Published in final edited form as:

Am J Cardiol. 2011 December 1; 108(11): 1606–1613. doi:10.1016/j.amjcard.2011.07.019.

Electrocardiographic Features of Sarcomere Mutations Carriers With versus Without Clinically Overt Hypertrophic Cardiomyopathy

Neal K. Lakdawala, MD^a, Jens Jakob Thune, MD, PhD^b, Barry J. Maron, MD^c, Allison L. Cirino, MS, CGC^a, Ole Havndrup, MD, PhD^b, Henning Bundgaard, MD, PhD^b, Michael Christiansen, MD^d, Christian M. Carlsen, MD^e, Jean-François Dorval, MD^a, Raymond Y. Kwong, MD^a, Steven D. Colan, MD^f, Lars V. Køber, MD, DMSC^b, and Carolyn Y. Ho, MD^a

^aCardiovascular Division, Brigham and Women's Hospital, Boston, MA

^bDepartment of Cardiology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

^cHypertrophic Cardiomyopathy Center. Minneapolis Heart Institute Foundation, Minneapolis, MN

^dDepartment of Clinical Biochemistry, Statens Serum Institut, Copenhagen, Denmark

^eDepartment of Cardiology, Bispebjerg Hospital, Copenhagen, Denmark

^fDepartment of Cardiology, Children's Hospital Boston, Boston, MA

Abstract

In hypertrophic cardiomyopathy (HC), ECG changes have been postulated to be an early marker of disease, detectable in sarcomere mutation carriers when LV wall thickness is still normal. However, the ECG features of mutation carriers have not been fully characterized. Therefore, we systematically analyzed ECG's in a genotyped HC population to: 1. Characterize ECG findings in mutation carriers (G+) with and without echocardiographic left ventricular hypertrophy (LVH), and 2. Evaluate the accuracy of the ECG to differentiate at-risk mutation carriers from genetically unaffected relatives during family screening. ECGs and echocardiograms were analyzed in 213 genotyped subjects (76 G+/LVH–, 57 G+/LVH+ overt HC, 80 genetically unaffected controls). Cardiac magnetic resonance imaging (CMR) was available on a subset. Q waves and repolarization abnormalities (QST) were highly specific (98%) markers for LVH– mutation carriers, present in 25% of G+/LVH– subjects and 3% of controls (p<0.001). QST ECG abnormalities remained independently predictive of carrying a sarcomere mutation after adjusting for age and impaired relaxation, another distinguishing feature of G+/LVH– subjects (OR 8.4, p=0.007). Myocardial scar or perfusion abnormalities were not detected on CMR in any G+/LVH– subjects, irrespective of ECG features. In overt HC, 75% had Q waves and/or repolarization changes but <25% demonstrated common isolated voltage criteria for LVH. In conclusion, Q waves and repolarization abnormalities are the most discriminating ECG features of sarcomere

© 2011 Excerpta Medica, Inc. All rights reserved.

Address for Correspondence: Carolyn Y. Ho, M.D., Department of Cardiovascular Medicine, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, Phone: 617-732-5685 Fax: 617-264-5265, Cho@partners.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

DISCLOSURES

The authors have no conflicts of interest to report.

mutation carriers with and without LVH. However, due to the limited sensitivity of ECG and echocardiographic screening, genetic testing is required to definitively identify at-risk family members.

Keywords

Hypertrophic Cardiomyopathy; Electrocardiography; Genetics; Sarcomere

INTRODUCTION

Hypertrophic cardiomyopathy (HC) is the most common monogenic cardiovascular disorder. Sarcomere mutations can be identified in approximately 60% of affected patients.¹ Conventionally, a clinical diagnosis of HC is made by identifying unexplained left ventricular hypertrophy (LVH) by cardiac imaging. However, LVH typically does not develop until adolescence or later in life. The delayed penetrance of this key diagnostic feature makes it difficult to identify family members who are at risk for developing HC early in life, when LV wall thickness is normal. In contrast, genetic testing allows definitive identification of such individuals: relatives who have inherited a pathogenic sarcomere mutation (G+) but do not yet have diagnostic clinical features of HC (LVH-; denoted G+/LVH-). However, genetic testing may not always be feasible or results may be ambiguous. As such, more precise characterization of the clinical features of G+/LVH- individuals is of great value.

Electrocardiographic (ECG) abnormalities are common in patients with overt HC and have been postulated to be an earlier and more sensitive manifestation of sarcomere mutations than increased LV wall thickness.^{2,3} Prior systematic investigation of ECGs in genotyped HC populations has been limited.³⁻⁶ Therefore, we analyzed ECGs of well-characterized G+/LVH-, G+/LVH+ overt HC, and healthy G- relatives (as normal controls) to both better define ECG features associated with sarcomere mutations, and to assess the ability of the ECG to predict the genetic status of apparently unaffected family members with normal LV wall thickness. By studying genotyped populations, the early manifestations of sarcomere mutations can be better characterized, improving our understanding of how mutations cause disease.

