies

Standard 12-lead EKGs were obtained with patients in the supine position and recorded at a paper speed of 25 mm/s. All EKGs were evaluated by two independent observers, who were blinded to the clinical information of the patients. Heart rate, PR interval, QRS axis, QRS duration, QT interval, and QT_c (using Bazett's formula) were measured automatically at acquisition and confirmed by manual measurements using electronic callipers. Patients with left (LBBB) and right bundle branch block (RBBB) were analyzed as a separate group because of secondary repolarization changes that occur due to BBB. EKG-LVH was defined using the Sokolow–Lyon criterion (S in V1+ R in V5 or V6 ≥35 mm) [10] or Cornell product ((SV3+ RaVL)×QRS duration ≥2,440 mm ms for men; (SV3+(RaVL+8 mm))×QRS duration ≥2,440 mm ms for women) [11]. A prolonged QT_c interval was defined as at least 450 ms for men and at least 470 ms for women in the absence of bundle branch block and intra-ventricular conduction defect (IVCD) [12]. Cardiac repolarization was carefully analyzed by specifying EKG leads to three groups: group1—high lateral (I and aVL), group2—antero-lateral (V4–V6), and group3—inferior (II, III, aVF) leads. We identified the following patterns: The classical *strain pattern* was defined by a down-sloping convex ST-segment depression ≥1 mm with an inverted asymmetrical T-wave opposite to the QRS axis in at least two contiguous leads [13]. *Early repolarization* was defined as slurring or notching of the terminal part of QRS complex and the beginning of the ST segment in at least two contiguous leads and J-point/ST elevation >1 mm. *Non-specific ST depression* (*STD*) was defined as ST-segment depression ≥1 mm below the baseline at 80 ms after the J point in at least two contiguous leads. *Non-specific T-wave inversion* (*TWI*) was defined as T-wave inversion >1 mm in at least 2 contiguous leads. *Giant T-wave inversion* was defined by a symmetrical, negative T-wave of 10 mm or more in at least two contiguous leads [14, 15]. *Non-specific ST elevation* was defined as ST-segment elevation ≥1 mm above the baseline at 80 ms after the J point in at least two contiguous leads. We combined patients who had either non-specific ST depression or non-specific T-wave inversion for analysis because of frequent overlap between these two features. Normal EKG was defined by lack of abnormal EKG features. Representative EKGs of patients with different repolarization patterns are illustrated in Fig. 2a–g.

Echocardiography Studies

Echocardiographic examinations were performed with patients in the left lateral decubitus position using a Vivid 7 cardiac ultrasound machine (General Electric, Milwaukee, WI, USA) equipped with a 3.5-MHz transducer. Echo analysis was performed by an experienced clinical echocardiographer, who was blinded to the EKG analysis and clinical information of the patients. Conventional measurements included left ventricular end-diastolic and end-systolic diameters and volume, inter-ventricular septum and posterior LV wall thickness at end diastole, ejection fraction by biplane Simpson's method, mitral inflow E/A ratio, deceleration time of E wave, peak left ventricular outflow tract pressure gradient at rest, and left atrial volume index.

A comprehensive analysis of cardiac mechanics was performed using tissue Doppler echocardiography. Tissue Doppler-based measurement of tissue velocity and strain rates/strain has been extensively validated to accurately represent regional and global systolic and diastolic left ventricular function, at high temporal and spatial resolution [16–19]. The apical four-chamber, two-chamber, and long axis views of color two-dimensional tissue Doppler images were acquired at a frame rate of 100–140 frames/s. Tissue Doppler-based parameters were measured in the longitudinal direction only at the basal and mid segments of six walls. Apical segments were excluded as reliable tissue velocity, and strain data are not feasible in these segments. Three consecutive cardiac cycles were measured, and the average was obtained. Global values for tissue velocity were averaged across six basal segments and global strain values across 12 basal and middle segments. Tissue Doppler-derived longitudinal velocity and strain were analyzed offline using GE EchoPAC software (version BT08). Inter- and intra-observer agreement was 92 and 96 %, respectively, for strain measurements.

We measured the following parameters, as sensitive indicators of systolic and diastolic left ventricular function (Fig. 3): Systolic velocity (Sm), systolic strain rate (sSR), and systolic strain (S) which reflect global and regional contractile function [19–23]; early diastolic velocity (Em) and strain rates (eSR) which provide information about global and regional relaxation properties [24–28]; late diastolic velocity (Am) and strain rate (aSR) which are determined by left atrial dP/dt, left atrial relaxation, LV end-diastolic pressure, and LV stiffness [26, 29]; and ratio of Mitral E velocity to Em (E/Em) which correlates well with mean pulmonary capillary wedge pressure and hence is an estimate of LV filling pressure [24].

Statistical Analysis

Continuous variables were expressed as mean±standard deviation; categorical variables were presented as absolute and percentage numbers. Statistical analysis was performed using JMP 8.0 software. The Student's *t* test or the Wilcoxon rank sum test was used to test significance between groups. Chi-square test was used for categorical variables. A p value<0.05 was considered statistically significant.

Results

Demographic and Clinical Characteristics

We analyzed data from 128 consecutive patients with a clinical diagnosis of HCM, who had adequate quality of echocardiograms and EKG (mean age 53±16 years; 90 men). Majority of the patients (82 %) were NYHA class I or II. Pre-syncope, syncope, and a confirmed family history of HCM were present in 13, 13, and 20 % of the patients, respectively. Only 33 % of patients had evidence of LV outflow tract obstruction at rest, using a cutoff of 30 mmHg. Demographic and echocardiographic data of the patients are presented in Table 1.

Electrocardiographic Features in HCM Patients

We analyzed rest EKGs of HCM patients; the results are summarized in Table 1. RBBB and LBBB were present in 11 and nine patients, respectively; these patients were excluded from other analysis. Of the remaining patients, 14 had normal EKGs, 54 had EKG evidence of LVH, 32 had QT_c prolongation, 21 had the classical strain pattern, 8 had early repolarization, 28 had non-specific TWI, and 6 had STD (Table 1; Fig. 4). The typical strain pattern and non-specific T-wave inversion were most frequently observed in high lateral (I, aVL) and anterolateral leads (V4–V6), whereas non-specific ST depression was more common in anterolateral (V4–V6) and inferior leads (II, III, aVF) (Table 2; Fig. 2a, e, f). Giant T-waves were seen in one patient (Fig. 2c). Majority (86 % or 18 of 21) of patients with the classical strain pattern had EKG-LVH, but only 33 % (18 of 54) of patients with EKG-LVH demonstrated the classical strain pattern (Fig. 4). A small proportion, namely 20 % (11 of 54) of patients with EKG-LVH, had no repolarization abnormalities.

Prevalence of ≥1 risk factors for sudden death (non-sustained ventricular tachycardia, unexplained syncope, family history of sudden death in a first degree relative, maximal LV wall thickness ≥3 cm, and abnormal BP response to exercise) was significantly higher in patients with EKG-LVH (p=0.01), QT_c prolongation (p=0.03), strain pattern (p=0.04), and non-specific STD/TWI (p=0.005).