METHODS

Genotyped HC probands and relatives identified via research protocols or through clinical evaluation were studied. Research subjects were recruited from 3 institutions; Brigham and Women's Hospital (n=106), The Minneapolis Heart Institute Foundation (n=57) and Copenhagen University Hospital (n=50). Genetic status was previously determined in the family proband by direct DNA sequencing of 8 sarcomere genes, including myosin binding protein C (*MYBPC3*), β -myosin heavy chain (*MYH7*), cardiac troponin T (*TNNT2*), cardiac troponin I (*TNNI3*), α -tropomyosin (*TPM1*); actin (*ACTC1*), myosin regulatory light chain (*MYL2*), and myosin essential light chain (*MYL3*) using standard methods. Mutation confirmation testing was performed on family members to determine if the family-specific mutation was present or absent.

Individuals were assigned to 3 different status groups based on genotype and echocardiographic wall thickness: G+/LVH- subjects, overt HC (G+/LVH+), and related normal control (G-/LVH-). The G+/LVH- group consisted of mutation carriers without echocardiographic LVH (maximal LV wall thickness <12 mm). This strict definition for G+/LVH- was chosen to avoid including subjects with borderline LVH and emerging or mild

clinical disease as G+/LVH− subjects. The overt HC group consisted of patients with a sarcomere gene mutation and diagnostic clinical features of HC, defined by a maximal echocardiographic left ventricular (LV) wall thickness of ≥ 12 mm in adults or z score ≥ 2 in children.⁷ Control subjects were healthy family members who did not carry the family-specific sarcomere mutation.

All subjects were assessed by history, physical examination, ECG, and echocardiography. Exclusion criteria included poor echocardiographic images, systemic hypertension (on medication or blood pressure $\geq 140/90$ mmHg), coronary artery disease, valvular heart disease, prior septal myectomy or alcohol septal ablation, or ventricular pacing. No subjects were taking cardiac glycosides. Informed consent was obtained from all participants in protocols approved by the Institutional Review Board of Brigham and Women's Hospital and the Local Science Ethics Committee, Copenhagen, Denmark.

Each subject underwent echocardiography with M-Mode, 2 dimensional and Doppler imaging according to standard clinical practice. Images were stored digitally and analyzed offline by two investigators blinded to clinical and genetic status. Standard measures of cardiac dimensions were made using the mean of 3 cardiac cycles in accordance with guidelines of the American Society of Echocardiography.⁸ Early myocardial tissue Doppler relaxation velocities (Ea) were measured at the lateral, septal, anterior, and inferior aspects of the mitral annulus. The mean Ea velocity of these four measurements was used to represent global Ea velocity. Statistical analyses were performed using global Ea.

Standard 12-lead ECGs were obtained at the time of echocardiographic examination with subjects resting quietly in the supine position. All ECGs were analyzed by a single investigator blinded to clinical, genetic, and echocardiographic information. Heart rate, QRS axis, intrinsicoid deflection, QRS and QT intervals were measured according to standard criteria.⁹ The QT interval was corrected for heart rate according to Bazett's formula ($QT_c = QT/\sqrt{RR}$). Criteria for defining ECG abnormalities are summarized in Table 1. Q waves in at least 2 contiguous leads were considered abnormal if they were of sufficient amplitude ($>1/3$ the height of the R wave) or duration (>30 ms). A more stringent definition of pathologic Q waves required both sufficient duration and amplitude.⁹

T wave inversion was considered if present in leads with R greater than S wave amplitude. T wave inversions in leads V1 – V3 were not considered pathologic in subjects younger than 18 years. ST segment depression was considered pathologic if present in at least 2 contiguous leads with depth greater than 0.1 mV if up-sloping or greater than 0.05 mV if horizontal or down-sloping. Non-specific ST or T-wave abnormalities (NSSTW) were considered present if there were abnormalities in the ST-segment or T waves that did not meet criteria for T wave inversion or ST-segment depression. LVH was defined by standard criteria including Romhilt-Estes¹⁰, Cornell¹¹, Sokolow-Lyon¹², and total voltage¹³ as described in Table 1. Major ECG abnormalities were considered present if diagnostic ST segment depression, T wave inversion, Q waves or any of the LVH criteria were identified. Minor ECG abnormalities included NSSTW, left atrial abnormality or delayed interventricular conduction (QRS >110 ms), in the absence of major abnormalities.¹⁴

Cardiac magnetic resonance (CMR) imaging was available in an unselected subset of subjects with sarcomere mutations who had studies performed at Brigham and Women's Hospital in the context of clinical evaluation or participation in other research studies examining G+ individuals. Images were analyzed by two investigators blinded to ECG characteristics and genotype. All patients were studied in either a 1.5-T (General Electric) or 3.0-T (Siemens) CMR system. Resting myocardial perfusion was assessed by the standard first-pass saturation-prepared T1-weighted fast gradient echo during injection of a

gadolinium contrast bolus (Magnevist, Bayer, Wayne, New Jersey).¹⁵ The CMR protocol included late gadolinium enhancement imaging (LGE) to evaluate for myocardial scar.¹⁶ Segmented inversion-recovery pulse sequence for LGE was used, starting 15 minutes after a cumulative 0.15-mmol/kg dose of gadolinium DTPA as previously described.¹⁷ Images were analyzed off-line using QMass (Medis, Leiden, Netherlands) and LGE was defined by any region of signal intensity greater than 2 standard deviations above the mean signal intensity of normal myocardium. In statistical analysis, LGE was described as a dichotomous variable, present or absent, for each individual.