Conventional Echocardiography vs. EKG

Conventional echo-cardiographic measurements were performed to assess LV geometry and function. LV outflow tract gradients were similar, but septal thickness was higher in patients with EKG-LVH (21±4 vs. 17±3 mm, p=0.001), QT_c prolongation (20±5 vs. 17±3 mm, p=0.019), strain pattern (21±4 vs. 17±3 mm, p=0.012), and non-specific ST depression/T-wave inversion (21±5 vs. 17±3 mm, p=0.012) when compared to patients with a normal EKG (Table 3).

Cardiac Mechanics vs. EKG

Tissue Doppler indices (Fig. 3) were analyzed as sensitive indicators of systolic and diastolic left ventricular function. Patients with EKG evidence of LVH or QT_c prolongation had lower Sm, S, sSR, Am, and aSR than patients with normal EKGs (Table 3), suggesting impaired contractile function, diastolic dysfunction, and higher LV stiffness. Patients with strain pattern or non-specific ST depression/T-wave inversion on EKG had lower Sm, S, sSR, Em, and Am when compared to patients with normal EKGs (Table 3), indicating the presence of impaired contractile function and diastolic dysfunction. The only statistically significant difference between patients with strain pattern and non-specific ST depression/T-wave inversion was lower late diastolic velocity (Am −2.6±1.2 vs. −3.7±1.6 cm/s, p=0.02) and late diastolic strain rate (aSR 0.7±0.3 vs. 1.0±0.4 s^{-1}, p=0.049) in patients with strain pattern on EKG, suggesting that patients with strain pattern on EKG have higher LV filling pressures and LV stiffness than patients with non-specific STD/TWI (Table 3).

Patients with EKG-LVH plus repolarization abnormality (n=43) demonstrated lower late diastolic strain rate (aSR 0.8±0.3 vs. 1.0±0.4 s^{-1}, p=0.039) when compared to patients with repolarization abnormality alone (n=25). Mean inter-ventricular septal thickness (22±4 vs. 19±5 mm, p=0.019) was also higher in patients with EKG-LVH plus repolarization abnormality (n=43) when compared to patients with only repolarization abnormality (n=25) (patients with QT_c prolongation, strain pattern, non-specific ST depression/T-wave inversion, non-specific ST elevation, and giant T-wave inversion were included in the abnormal repolarization group).

Imaging Features of HCM Patients with Normal EKGs

HCM patients with normal EKGs had evidence of asymmetric septal hypertrophy. LV end-systolic and end-diastolic diameters, LV end-systolic and end-diastolic volumes, and ejection fraction were all within the normal range [30]. Of these, 36 % (five of 14) of the patients had non-obstructive HCM. These patients had evidence of elevated LV filling pressure and grade II (pseudo-normal pattern) diastolic dysfunction based on their E/A ratio, deceleration time, and E/Em values. Diastolic mechanics were reduced compared to historic controls (Em −4.8±1.8 cm/s, Am −4.5±1.4 cm/s; eSR 1.2±0.3 s^{-1}, aSR 1.1±0.3 s^{-1}) [27], while systolic mechanics were borderline normal (sSR −1.1±0.2 s^{-1} and S −16±3 %).

Discussion

Our study indicates an association between cardiac repolarization abnormalities and deformation changes in HCM. The novel findings of our study are that HCM patients with repolarization abnormalities consisting of QT_c prolongation, EKG strain pattern, or non-specific ST depression/T-wave inversion had greater impairment of systolic and diastolic cardiac mechanics (despite a preserved LVEF), when compared to patients with normal EKGs. Furthermore, HCM patients with strain pattern demonstrated greater impairment of late diastolic mechanics compared to those with non-specific ST depression/T-wave inversion. These findings have not been previously reported in HCM but are not unexpected given that key aberrations in cellular physiology such as Ca^{2+} can underlie both electrical repolarization and mechanical perturbations. Using EKG and mechanics together rather than separately may allow more granular characterization of the wider HCM population with direct clinical implications.

Normal EKG

We found that 11 % (14 of 128) of the patients in our HCM population had normal EKGs. These patients had better systolic and diastolic mechanics than patients with repolarization abnormalities on EKG, suggesting a mild phenotype or early disease [31]. Our findings are concordant with a previous HCM study which found normal EKGs in 6 % of their patients, lower septal wall thickness, fewer symptoms, and need for implantable cardioverter defibrillator implantation as well as better long-term outcomes [32].

EKG-LVH

After excluding patients with bundle branch block, 50 % (54 of 108) of the HCM patients had EKG-LVH using the Sokolow–Lyon and/or Cornell criteria. Evidence of EKG-LVH has been shown to be an important predictor of cardiovascular morbidity and mortality in patients with hypertension and a predictor of sudden death in patients with HCM [33–35]. However, EKG-LVH is also frequently seen in athletes in response to physical training, but not associated with adverse consequences. In this study, we found that patients with EKG-LVH exhibited greater impairment of systolic and diastolic mechanics than patients with normal EKGs, suggesting that evidence of LVH on surface EKG is indicative of adverse cardiac remodeling in patients with HCM.

Repolarization Changes

The QT interval represents the time taken to activate the ventricle (reflected in the QRS duration) and completely repolarize (ST segment) (Fig. 1). The polarity of the ST segment and the T-wave on the surface EKG result from several simultaneous voltage gradients during repolarization, which in turn depend on heterogeneity of action potential morphology and duration in the left and right ventricles (LV and RV [36]) as well as intra-ventricular

conduction velocity or activation time [7]. It is known that even a small net gradient in a predominant direction can change the polarity of the T-wave and ST segments [7].

QT_c prolongation at rest is frequently seen in patients with heart failure and pathologic LVH, but not in athletes with physiologic hypertrophy [37]. Patch clamp studies in experimental models indicate that decrease in functional repolarizing K^+ current densities in hypertrophied myocytes (reduced repolarization reserve) is the main cause of QT_c prolongation and arrhythmias in pathologic hypertrophy. In contrast, exercise training was found to increase the amplitudes of repolarizing K^+ current densities in hypertrophied myocytes, preventing an increase in QT_c interval [38]. QT_c prolongation was seen in 34 % (32 of 93) of the HCM patients that we studied, after excluding BBB and IVCD. Patients with QT_c prolongation also had evidence of impaired contractile function, diastolic dysfunction, and higher LV stiffness, when compared to patients with normal EKGs, suggesting that QT_c prolongation in HCM patients is a marker of adverse electrical and mechanical remodeling.

A prolonged QT interval accompanied by an increase in the spatial dispersion of repolarization, manifested by abnormal T-waves, creates a substrate for reentrant arrhythmias [39]. However, agents (e.g., amiodarone) that prolong the QT_c interval without increasing the spatial dispersion of repolarization may not be pro-arrhythmic, suggesting that QT_c prolongation is not the sole determinant of arrhythmias [39]. On the other hand, isolated ST and T-wave changes which are commonly seen in patients with hypertension, athletes, and HCM are attributed to a change in the sequence of repolarization, and may not be a pro-arrhythmic marker in the absence of prolonged repolarization (QT_c interval). The presence of ST-T changes in the setting of QT_c prolongation may indicate an increased spatial dispersion of repolarization and could be a marker of an arrhythmogenic substrate; these features were present in 16 % (21 of 128) of our HCM patients (Fig. 4). Patients with strain pattern or non-specific STD/TWI had greater impairment of systolic and diastolic mechanics when compared to patients with normal EKGs, suggesting that these repolarization changes on the surface EKG also are markers for adverse mechanical remodeling in HCM.