Clinical, echocardiographic, ECG and CMR characteristics are presented for each of the 3 status groups as frequency and percent or mean values and standard deviations. Statistical analysis was performed with SAS version 9.1 (SAS Institute Inc., Cary, NC, USA). To test for differences between the 3 groups and adjust for the influence of relationships between family members, the GenMod procedure was used to perform analysis of variance (ANOVA) with clustering, assuming an exchangeable correlation structure. A p-value <0.017 was considered statistically significant to apply post-hoc Bonferroni correction for multiple comparisons across the 3 status groups. Logistic regression using the GenMod procedure was performed to evaluate multiple predictors simultaneously, adjust for confounders, and adjust for the influence of age on the penetrance of LVH and impact on Ea velocity, logistic regression. P values < 0.05 considered statistically significant in comparing the G+/LVH- and control cohorts.

RESULTS

213 individuals from 60 different families were evaluated, including 76 G+/LVH- subjects, 57 overt (G+/LVH+) HC, and 80 genotype-negative (G-) healthy relatives who served as normal controls. Clinical and echocardiographic characteristics are summarized in Table 2. Reflecting the age-dependent penetrance of LVH, the overt HC cohort was nearly 2 decades older than the G+/LVH- cohort. Pediatric subjects (<18 years) comprised 42% of the G+/LVH- cohort, compared to 33% and 4% in controls and overt HC respectively. Fifty-eight different mutations were represented (a full listing of all sarcomere mutations present in this cohort are provided in the supplementary table). As typically seen, mutations in *MYH7* (n=69; 52%) and *MYBPC3* (n=48; 36%) were most prevalent. Although minor differences in heart rate and blood pressure were noted among status groups, all were within normal ranges.

The ECG features of the 3 study cohorts are summarized in Table 3. In G+ and G- family members with normal LV wall thickness, Q waves and repolarization abnormalities (T wave inversions and ST depression) were significantly more prevalent in mutation carriers (p=0.01 and p=0.03, respectively) than G- normal controls. Representative tracings are shown in Figure 1. Other isolated and composite ECG abnormalities did not discriminate G+/LVH- subjects from controls. Collectively, Q waves and repolarization changes (the presence of either is denoted QST) were present in 25% of G+/LVH- subjects as compared to 2% of controls (Figure 2), and most commonly seen in the inferior leads. Fourteen (18%) G+/LVH- subjects had Q waves, including 10 with pathologic Q waves, in contrast to only 2 (3%) and 1 (1%) of control subjects, respectively. Notably, repolarization abnormalities were completely absent in control subjects. Only one G+/LVH- subject had both repolarization abnormalities and Q waves. Fifty-four percent of G+/LVH- subjects had an entirely normal ECG, compared to 64% of controls (p=0.19).

Despite the excellent specificity (98%) of QST for discriminating G+/LVH- subjects from G- normal controls, these ECG features were rare, resulting in 25% sensitivity. This level of discrimination is similar to that demonstrated by another marker of G+/LVH- subjects,

diminished Ea velocity. The test performance for ECG and echocardiographic abnormalities in differentiating G+/LVH− relatives from normal controls is summarized in Table 4.

G+/LVH− subjects with QST ECG abnormalities were more likely to have other ECG abnormalities and lower Ea velocities than those without QST, but no other significant associations were identified (Table 5). None of the 31 G+/LVH− subjects who underwent CMR had evidence of late gadolinium enhancement (LGE) or first pass perfusion abnormalities, including those with QST.

In overt HC, ECG abnormalities were commonly seen, with 86% of subjects showing major or minor findings (Table 3). As seen in G+/LVH− subjects, Q waves and repolarization abnormalities were most frequent (Figure 2). Notably, ECG criteria for LVH based on isolated increased QRS voltage alone (without repolarization abnormalities) were not uniformly present, despite increased echocardiographic LV wall thickness in all overt HC subjects. The most commonly used Sokolow-Lyon and Cornell criteria were least sensitive, seen in only 25% and 18% of overt HC subjects, respectively (Table 3). The prevalence of ECG criteria for LVH was higher using total voltage (49%) and Romhilt-Estes (48%) criteria. Nonetheless, 20 individuals with overt HC (35%) did not meet any of the standard ECG criteria for LVH. In contrast, Q waves and/or repolarization abnormalities (QST) were present in 74% of subjects. The presence of QST was associated with older age, other ECG abnormalities and a greater degree echocardiographic LVH, but no other significant associations were identified (Table 5).

DISCUSSION

Q waves and repolarization abnormalities are the most distinguishing ECG manifestations of sarcomere mutations in both early (G+/LVH−) and overt (G+/LVH+) hypertrophic cardiomyopathy. Despite the key role that increased LV wall thickness plays in the diagnosis of disease, isolated ECG voltage criteria for LVH are neither sensitive nor specific markers of HC. Voltage criteria without accompanying repolarization abnormalities are frequently absent in sarcomere mutation carriers, including those with clinically overt disease. These findings support and enhance prior studies using smaller cohorts with less generalizable genetic backgrounds,^{4–6} thereby improving our appreciation of the ECG features of sarcomere mutations in a larger, more diverse, and representative population.

A major goal of this study was to determine whether specific ECG features are consistently present in sarcomere mutation carriers, prior to the development of echocardiographic LVH and clinical diagnosis of HC. Such a finding would help identify which family members with normal LV wall thickness are truly at risk for developing disease. We found that Q waves and/or repolarization abnormalities (QST) were highly specific (98%) markers for the presence of a mutation in family members without LVH, and the only ECG features that could discriminate at-risk mutation carriers from non-carriers. These findings indicate that Q waves and repolarization abnormalities are another early phenotype of sarcomere mutations. As with impaired left ventricular relaxation, (as reflected by reduced Ea velocities^{18,19}), and increased collagen synthesis,²⁰ the presence of these ECG features in a family member with normal LV wall thickness suggests that a mutation is present. In contrast, non-specific ECG changes and isolated voltage criteria for LVH were relatively common in normal controls and do not necessarily indicate genetic susceptibility to developing HC.

However, the clinical utility of QST is importantly limited by their low sensitivity (25%). Indeed, the majority of G+/LVH− subjects had normal ECG tracings. In screening family members, a normal ECG is therefore non-informative and does not reliably indicate that a sarcomere mutation is absent. The low sensitivity of ECG features is consistent with prior

smaller studies,²¹ and has similarly limited the practical application of reduced Ea velocity in family evaluation. Accurate identification of at-risk adult relatives can be improved if both early phenotypes of sarcomere mutations are present. The combination of reduced Ea velocity and QST ECG abnormalities was associated with 100% positive and 65% negative predictive value for identifying G+/LVH- subjects older than 18 years. Nonetheless, completely normal ECGs and Ea velocity were present in 29% of G+/LVH- subjects and 43% of normal controls (p=0.09). Therefore, genetic testing remains the gold standard for definitive identification of at-risk family members.

As seen in other studies of genotyped^{4,5} and non-genotyped HC populations,^{22,23} the great majority of our cohort with overt sarcomeric HC (G+/LVH+) had major ECG abnormalities. As with mutation carriers without LVH, Q waves and repolarization abnormalities were most common. Notably, less than 25% of patients demonstrated ECG evidence of LVH using the most widely used isolated voltage criteria (Cornell or Sokolow-Lyon), and 35% had no ECG evidence of LVH through any standard ECG criteria. The poor correlation between isolated ECG voltage criteria and morphologic LVH has been previously reported in non-genotyped HC patients²⁴ and is not unique to this condition. Indeed, the ECG is similarly insensitive to secondary LVH due to hypertension or valvular heart disease.^{25,26} Furthermore, the *specificity* of isolated ECG voltage criteria for LVH is limited. This may be particularly relevant when evaluating highly trained athletes where major abnormalities, particularly increased voltage, are relatively poor predictors of pathologic cardiac hypertrophy.^{27,28} In contrast, major repolarization abnormalities are rarely seen in physiologic remodeling.²⁹ As with recent guidelines for the use of ECGs in pre-participation screening,^{27,28} accurate detection of pathologic cardiac hypertrophy in HC requires careful inspection for repolarization changes, QRS axis deviation and other associated abnormalities. Isolated voltage criteria for LVH without accompanying repolarization changes have poor diagnostic accuracy.

The etiology of Q waves and repolarization abnormalities in HC remains unclear, particularly in mutation carriers without LVH. In overt HC, these changes have been speculated to reflect myocardial scar, subendocardial ischemia, microvascular disease and hypertrophy. Previous studies attempting to clarify the anatomic basis of Q waves in HC through CMR imaging have yielded conflicting explanations.^{30,31} Similarly, we were unable to identify instructive imaging or clinical correlates of these ECG changes in overt HC or G+/LVH- subjects, including LGE as a reflection of gross myocardial scar.

Beyond clinical utility, identifying the early manifestations of sarcomere mutations, prior to the development of increased LV wall thickness, serves an important role by providing insights into disease pathogenesis. The presence of Q waves, repolarization abnormalities, impaired relaxation,^{18,19} and increased collagen synthesis²⁰ in mutation carriers with normal LV wall thickness demonstrate that sarcomere mutations have early consequences on myocardial biology, before a clinical diagnosis of HC can be made.¹⁸⁻²⁰ Longitudinal studies on a diverse population of G+/LVH- subjects are needed to characterize the full, dynamic range of phenotypes associated with sarcomere mutations, to understand the relationship between early manifestations and overt disease expression, and to characterize how early phenotypes may relate to adverse consequences of HC, such as susceptibility to arrhythmias and heart failure. For example, in this cohort, 4 of 42 mutation carriers with completely normal ECGs and Ea velocity were over 30 years of age. It is intriguing to speculate that such individuals with no apparent phenotype at an older age may represent a subgroup with markedly delayed or even non-penetrant mutations that are destined for more benign clinical outcomes. Such individuals may ultimately *not* develop overt HC despite the presence of a mutation, or manifestations may be less severe and substantially delayed to late adulthood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are indebted to Dr. Calum A. MacRae for his careful reading of our manuscript and insightful comments.

Sources of Funding:

This work was supported by grants from the National Institutes of Health [CYH, grant number K23 HL078901], Hearst Foundation, New York City (BJM) and the American College of Cardiology/Merck research foundation (NKL).