Ventricular activation normally propagates via the His-Purkinje system from endocardium to epicardium, but repolarization proceeds from epicardium to endocardium because of differences in repolarization properties of the three main electrophysiologically distinct cell types (epicardial, endocardial, and M cells) that comprise the ventricular myocardium [40]. The ST segment corresponds temporally to the plateau phase of the action potential, the repolarization of M cells is temporally aligned with the end of the T-wave, and repolarization of the epicardium is coincident with the peak of the T-wave [40]. Accentuation of spatial dispersion of repolarization due to an increase of transmural, transseptal, or apicobasal dispersion of repolarization can be expected in HCM which can manifest with varying patterns of hypertrophy (e.g., septal, apical, concentric) [41], regional ischemia due to microvascular dysfunction [42], and activation delays [43] due to fibrosis and ion channel/gap junction remodeling [44] which could alter the polarity of the ST segment and T-wave. This could explain our findings of (1) patients with repolarization abnormalities on EKG having greater impairment of cardiac mechanics than patients with normal EKGs and (2) similarity between the effect of classical strain pattern and non-specific ST depression/T-wave inversion on cardiac mechanics.

Clinical Implications

We have identified two main electromechanical profiles in HCM, namely patients with *normal* baseline EKGs and patients with evidence of *LVH+abnormal repolarization* (Fig. 5). HCM patients with normal EKGs who have been reported to have fewer arrhythmias,

symptoms, and better outcomes [32] could have early disease and/or a mild phenotype consisting of very little myocardial fibrosis (which can slow conduction and worsen diastolic mechanics), less hypertrophy and electrical remodeling (which can promote spatial dispersion of repolarization and slow conduction), and less disarray (which slows conduction and may reduce systolic strain). In contrast, one may expect that patients with EKG evidence of LVH+repolarization abnormalities, who were found to have worse diastolic and systolic mechanics in our study, when compared to patients with only repolarization abnormalities, could be at higher risk for ventricular arrhythmias and sudden cardiac death because of increased spatial dispersion of repolarization and greater amounts of fibrosis which can promote reentry. Larger studies with clinical outcomes data will be needed to examine the clinical value of these electromechanical profiles. Since electromechanical abnormalities may reflect the state of fundamental pathologic processes in HCM, they may provide superior prognostic information.

Study Limitations

Although we have a relatively large study cohort, we do not have follow-up information to test the clinical value of our electromechanical subgroups in HCM. We used tissue Doppler-based strain measurements. Although speckle tracking strain is gaining popularity due to ease of use, in our hands we have superior signal fidelity and reliability with high frame rate tissue Doppler-based strain echocardiography. Moreover, the challenges with reliable measurement of strain rates using standard frame rate speckle tracking are well-known. We performed tissue Doppler and speckle tracking strain in 100 consecutive patients and selected tissue Doppler-based strain for its reproducibility and signal quality. We measured only longitudinal deformation. Longitudinal strain has the best signal quality, is well validated, and is more reproducible by echocardiography than radial or circumferential strain.

We did not perform genotyping. Genotyping is not routinely performed in clinical practice and does not influence therapy. Moreover, a causal mutation is not identified in up to 50 % of patients with HCM morphology [45]. To reduce the likelihood of mis-classifying non-HCM patients as HCM, we applied very stringent morphologic criteria for diagnosis of HCM. Also, blood and urine tests were performed in all subjects to rule out phenocopy conditions such as amyloidosis and Fabry's disease. Lastly, due to considerable overlap between individual repolarization abnormalities (Fig. 4), it was not feasible to study the associated mechanics abnormalities for individual repolarization abnormalities.

Conclusion

In HCM, EKG abnormalities such as LVH, prolonged QT_C, strain pattern, and non-specific ST depression/T-wave inversion are markers of impaired systolic and diastolic mechanics. Larger series with outcomes data will help determine whether HCM patients' electromechanical profiles will provide incremental prognostic information.

Acknowledgments

Funding for this study was provided by National Institutes of Health grant # HL 098046. Dr. Lin was partially supported by the China Scholarship Council. The experiments comply with the current laws of the USA.

References

1. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. Journal of the American Medical Association. 2002; 287(10):1308–1320. [PubMed: 11886323]

2. Serri K, Reant P, Lafitte M, Berhouet M, Le Bouffos V, Roudaut R, Lafitte S. Global and regional myocardial function quantification by two-dimensional strain: application in hypertrophic cardiomyopathy. Journal of the American College of Cardiology. 2006; 47(6):1175–1181.10.1016/j.jacc.2005.10.061 [PubMed: 16545649]
3. Yang H, Sun JP, Lever HM, Popovic ZB, Drinko JK, Greenberg NL, Shiota T, Thomas JD, Garcia MJ. Use of strain imaging in detecting segmental dysfunction in patients with hypertrophic cardiomyopathy. Journal of the American Society of Echocardiography. 2003; 16(3):233–239.10.1067/mje.2003.60S0894731702745367 [PubMed: 12618731]
4. Sengupta PP, Mehta V, Arora R, Mohan JC, Khandheria BK. Quantification of regional nonuniformity and paradoxical intramural mechanics in hypertrophic cardiomyopathy by high frame rate ultrasound myocardial strain mapping. Journal of the American Society of Echocardiography. 2005; 18(7):737–742.10.1016/j.echo.2005.03.008 [PubMed: 16003271]
5. Ganame J, Mertens L, Eidem BW, Claus P, D'Hooge J, Havemann LM, McMahon CJ, Elayda MA, Vaughn WK, Towbin JA, Ayres NA, Pignatelli RH. Regional myocardial deformation in children with hypertrophic cardiomyopathy: morphological and clinical correlations. European Heart Journal. 2007; 28(23):2886–2894.10.1093/eurheartj/ehm444 [PubMed: 17971400]
6. Nass RD, Aiba T, Tomaselli GF, Akar FG. Mechanisms of disease: ion channel remodeling in the failing ventricle. Nature Clinical Practice. Cardiovascular Medicine. 2008; 5(4):196–207.10.1038/ncpcardio1130
7. Franz MR, Bargheer K, Rafflenbeul W, Haverich A, Lichtlen PR. Monophasic action potential mapping in human subjects with normal electrocardiograms: direct evidence for the genesis of the T wave. Circulation. 1987; 75(2):379–386. [PubMed: 3802441]
8. Shah M, Akar FG, Tomaselli GF. Molecular basis of arrhythmias. Circulation. 2005; 112(16):2517–2529.10.1161/CIRCULATIONAHA.104.494476 [PubMed: 16230503]
9. Eriksson MJ, Sonnenberg B, Woo A, Rakowski P, Parker TG, Wigle ED, Rakowski H. Long-term outcome in patients with apical hypertrophic cardiomyopathy. Journal of the American College of Cardiology. 2002; 39(4):638–645. [PubMed: 11849863]
10. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. American Heart Journal. 1949; 37(2):161–186. [PubMed: 18107386]
11. Molloy TJ, Okin PM, Devereux RB, Kligfield P. Electrocardiographic detection of left ventricular hypertrophy by the simple QRS voltage-duration product. Journal of the American College of Cardiology. 1992; 20(5):1180–1186. [PubMed: 1401620]
12. Straus SM, Kors JA, De Bruin ML, van der Hooft CS, Hofman A, Heeringa J, Deckers JW, Kingma JH, Sturkenboom MC, Stricker BH, Witteman JC. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. Journal of the American College of Cardiology. 2006; 47(2):362–367.10.1016/j.jacc.2005.08.067 [PubMed: 16412861]
13. Roman MJ, Kligfield P, Devereux RB, Niles NW, Hochreiter C, Halle A, Sato N, Borer JS. Geometric and functional correlates of electrocardiographic repolarization and voltage abnormalities in aortic regurgitation. Journal of the American College of Cardiology. 1987; 9(3):500–508. [PubMed: 3819197]
14. Sakamoto T, Tei C, Murayama M, Ichiyasu H, Hada Y. Giant T wave inversion as a manifestation of asymmetrical apical hypertrophy (AAH) of the left ventricle. Echocardiographic and ultrasono-cardiotomographic study. Japan Heart Journal. 1976; 17(5):611–629.
15. Yamaguchi H, Nishiyama S, Nakanishi S, Nishimura S. Electrocardiographic, echocardiographic and ventriculographic characterization of hypertrophic non-obstructive cardiomyopathy. European Heart Journal. 1983; 4:105–119. Suppl F. [PubMed: 6686526]
16. Fleming AD, McDicken WN, Sutherland GR, Hoskins PR. Assessment of colour Doppler tissue imaging using test-phantoms. Ultrasound in Medicine and Biology. 1994; 20(9):937–951. [PubMed: 7886853]
17. Miyatake K, Yamagishi M, Tanaka N, Uematsu M, Yamazaki N, Mine Y, Sano A, Hirama M. New method for evaluating left ventricular wall motion by color-coded tissue Doppler imaging: in vitro and in vivo studies. Journal of the American College of Cardiology. 1995; 25(3):717–724.10.1016/0735-1097(94)00421-L [PubMed: 7860919]