REFERENCES

1. Richard P, Charron P, Carrier L, Ledeuil C, Cheav T, Pichereau C, Benaiche A, Isnard R, Dubourg O, Burban M, Gueffet J-P, Millaire A, Desnos M, Schwartz K, Hainque B, Komajda M. for the EUROGENE Heart Failure Project. Hypertrophic Cardiomyopathy: Distribution of Disease Genes, Spectrum of Mutations, and Implications for a Molecular Diagnosis Strategy. *Circulation*. 2003; 107:2227–2232. [PubMed: 12707239]
2. al-Mahdawi S, Chamberlain S, Chojnowska L, Michalak E, Nihoyannopoulos P, Ryan M, Kusnierczyk B, French JA, Gilligan DM, Cleland J. The electrocardiogram is a more sensitive indicator than echocardiography of hypertrophic cardiomyopathy in families with a mutation in the MYH7 gene. *Br. Heart J*. 1994; 72:105–111. [PubMed: 7848420]
3. Ryan MP, Cleland JG, French JA, Joshi J, Choudhury L, Chojnowska L, Michalak E, al-Mahdawi S, Nihoyannopoulos P, Oakley CM. The standard electrocardiogram as a screening test for hypertrophic cardiomyopathy. *Am J Cardiol*. 1995; 76:689–694. [PubMed: 7572626]
4. Charron P, Dubourg O, Desnos M, Isnard R, Hagege A, Millaire A, Carrier L, Bonne G, Tesson F, Richard P, Bouhour J-B, Schwartz K, Komajda M. Diagnostic Value of Electrocardiography and Echocardiography for Familial Hypertrophic Cardiomyopathy in a Genotyped Adult Population. *Circulation*. 1997; 96:214–219. [PubMed: 9236436]
5. Konno T, Shimizu M, Ino H, Fujino N, Hayashi K, Uchiyama K, Kaneda T, Inoue M, Fujita T, Masuta E, Funada A, Mabuchi H. Differences in diagnostic value of four electrocardiographic voltage criteria for hypertrophic cardiomyopathy in a genotyped population. *Am J Cardiol*. 2005; 96:1308–1312. [PubMed: 16253604]
6. Havndrup O, Bundgaard H, Andersen PS, Allan Larsen L, Vuust J, Kjeldsen K, Christiansen M. Outcome of clinical versus genetic family screening in hypertrophic cardiomyopathy with focus on cardiac beta-myosin gene mutations. *Cardiovasc Res*. 2003; 57:347–357. [PubMed: 12566107]
7. Lopez L, Colan SD, Frommelt PC, Ensing GJ, Kendall K, Younoszai AK, Lai WW, Geva T. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. *J Am Soc Echocardiogr*. 2010; 23:465–495. quiz 576–577. [PubMed: 20451803]
8. 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. *J Am Soc Echocardiogr*. 2005; 18:1440–1463. [PubMed: 16376782]
9. Wagner, GS.; Marriott, HJL. *Marriott's Practical Electrocardiography*. Philadelphia, PA: Lippincott Williams & Wilkins; 2001.
10. Romhilt DW, Estes EH Jr. A point-score system for the ECG diagnosis of left ventricular hypertrophy. *Am Heart J*. 1968; 75:752–758. [PubMed: 4231231]