18. Urheim S, Edvardsen T, Torp H, Angelsen B, Smiseth OA. Myocardial strain by Doppler echocardiography. Validation of a new method to quantify regional myocardial function. Circulation. 2000; 102(10):1158–1164. [PubMed: 10973846]

19. Abraham TP, Laskowski C, Zhan WZ, Belohlavek M, Martin EA, Greenleaf JF, Sieck GC. Myocardial contractility by strain echocardiography: comparison with physiological measurements in an in vitro model. American Journal of Physiology—Heart and Circulatory Physiology. 2003; 285(6):H2599–2604.10.1152/ajpheart.00994.200200994.2002 [PubMed: 12907429]

20. Gulati VK, Katz WE, Follansbee WP, Gorcsan J 3rd. Mitral annular descent velocity by tissue Doppler echocardiography as an index of global left ventricular function. American Journal of Cardiology. 1996; 77(11):979–984. [PubMed: 8644649]

21. Gorcsan J 3rd, Strum DP, Mandarino WA, Gulati VK, Pinsky MR. Quantitative assessment of alterations in regional left ventricular contractility with color-coded tissue Doppler echocardiography. Comparison with sonomicrometry and pressure-volume relations. Circulation. 1997; 95(10):2423–2433. [PubMed: 9170406]

22. Greenberg NL, Firstenberg MS, Castro PL, Main M, Travaglini A, Odabashian JA, Drinko JK, Rodriguez LL, Thomas JD, Garcia MJ. Doppler-derived myocardial systolic strain rate is a strong index of left ventricular contractility. Circulation. 2002; 105(1):99–105. [PubMed: 11772883]

23. Voigt JU, Arnold MF, Karlsson M, Hubbert L, Kukulski T, Hatle L, Sutherland GR. Assessment of regional longitudinal myocardial strain rate derived from Doppler myocardial imaging indexes in normal and infarcted myocardium. Journal of the American Society of Echocardiography. 2000; 13(6):588–598. [PubMed: 10849513]

24. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. Journal of the American College of Cardiology. 1997; 30(6):1527–1533. [PubMed: 9362412]

25. Sohn DW, Chai IH, Lee DJ, Kim HC, Kim HS, Oh BH, Lee MM, Park YB, Choi YS, Seo JD, Lee YW. Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. Journal of the American College of Cardiology. 1997; 30(2):474–480. [PubMed: 9247521]

26. Nagueh SF, Sun H, Kopelen HA, Middleton KJ, Khoury DS. Hemodynamic determinants of the mitral annulus diastolic velocities by tissue Doppler. Journal of the American College of Cardiology. 2001; 37(1):278–285. [PubMed: 11153752]

27. Takemoto Y, Pellikka PA, Wang J, Modesto KM, Cauduro S, Belohlavek M, Seward JB, Thomson HL, Khandheria B, Abraham TP. Analysis of the interaction between segmental relaxation patterns and global diastolic function by strain echocardiography. Journal of the American Society of Echocardiography. 2005; 18(9):901–906.10.1016/j.echo.2005.05.008 [PubMed: 16153511]

28. Okada K, Mikami T, Kaga S, Onozuka H, Inoue M, Yokoyama S, Nishino H, Nishida M, Matsuno K, Iwano H, Yamada S, Tsutsui H. Early diastolic mitral annular velocity at the interventricular septal annulus correctly reflects left ventricular longitudinal myocardial relaxation. European Journal of Echocardiography. 2011; 12(12):917–923.10.1093/ejechocard/jer154 [PubMed: 21908514]

29. Pislaru C, Bruce CJ, Anagnostopoulos PC, Allen JL, Seward JB, Pellikka PA, Ritman EL, Greenleaf JF. Ultrasound strain imaging of altered myocardial stiffness: stunned versus infarcted reperfused myocardium. Circulation. 2004; 109(23):2905–2910.10.1161/01.CIR.0000129311.73402.EF01.CIR.0000129311.73402.EF [PubMed: 15173032]

30. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. Journal of the American Society of Echocardiography. 2005; 18(12):1440–1463.10.1016/j.echo.2005.10.005 [PubMed: 16376782]

31. Bacharova L, Michalak K, Kyselovic J, Klimas J. Relation between QRS amplitude and left ventricular mass in the initial stage of exercise-induced left ventricular hypertrophy in rats.

Clinical and Experimental Hypertension. 2005; 27(6):533–541.10.1081/CEH-200068802 [PubMed: 16081345]