11. Casale PN, Devereux RB, Kligfield P, Eisenberg RR, Miller DH, Chaudhary BS, Phillips MC. Electrocardiographic detection of left ventricular hypertrophy: development and prospective validation of improved criteria. *J Am Coll Cardiol.* 1985; 6:572–580. [PubMed: 3161926]
12. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. *Am Heart J.* 1949; 37:161–186. [PubMed: 18107386]
13. Dollar AL, Roberts WC. Usefulness of total 12-lead QRS voltage compared with other criteria for determining left ventricular hypertrophy in hypertrophic cardiomyopathy: analysis of 57 patients studied at necropsy. *Am J Med.* 1989; 87:377–381. [PubMed: 2529761]
14. McKenna WJ, Spirito P, Desnos M, Dubourg O, Komajda M. Experience from clinical genetics in hypertrophic cardiomyopathy: proposal for new diagnostic criteria in adult members of affected families. *Heart.* 1997; 77:130–132. [PubMed: 9068395]
15. Steel K, Broderick R, Gandla V, Larose E, Resnic F, Jerosch-Herold M, Brown KA, Kwong RY. Complementary prognostic values of stress myocardial perfusion and late gadolinium enhancement imaging by cardiac magnetic resonance in patients with known or suspected coronary artery disease. *Circulation.* 2009; 120:1390–1400. [PubMed: 19770399]
16. Kim RJ, Fieno DS, Parrish TB, Harris K, Chen EL, Simonetti O, Bundy J, Finn JP, Klocke FJ, Judd RM. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. *Circulation.* 1999; 100:1992–2002. [PubMed: 10556226]
17. Kwong RY, Sattar H, Wu H, Vorobiof G, Gandla V, Steel K, Siu S, Brown KA. Incidence and Prognostic Implication of Unrecognized Myocardial Scar Characterized by Cardiac Magnetic Resonance in Diabetic Patients Without Clinical Evidence of Myocardial Infarction. *Circulation.* 2008; 118:1011–1020. [PubMed: 18725488]
18. Nagueh SF, Bachinski LL, Meyer D, Hill R, Zoghbi WA, Tam JW, Quinones MA, Roberts R, Marian AJ. Tissue Doppler imaging consistently detects myocardial abnormalities in patients with hypertrophic cardiomyopathy and provides a novel means for an early diagnosis before and independently of hypertrophy. *Circulation.* 2001; 104:128–130. [PubMed: 11447072]
19. Ho CY, Sweitzer NK, McDonough B, Maron BJ, Casey SA, Seidman JG, Seidman CE, Solomon SD. Assessment of diastolic function with Doppler tissue imaging to predict genotype in preclinical hypertrophic cardiomyopathy. *Circulation.* 2002; 105:2992–2997. [PubMed: 12081993]
20. Ho CY, Lopez B, Coelho-Filho OR, Lakdawala NK, Cirino AL, Jarolim P, Kwong R, Gonzalez A, Colan SD, Seidman JG, Diez J, Seidman CE. Myocardial fibrosis as an early manifestation of hypertrophic cardiomyopathy. *N Engl J Med.* 2010; 363:552–563. [PubMed: 20818890]
21. Maron BJ, Niimura H, Casey SA, Soper MK, Wright GB, Seidman JG, Seidman CE. Development of left ventricular hypertrophy in adults in hypertrophic cardiomyopathy caused by cardiac myosin-binding protein C gene mutations. *J Am Coll Cardiol.* 2001; 38:315–321. [PubMed: 11499718]
22. McLeod CJ, Ackerman MJ, Nishimura RA, Tajik AJ, Gersh BJ, Ommen SR. Outcome of patients with hypertrophic cardiomyopathy and a normal electrocardiogram. *J Am Coll Cardiol.* 2009; 54:229–233. [PubMed: 19589435]
23. Maron BJ, Wolfson JK, Ciro E, Spirito P. Relation of electrocardiographic abnormalities and patterns of left ventricular hypertrophy identified by 2-dimensional echocardiography in patients with hypertrophic cardiomyopathy. *Am J Cardiol.* 1983; 51:189–194. [PubMed: 6217739]
24. Montgomery JV, Harris KM, Casey SA, Zenovich AG, Maron BJ. Relation of Electrocardiographic Patterns to Phenotypic Expression and Clinical Outcome in Hypertrophic Cardiomyopathy. *Am J Cardiol.* 2005; 96:270–275. [PubMed: 16018856]
25. Devereux RB. Is the electrocardiogram still useful for detection of left ventricular hypertrophy? *Circulation.* 1990; 81:1144–1146. [PubMed: 2137731]
26. Rivenes SM, Colan SD, Easley KA, Kaplan S, Jenkins KJ, Khan MN, Lai WW, Lipshultz SE, Moodie DS, Starc TJ, Sopko G, Zhang W, Bricker JT. Usefulness of the pediatric electrocardiogram in detecting left ventricular hypertrophy: results from the Prospective Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection (P2C2 HIV) multicenter study. *Am Heart J.* 2003; 145:716–723. [PubMed: 12679770]

27. Pelliccia A, Maron BJ, Culasso F, Di Paolo FM, Spataro A, Biffi A, Caselli G, Piovano P. Clinical Significance of Abnormal Electrocardiographic Patterns in Trained Athletes. *Circulation*. 2000; 102:278–284. [PubMed: 10899089]
28. Corrado D, Pelliccia A, Heidbuchel H, Sharma S, Link M, Basso C, Biffi A, Buja G, Delise P, Gussac I, Anastakis A, Borjesson M, Bjornstad HH, Carre F, Deligiannis A, Dugmore D, Fagard R, Hoogsteen J, Mellwig KP, Panhuyzen-Goedkoop N, Solberg E, Vanhees L, Drezner J, Estes NA 3rd, Iliceto S, Maron BJ, Peidro R, Schwartz PJ, Stein R, Thiene G, Zeppilli P, McKenna WJ. Recommendations for interpretation of 12-lead electrocardiogram in the athlete. *Eur Heart J*. 2010; 31:243–259. [PubMed: 19933514]
29. Baggish AL, Hutter AM Jr, Wang F, Yared K, Weiner RB, Kupperman E, Picard MH, Wood MJ. Cardiovascular screening in college athletes with and without electrocardiography: A cross-sectional study. *Ann Intern Med*. 2010; 152:269–275. [PubMed: 20194232]
30. Papavassiliu T, Fluchter S, Haghi D, Suselbeck T, Wolpert C, Dinter D, Kuhl H, Borggrefe M. Extent of myocardial hyperenhancement on late gadolinium-enhanced cardiovascular magnetic resonance correlates with q waves in hypertrophic cardiomyopathy. *J Cardiovasc Magn Reson*. 2007; 9:595–603. [PubMed: 17365241]
31. Dumont CA, Monserrat L, Soler R, Rodriguez E, Fernandez X, Peteiro J, Bouzas A, Bouzas B, Castro-Beiras A. Interpretation of electrocardiographic abnormalities in hypertrophic cardiomyopathy with cardiac magnetic resonance. *Eur Heart J*. 2006; 27:1725–1731. [PubMed: 16774982]

A. Q Waves **B. Tw Inversions** **C. ST Depressions**

9 year old ♀
MYH7 Arg719Gln
 IVS 7.6 mm

22 year old ♂
MYH7 Arg653Gly
 IVS 8.1 mm

12 year old ♂
MYH7 Arg719Gln
 IVS 8.1 mm

Figure 1. Distinguishing ECG Abnormalities in G+/LVH- Subjects

Panels A, B, C: Q waves (black arrows), and repolarization changes (T wave inversions (asterisks) and/or ST segment depressions (grey arrows)) were significantly more common in G+/LVH- subjects than G- normal control relatives. IVS = interventricular septum thickness by echo.