32. McLeod CJ, Ackerman MJ, Nishimura RA, Tajik AJ, Gersh BJ, Ommen SR. Outcome of patients with hypertrophic cardiomyopathy and a normal electrocardiogram. Journal of the American College of Cardiology. 2009; 54(3):229–233.10.1016/j.jacc.2009.02.071 [PubMed: 19589435]
33. Kohsaka S, Sciacca RR, Sugioka K, Sacco RL, Homma S, Di Tullio MR. Additional impact of electrocardiographic over echocardiographic diagnosis of left ventricular hypertrophy for predicting the risk of ischemic stroke. American Heart Journal. 2005; 149(1):181–186.10.1016/j.ahj.2004.06.006 [PubMed: 15660051]
34. Ostman-Smith I, Wisten A, Nylander E, Bratt EL, Granelli AW, Oulhaj A, Ljungstrom E. Electrocardiographic amplitudes: a new risk factor for sudden death in hypertrophic cardiomyopathy. European Heart Journal. 2010; 31(4):439–449. [PubMed: 19897498]
35. Hsieh BP, Pham MX, Froelicher VF. Prognostic value of electrocardiographic criteria for left ventricular hypertrophy. American Heart Journal. 2005; 150(1):161–167. [PubMed: 16084164]
36. Antzelevitch C. Ionic, molecular, and cellular bases of QT-interval prolongation and torsade de pointes. Europace. 2007; 9(Suppl 4):iv4–15.10.1093/europace/eum166 [PubMed: 17766323]
37. Rajappan K, O'Connell C, Sheridan DJ. Changes in QT interval with exercise in elite male rowers and controls. International Journal of Cardiology. 2003; 87(2–3):217–222. [PubMed: 12559542]
38. Yang KC, Foeger NC, Marionneau C, Jay PY, McMullen JR, Nerbonne JM. Homeostatic regulation of electrical excitability in physiological cardiac hypertrophy. The Journal of Physiology. 2010; 588(Pt 24):5015–5032.10.1113/jphysiol.2010.197418 [PubMed: 20974681]
39. Antzelevitch C. Role of transmural dispersion of repolarization in the genesis of drug-induced torsades de pointes. Heart Rhythm. 2005; 2(2 Suppl):S9–15.10.1016/j.hrthm.2004.09.011 [PubMed: 16253930]
40. Yan GX, Lankipalli RS, Burke JF, Musco S, Kowey PR. Ventricular repolarization components on the electrocardiogram: cellular basis and clinical significance. Journal of the American College of Cardiology. 2003; 42(3):401–409. [PubMed: 12906963]
41. Klues HG, Schiffers A, Maron BJ. Phenotypic spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: morphologic observations and significance as assessed by two-dimensional echocardiography in 600 patients. Journal of the American College of Cardiology. 1995; 26(7):1699–1708.10.1016/0735-1097(95)00390-8 [PubMed: 7594106]
42. Petersen SE, Jerosch-Herold M, Hudsmith LE, Robson MD, Francis JM, Doll HA, Selvanayagam JB, Neubauer S, Watkins H. Evidence for microvascular dysfunction in hypertrophic cardiomyopathy: new insights from multiparametric magnetic resonance imaging. Circulation. 2007; 115(18):2418–2425.10.1161/CIRCULATIONAHA.106.657023 [PubMed: 17452610]
43. Schumacher B, Gietzen FH, Neuser H, Schummelfeder J, Schneider M, Kerber S, Schimpf R, Wolpert C, Borggrefe M. Electrophysiological characteristics of septal hypertrophy in patients with hypertrophic obstructive cardiomyopathy and moderate to severe symptoms. Circulation. 2005; 112(14):2096–2101.10.1161/CIRCULATIONAHA.104.515643 [PubMed: 16186424]
44. Ripplinger CM, Li W, Hadley J, Chen J, Rothenberg F, Lombardi R, Wickline SA, Marian AJ, Efimov IR. Enhanced transmural fiber rotation and connexin 43 heterogeneity are associated with an increased upper limit of vulnerability in a transgenic rabbit model of human hypertrophic cardiomyopathy. Circulation Research. 2007; 101(10):1049–1057.10.1161/CIRCRESAHA.107.161240 [PubMed: 17885214]
45. Marian AJ. Genetic determinants of cardiac hypertrophy. Current Opinion in Cardiology. 2008; 23(3):199–205.10.1097/HCO.0b013e3282fc27d900001573-200805000-00006 [PubMed: 18382207]

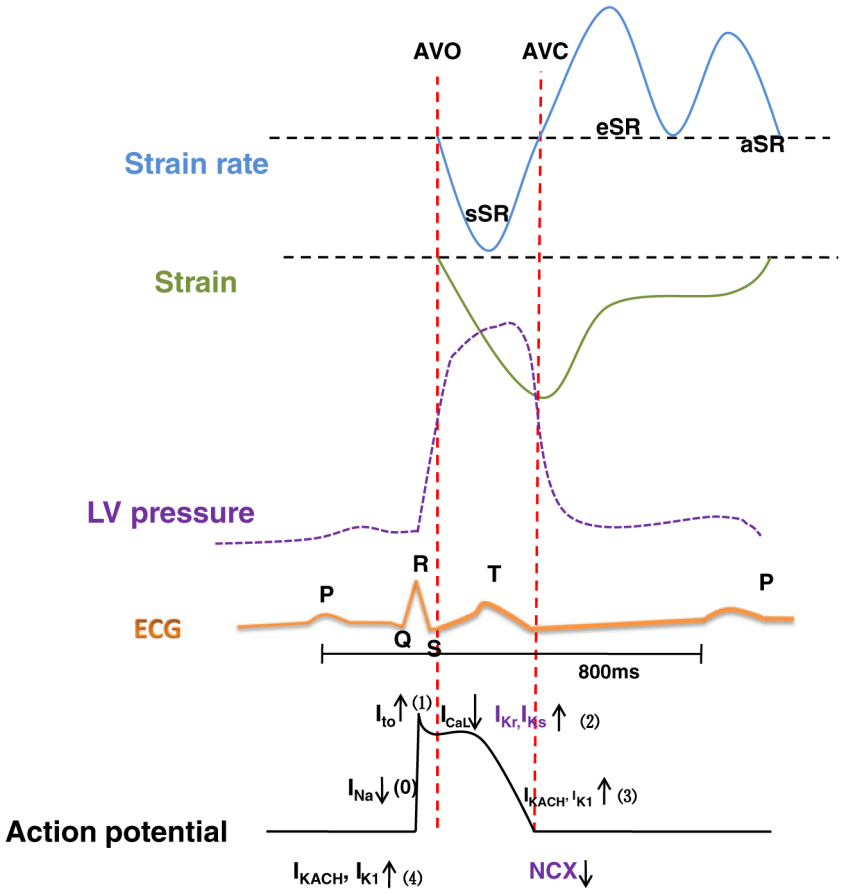
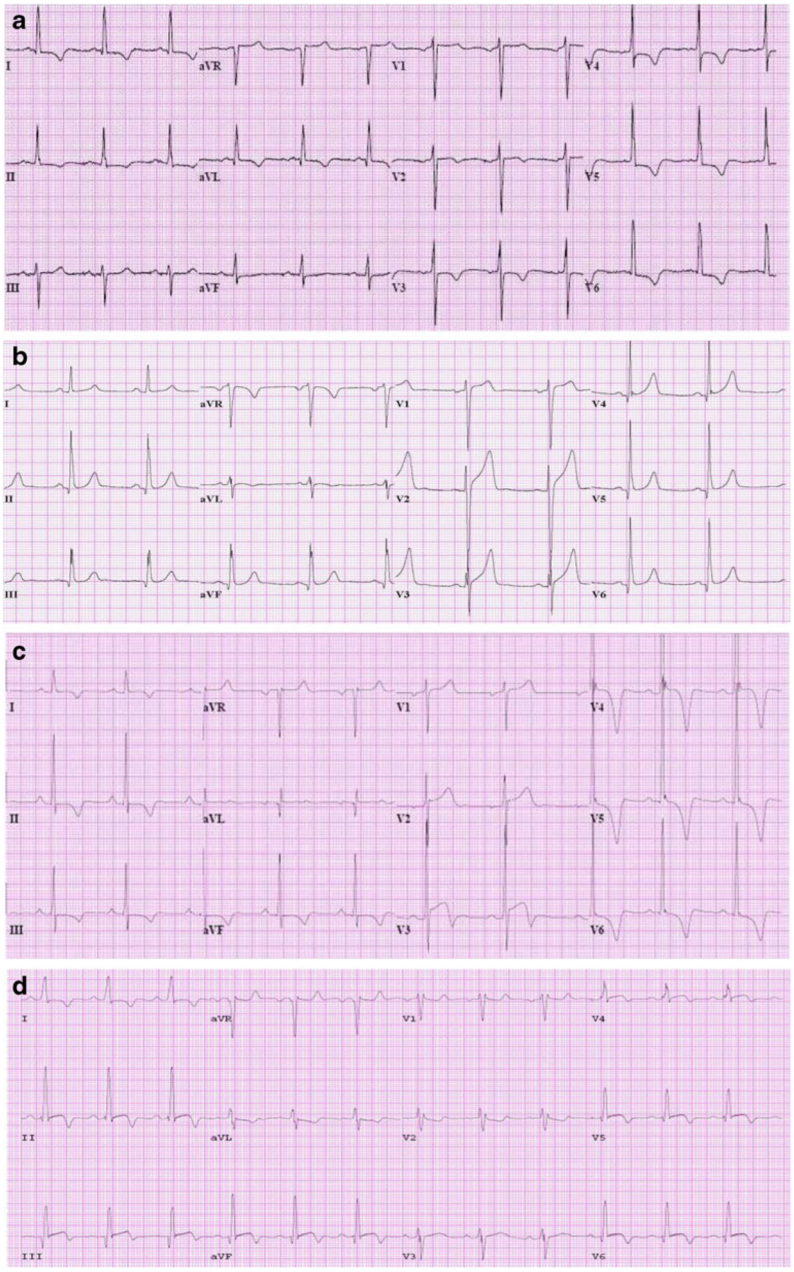


Fig. 1.

Schematic describing the relationship between LV mechanics, LV pressure, EKG, and ion channels. *AVO* aortic valve opening, *AVC* aortic valve closure, *sSR* systolic strain rate, *eSR* early diastolic strain rate, *aSR* late diastolic strain rate. Action potential phases: *(4)* resting, *(0)* upstroke, *(1)* early rapid repolarization, *(2)* plateau, *(3)* final rapid repolarization



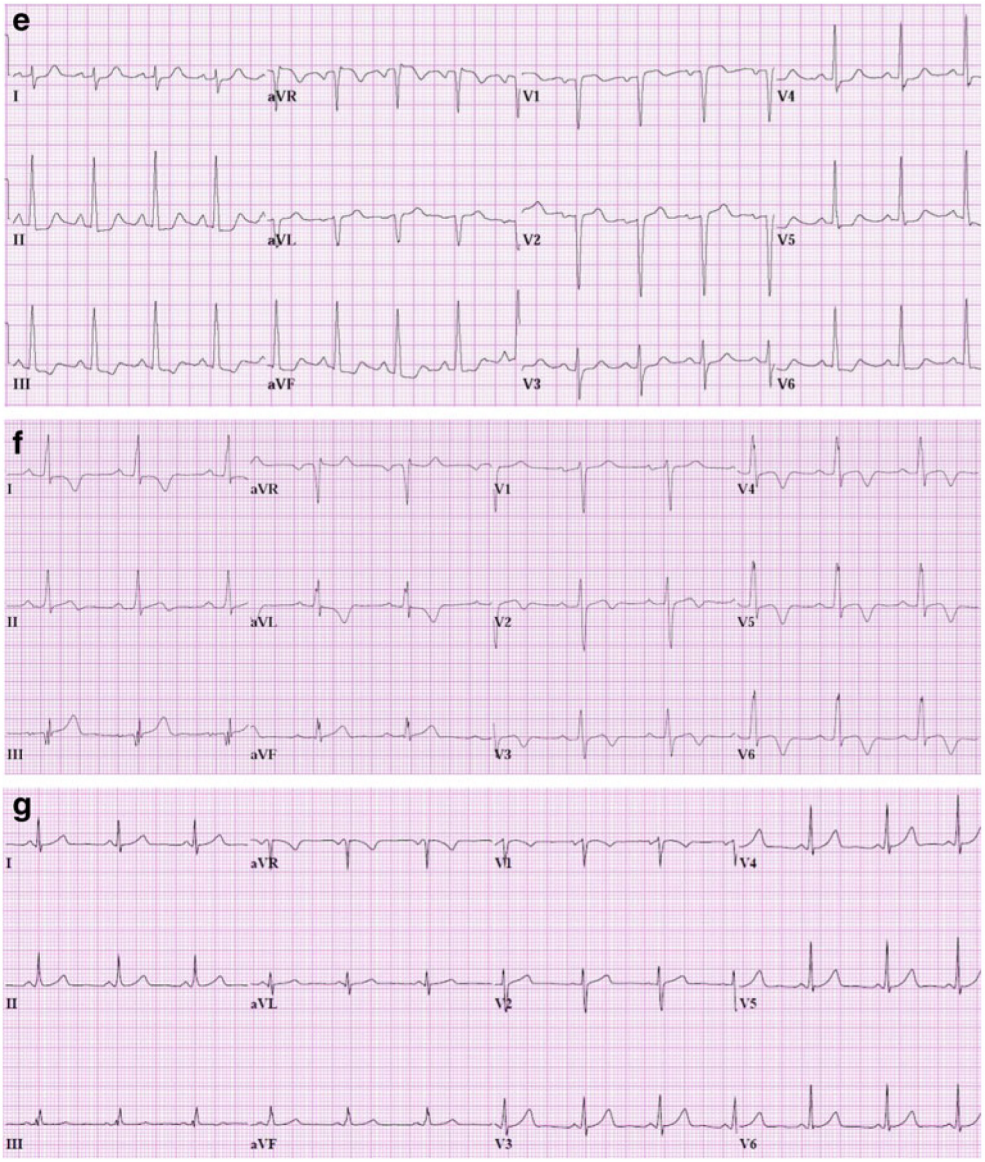


Fig. 2.

Representative electrocardiograms in HCM patients: **a** *strain pattern*: down-sloping convex ST-segment depression ≥1 mm with an inverted asymmetrical T-wave opposite to the QRS axis in at least two contiguous leads. See lead V4–V6; **b** *early repolarization:* slurring or notching of the terminal part of QRS complex and the beginning of the ST segment in at least two contiguous leads and J-point/ST elevation >1 mm. See *I*, V4–V6; *II*, *III*, aVF; **c** *giant T-wave inversion*: symmetrical negative T-wave of 10 mm or more in at least two contiguous leads. See lead V4 and V5; **d** *non-specific ST elevation*: ST-segment elevation ≥1 mm above the baseline at 80 ms after the J point in at least two contiguous leads. See *II*, *III*, V4–V6; **e** *non-specific ST depression*: ST-segment depression ≥1 mm below the baseline at 80 ms after the J point in at least two contiguous leads. See V4–V6; *II*, *III*, aVF; **f** *non-specific T-wave inversion*. T-wave inversion >1 mm in at least two contiguous leads. See *I*, aVL, V4–V6; **g** *normal EKG*