Figure 2. The Frequency of Key ECG Abnormalities

Q waves, repolarization abnormalities, or the presence of either (QST) were significantly more prevalent in G+/LVH- subjects than controls. QST was also the most common and distinguishing abnormality in overt HC (G+/LVH+). Notably, commonly used isolated LVH voltage criteria (Sokolow-Lyon, Cornell) were not more common in G+/LVH- subjects and were present in only a minority of patients with overt HC. Normal = absence of major or minor ECG abnormalities; Qw = Q waves; SL = Sokolow-Lyon; Repol. = T wave inversions and/or ST segment depressions; QST = Q waves, T wave inversions and/or ST segment depressions. * $p < 0.05$, ** $p < 0.01$ adjusted for age and family relations.

Table 1

Definitions for ECG Abnormalities

Q Waves	
Q waves	Present in ≥ 2 contiguous leads and $> 1/3$ subsequent R wave or > 0.3 mV or > 30 ms duration
Pathologic Q waves	Present in ≥ 2 contiguous leads and $> 1/3$ subsequent R wave or > 0.3 mV and > 30 ms duration
Repolarization Abnormalities	
T Wave Inversion	≥ 0.1 mV in ≥ 2 contiguous leads
ST-segment Depression	<u>Upsloping</u> : ≥ 0.1 mV in ≥ 2 contiguous leads <u>Downsloping or flat</u> : ≥ 0.05 mV in ≥ 2 contiguous leads
Left Ventricular Hypertrophy	
Total Voltage	Sum of greatest positive and negative QRS deflection in 12 standard leads > 17.5 mV
Romhilt Estes*	Score ≥ 4
Sokolow-Lyon	$S_{V1} + R_{V5 \text{ or } V6} \geq 35$ mV
Cornell	$S_{V3} + R_{aVL} \geq 21$ mV (women) or 29 mV (men)
Composite Abnormalities	
Major Abnormality	Q waves, or Repolarization abnormality (excluding non-specific abnormalities), or Any LVH Criteria
Minor Abnormality [†]	Left atrial abnormality [‡] , or Prolonged interventricular conduction [§] , or Non-specific ST or T wave abnormalities
QST	Q waves, or T Wave Inversion, or ST-segment Depression

* The Romhilt-Estes score assigns points for the presence of increased voltage (3 points), repolarization abnormalities (3 points), intrinsicoid deflection > 50 ms (1 point), QRS duration > 90 ms (1 point), QRS axis left of -15° (2 points) and left atrial abnormality (3 points).

[†] In the absence of any major abnormality

[‡] P wave inversion in lead V1 at least 40 ms in duration and 1 mV in depth;

[§] QRS duration ≥ 110 ms.

Table 2

Clinical and Echocardiographic Features

Variable	Related Controls N=80	P-value G+/LVH- vs. Control	G+/LVH- N=76	P-value HC vs. G+/LVH-	Overt HC N=57	P-value HC vs. Control
Age (years) [range]	27.7 ± 11.8 [3–56]	0.004	22.8 ± 11.9 [4–47]	<0.001	40.0 ± 12.8 [14–75]	<0.001
Female	42 (53%)	0.27	47 (62%)	0.03	21 (37%)	0.11
Genotype (n)						
<i>MYH7</i>			40		29	
<i>MYBPC3</i>			28		19	
<i>TNNI2</i>			5		6	
<i>TNNI3</i>			3		2	
<i>TPM1</i>					1	
Body surface area (m ²)	1.79 ± 0.35	0.09	1.68 ± 0.38	<0.001	1.95 ± 0.22	0.003
Systolic blood pressure (mmHg)	121 ± 12	<0.001	111 ± 13	0.01	118 ± 11	0.27
Diastolic blood pressure (mmHg)	72 ± 10	<0.001	66 ± 8	<0.001	74 ± 9	0.50
Heart rate (bpm)	68 ± 11	0.91	68 ± 13	0.06	63 ± 12	0.01
Interventricular septal thickness (cm)	0.9 ± 0.1	0.94	0.9 ± 0.2	<0.001	1.7 ± 0.5	<0.001
Posterior wall thickness (cm)	0.8 ± 0.2	0.35	0.8 ± 0.1	<0.001	1.1 ± 0.3	<0.001
Global Ea * cm/sec ± standard error	14.4 ± 0.3	<0.001	12.7 ± 0.3	<0.001	10.0 ± 0.4	<0.001
Left ventricular ejection fraction (%)	65 ± 5	<0.001	70 ± 6	0.92	69 ± 8	0.001

Values are given as mean ± standard deviation unless otherwise noted. P values < 0.017 are considered statistically significant and reflect adjustment for family relations.

* Reflects adjustment for age and family relations.