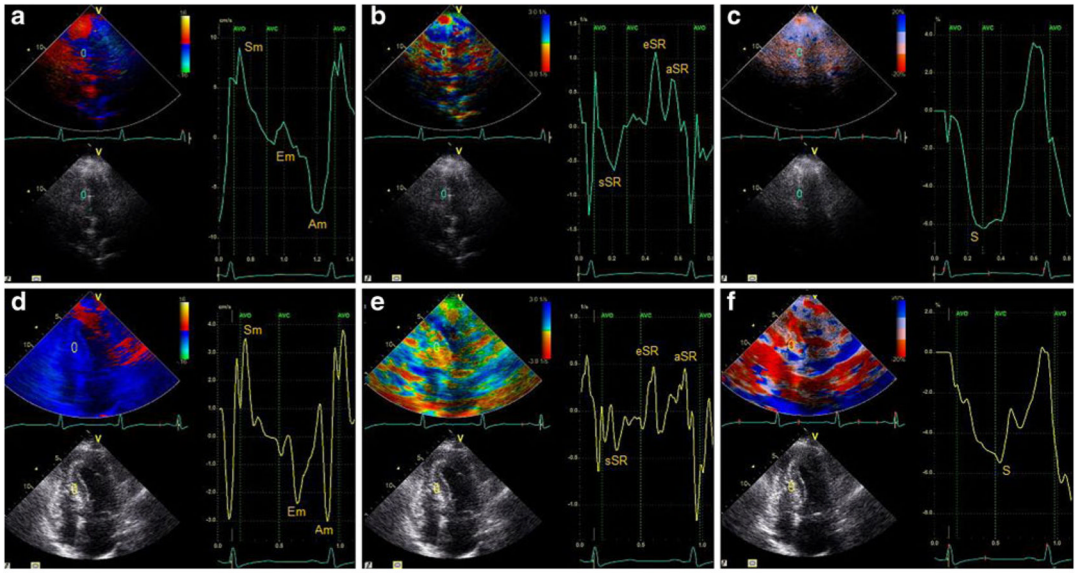


Fig. 3.

Representative tissue Doppler echocardiograms in an HCM patient with normal EKG (*upper*) and an HCM patient with strain pattern (*lower*). Tissue velocity (**a**, **d**): *Sm* systolic velocity, *Em* early diastolic velocity, *Am* late diastolic velocity; strain rate (**b**, **e**): *sSR* systolic strain rate, *eSR* early diastolic strain rate, *aSR* late diastolic strain rate; strain (**c**, **f**): *S* maximal systolic strain

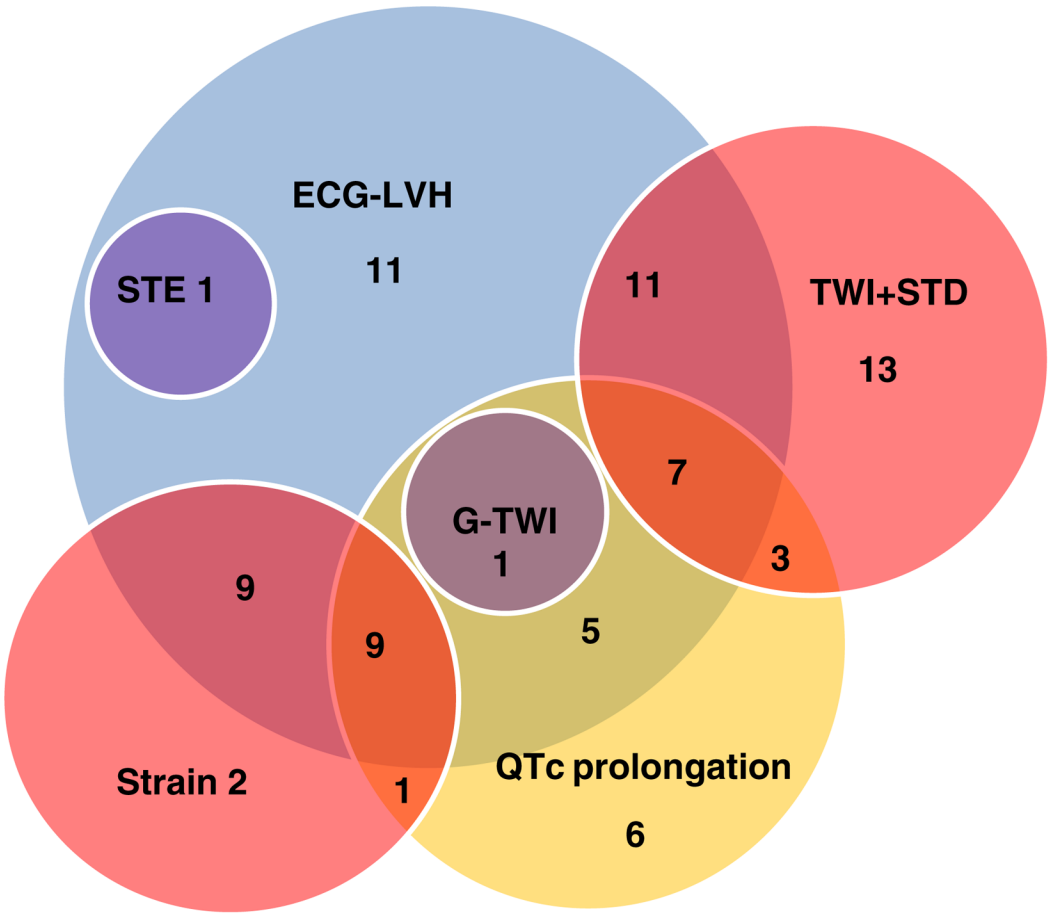


Fig. 4.

Venn diagram representing the overlap between LVH and abnormal repolarization on EKG in HCM patients. *LVH* left ventricular hypertrophy, *STE* non-specific ST elevation, *strain* EKG strain, *G-TWI* giant T-wave inversion, *STD+TWI* non-specific ST depression or T-wave inversion (patients with BBB (n=20), IVCD (n=15), early repolarization (n=8), and pathologic Q waves (n=10) are not represented here)

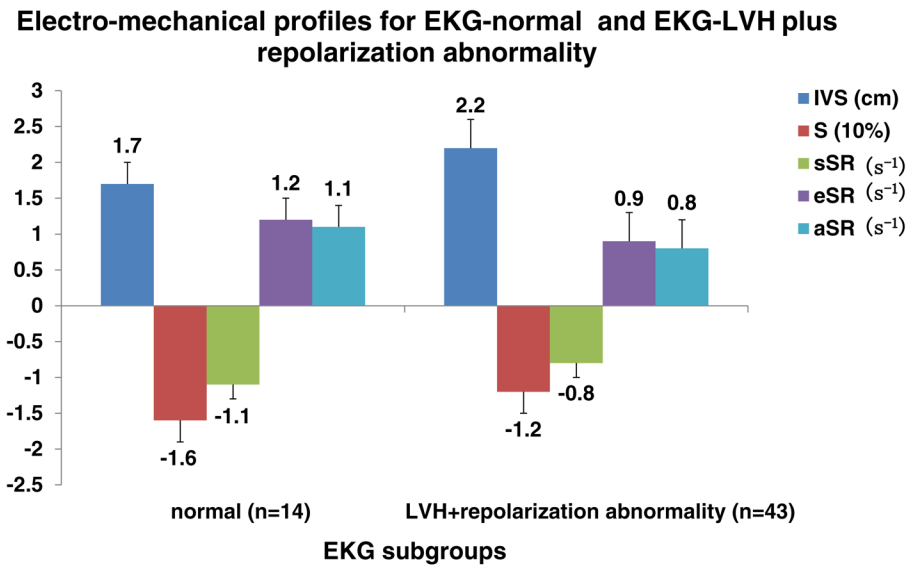


Fig. 5.

Electromechanical profiles for patients with normal EKGs and patients with evidence of LV H and repolarization abnormality on surface EKG (abnormal repolarization refers to QT_C prolongation, strain pattern, non-specific ST depression/T-wave inversion, non-specific ST elevation, and/or giant T-wave inversion). *LVH* left ventricular hypertrophy, *IVS* mean interventricular septum, *sSR* mean systolic strain rate, *eSR* mean early diastolic strain rate, *aSR* mean late diastolic strain rate, *S* maximal systolic strain

Table 1

Demographics, clinical characteristics, and EKG features

Patients number	**128**
Age (years)	53±16
Male	90 (70 %)
Caucasian	93 (73 %)
Clinical symptoms	
CHF (NYHA class I or II)	105 (82 %)
Angina	25 (20 %)
Presyncope	16 (13 %)
Syncope	17 (13 %)
Past history	
Diabetes mellitus	13 (10 %)
Atrial fibrillation	9 (7 %)
Coronary artery disease	14 (11 %)
Myectomy or alcohol septal ablation	24 (19 %)
Family history	
Hypertrophic cardiomyopathy	25 (20 %)
Sudden cardiac death	18 (14 %)
Electrocardiogram	
RBBB	11 (9 %)
LBBB	9 (7 %)
Strain pattern	21 (19 %)
Early repolarization pattern	8 (7 %)
Giant T-wave inversion	1 (1 %)
Non specific ST elevation	1 (1 %)
Non-specific ST depression	6 (6 %)
Non specific T-wave inversion	28 (26 %)
QT_c prolongation	32 (34 %)
Abnormal Q wave	10 (9 %)
IVCD	15 (14 %)
LVH (Sokolow–Lyon index)	30 (28 %)
LVH (Cornell product)	37 (34 %)
LVH (combination)	54 (50 %)
Normal	14 (11 %)
Echocardiography	
Max IVS/LVPW	1.8±0.3
SAM of mitral valve	107 (84 %)
LVOTPG (mmHg)	30±34
Mean Sm (cm/s)	3.6±1.1
Mean Em (cm/s)	−4.1±1.7
Mean Am (cm/s)	−3.6±1.5

Patients number	**128**
Mean sSR (s^{-1})	−0.9±0.3
Mean eSR (s^{-1})	1.0±0.4
Mean S (%)	−13.8±3.9
Mean aSR (s^{-1})	1.0±0.4
Medication	
Beta blocker	84 (66 %)
Ca channel blocker	35 (27 %)
ACEI or ARB	28 (22 %)
Patients number	128
Diuretics	17(13 %)
Amiodarone	2 (2 %)

CHF congestive heart failure, *BBB* bundle branch block, *IVCD* intra-ventricular conduction defect, *LVH* left ventricular hypertrophy, *combination* combination of Sokolow–Lyon index and Cornell product, *IVS* basal interventricular septum, *LVPW* LV posterior wall, *SAM* systolic anterior motion, *LVOT PG* left ventricular outflow tract pressure gradient, *Sm* systolic tissue velocity, *Em* early diastolic tissue velocity, *Am* late diastolic tissue velocity, *sSR* systolic strain rate, *eSR* early diastolic strain rate, *aSR* late diastolic strain, *S* strain, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker

Table 2

Lead breakup for EKG repolarization abnormalities

EKG characters	High lateral (I, aVL)	Anterolateral (V4–V6)	Inferior (II, III, aVF)	Any group
Strain pattern	11	12	8	21
Early repolarization	0	4	6	8
Giant T-wave inversion	0	1	0	1
Non-specific ST depression	0	3	6	6
Non-specific ST elevation	0	1	1	1
Non-specific T-wave inversion	17	20	10	28

Table 3

Echocardiographic measurements classified by EKG features in HCM

	Normal EKG *N*=14	EKG-LVH *N*=54	QT_c *N*=32	Strain pattern *N*=21	STD/TWI *N*=34
Age	50±13	53±17	50±15	53±16	56±15
CAD	2 (14 %)	6 (11 %)	2 (7 %)	4 (19 %)	3 (9 %)
Diabetes	1 (7 %)	7 (13 %)	4 (12 %)	0 (0 %)	5 (15 %)
Mean IVS (mm)	17±3	21±4[a]	20±5[a]	21±4[a]	21±5[a]
Max IVS/LVPW	1.8±0.3	1.9±0.5	2.0±0.6	1.8±0.4	2.0±0.5
LVIDs (mm)	25±4	25±5	24±4	26±4	25±5
LVIDd (mm)	42±5	43±5	43±5	45±5	43±5
EF (%)	68±10	67±10	66±12	66±10	67±11
LAVI (ml/m^2)	32±15	45±15	40±14	43±15	40±15
E wave (m/s)	0.8±0.1	0.9±0.4	0.8±0.2	0.8±0.3	0.9±0.4
A wave (m/s)	0.8±0.2	0.7±0.3	0.6±0.3[a]	0.6±0.3[a]	0.7±0.3
E/A	1.1±0.2	1.4±0.6[a]	1.5±0.6[a]	1.7±0.8[a,b]	1.4±0.7
MV DT(ms)	253±66	251±87	221±81	256±85	241±84
E/Em′	26±10	29±12	27±12	30±11	28±13
LVOTPG (mmHg)	22±24	32±32	23±23	24±28	35±39
Mean Sm (cm/s)	4.5±1.0	3.5±1.1[a]	3.6±1.0[a]	3.4±1.1[a]	3.4±1.2[a]
Mean Em (cm/s)	−4.8±1.8	−3.7±1.6	−3.9±1.5	−3.5±1.8[a]	−3.7±1.2[a]
Mean Am (cm/s)	−4.5±1.4	−3.2±1.4[a]	−3.3±1.4[a]	−2.6±1.2[a,b]	−3.7±1.6[a]
Mean sSR (s^{-1})	−1.1±0.2	−0.8±0.3[a]	−0.9±0.2[a]	−0.8±0.2[a]	−0.9±0.3[a]
Mean eSR (s^{-1})	1.2±0.3	0.9±0.3[a]	1.0±0.3	1.0±0.3	1.0±0.4
Mean aSR (s^{-1})	1.1±0.3	0.9±0.4[a]	0.9±0.4[a]	0.7±0.3[a,b]	1.0±0.4
Mean S (%)	−16±3	−13±3[a]	−13±3[a]	−12±3[a]	−13±3[a]

CAD coronary artery disease, *IVS* interventricular septum, *LVPW* LV posterior wall, *LVIDs* LV internal dimension at end systole, *LVIDd* LV internal dimension at end diastole, *EF* ejection fraction, *LAVI* left atrial volume index, *MV DT* deceleration time of mitral E wave, *LVOT PG* left ventricular outflow tract pressure gradient, *Sm* systolic tissue velocity, *Em* early diastolic tissue velocity, *Am* late diastolic tissue velocity, *sSR* systolic strain rate, *eSR* early diastolic strain rate, *aSR* late diastolic strain, *S* strain

[a]<0.05 vs. normal EKG

[b]<0.05 vs. STD/TWI