Table 3

Electrocardiographic Features

Variable	Related Controls N=80	P-value G+/LVH- vs. Control	G+/LVH- N=76	P-value HC vs. G+/LVH-	Overt HC N=57	P-value HC vs. Control
Rhythm						
Sinus	78* (98%)	1.00	75* (99%)	0.19	55 (96%)	0.18
Atrial Fibrillation	0		0		2 (4%)	
QRS Axis (°)	55 ± 32	0.68	52 ± 31	0.12	38 ± 48	0.05
Conduction Disturbance						
Interventricular conduction delay	3 (4%)		2 (3%)		9 (16%)	
Left bundle branch block		1.00		0.002	1 (2%)	0.004
Right bundle branch block					1 (2%)	
Q wave	2 (3%)	0.028	14 (18%)	<0.001	24 (42%)	<0.001
Q wave Location						
Inferior	2 (2%)		8 (10%)		7 (12%)	
Anterior	0	1.00	1 (1%)	0.41	4 (7%)	0.78
Lateral	0		2 (3%)		8 (14%)	
Multiple	0		3 (4%)		5 (9%)	
Repolarization Abnormalities						
ST depression	0 (0)	0.12	3 (4)	<0.001	26 (46)	<0.001
T wave Inversion	0 (0)	0.12	3 (4)	<0.001	31 (54)	<0.001
ECG Criteria for Left Ventricular Hypertrophy						
Sokolow-Lyon	6 (8%)	0.52	7 (9%)	0.03	14 (25%)	0.007
Cornell	3 (4%)	0.43	5 (6%)	0.06	10 (18%)	0.015
Total 12-lead QRS Voltage > 17.5 mV	17 (21%)	0.45	20 (26%)	0.006	29 (49%)	<0.001

Variable	Related Controls N=80	P-value G+/LVH- vs. Control	G+/LVH- N= 76	P-value HC vs. G+/LVH-	Overt HC N=57	P-value HC vs. Control
Total 12-lead QRS Voltage (mV)	14.7 ± 4.0	0.45	15.1 ± 4.4	0.006	18.6 ± 5.9	<0.001
Romhilt-Estes	5 (6%)	0.43	7 (9%)	<0.001	28 (48%)	<0.001
Composite ECG Findings						
Any ECG Criteria for LVH	23 (29%)	0.70	24 (32%)	<0.001	37 (65%)	<0.001
Any Major or Minor ECG finding	29 (36%)	0.19	35 (46%)	<0.001	49 (86%)	<0.001

* Ectopic atrial rhythm was present in one G+/LVH- and two control subjects. Q waves and major/minor ECG criteria as defined in Table 1. P values < 0.017 are considered statistically significant and reflect adjustment for family relations.

Table 4

Test characteristics to distinguish G+/LVH− subjects from normal controls

	Specificity	Sensitivity	PPV	NPV
QST	98%	25%	90%	5%
<18 years old: Ea<13.5 cm/sec	76%	18%	69%	36%
≥18 years old: Ea<13.5 cm/sec	60%	68%	55%	73%
<18 years old: QST <u>and</u> Ea<13.5 cm/sec	88%	16%	71%	36%
≥18 years old: QST <u>and</u> Ea<13.5 cm/sec	100%	23%	100%	65%

Ea = global Ea; NPV = negative predictive value; PPV = positive predictive value; QST = Q waves, T wave inversion, and/or ST segment depression

Table 5
Clinical and Genetic Associations with Q waves and Repolarization Abnormalities in Mutation Carriers

Variable	G+/LVH-			Overt HC		
	QST Present N=19	QST Absent N=57	P-value	QST Present N=43	QST Absent N=14	P-value
Age (years)	22.0 ± 2.3	22.4 ± 2.1	0.87	38.4 ± 1.8	46.1 ± 3.0	0.005
Female	8 (42%)	39 (68%)	0.06	16 (37%)	5 (35%)	0.50
LVH Voltage Criteria *	10 (52%)	12 (21%)	0.003	27 (63%)	4 (29%)	0.01
Maximal wall thickness (cm)	0.9 ± 0.4	0.9 ± 0.2	0.85	1.8 ± 0.8	1.4 ± 0.5	<0.001
IVS/PWT ratio	1.1 ± 0.04	1.1 ± 0.01	0.79	1.6 ± 0.1	1.4 ± 0.1	0.12
Left ventricular ejection fraction (%)	70 ± 1.1	69 ± 1.0	0.41	69 ± 9	72 ± 6	0.23
Ea [†] (cm/sec)	12.3 ± 0.5	14.1 ± 0.3	<0.001	8.8 ± 0.3	9.7 ± 0.4	0.06
Genotype:						
MYH7 mutation	11 (58%)	29 (51%)	0.13	19 (44%)	9 (64%)	0.75
MYBPC3 mutation	3 (16%)	25 (44%)		15 (35%)	5 (36%)	

Values are given as mean ± standard error unless otherwise noted. P values < 0.05 are considered statistically significant and reflect adjustment for family relations.

* Presence of the Cornell, Sokolow-Lyon and/or 12-lead Voltage Criteria for LVH.

[†] Reflects adjustment for age and family relations.

IVS/PWT ratio = ratio of septal to posterior wall thickness (echo); Ea = Global early diastolic myocardial tissue velocity; QST = Presence of Q waves, ST segment depression and/or T wave inversion.