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Relationship of ECG findings to phenotypic expression in patients with hypertrophic cardiomyopathy: A cardiac magnetic resonance study ☆

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ABSTRACT

Background: The 12-lead electrocardiogram (ECG) is considered an essential screening tool for hypertrophic cardiomyopathy (HCM). A vast array of ECG abnormalities has been described in HCM, although their relationship to left ventricle (LV) morphology and degree of hypertrophy appears elusive. Aim of this study was to assess the relationship of ECG patterns with the HCM phenotype assessed according to the novel opportunities offered by cardiac magnetic imaging (CMR).

Methods: CMR and 12-lead ECG were performed in 257 HCM patients. Severity of ECG abnormalities was defined by the sum of 9 criteria: abnormal cardiac rhythm, QRS duration ≥ 100 ms, Romhilt–Estes score ≥ 5, fascicular block (LAHB) and/or bundle-branch block (LBBB or RBBB), ST-T abnormalities, ST-T segment elevation ≥ 0.2 mV, prolonged QTc interval, pathological Q waves, absence of normal Q wave. Four ECG groups were identified: normal (0 criteria); mildly abnormal (1–3 criteria); moderately abnormal (4–6 criteria); markedly abnormal (7–9 criteria).

Results: There was a direct relationship between severity of ECG abnormalities and HCM phenotype. LV mass index was normal in most patients with normal ECG and progressively increased with each class of ECG score, from 70.9 ± 18.6 g/m^2 in patients with normal ECG to 107.1 ± 55.1 g/m^2 among those with markedly abnormal ECG ($p = <0.0001$). Likewise, the prevalence and extent of late gadolinium enhancement (LGE) increased significantly with the ECG score, from 37% in patients with normal ECG to 93% in patients with markedly abnormal ECG (overall $p = 0.0012$). A normal ECG had a negative predictive accuracy of 96% for markedly increased LV mass (>91 g/m^2 for men and >69 g/m^2 for women), and of 100% for maximum LV thickness ≥ 30 mm.

Conclusions: In a large HCM cohort, the number and severity of ECG abnormalities were directly related to phenotypic expression as revealed by CMR. Although false negative ECG findings remain a challenge in population screenings for HCM, a normal ECG proved effective in ruling out severe LV hypertrophy, suggesting potential implications for long-term follow-up of HCM patients and family members. A simple score for quantification of ECG abnormalities in HCM patients is proposed.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is the most frequent genetic heart disease [1,2] and represents the most common cause of sudden cardiac death (SCD) in young people, including trained athletes [3–6]. The 12-lead electrocardiogram (ECG) is considered an essential screening tool for HCM in pre-participation athletic screening programs [7–9], and is more sensitive than echocardiography in identifying affected family members. A vast array of ECG abnormalities has been described in HCM [10–12], although their relationship to left ventricle (LV) morphology and degree of hypertrophy appears elusive. This concept, however, is based on a limited number of studies mostly performed in the early echocardiographic era [13–17]. Recent advances in cardiac magnetic (CMR) imaging, by virtue of its high-resolution volumetric reconstruction of LV chamber, currently afford a highly accurate and reproducible quantitative assessment of LV chamber morphology and mass, a precise characterization of the

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pattern and the distribution of LV hypertrophy [18–24], and the possibility to identify myocardial fibrosis areas using gadolinium [25–31]. Therefore, we took advantages of these unique features of CMR to assess the relationship of the HCM phenotype with standard 12-lead ECG patterns, as observed in two referral centers with specific expertise in cardiomyopathies.

2. Materials and methods

2.1. Patient selection

The study population included 257 patients with definite diagnosis of HCM (age 49 ± 16 years; 70% men), consecutively assessed by cardiac magnetic resonance (CMR) at the two participating institutions (Ospedale Cardinal Massaia, Asti, Italy [n = 124], and Azienda Ospedaliera Careggi, Florence, Italy [n = 133]) between March 2004 and October 2009. Patients with a history of coronary artery disease, chronic antiarrhythmic therapy, prior cardiac surgery or alcohol septal ablation, or contraindications to CMR (including pacemakers or implantable defibrillators) were excluded. All patients were assessed by CMR within one month from clinical evaluation, 12-lead ECG and echocardiography. The diagnosis of HCM was based on 2-dimensional echocardiographic evidence of a hypertrophied, non-dilated LV (maximal wall thickness ≥ 15 mm), in the absence of another cardiac or systemic disease that could produce the magnitude of hypertrophy evident [1,2]. The study protocol was approved by the internal review board of each institution.

2.2. Assessment of the 12-Lead ECG

A standard 12-lead ECG was performed in all patients in supine position during quiet respiration, and comprehensively analyzed in several aspects as recommended by the 2009 AHA guidelines [32] and according to the criteria described by Savage et al. [10], Friedmann and Romhilt and Estes [33–35]. With regard to LV hypertrophy assessment, we employed the following criteria: Romhilt–Estes, Sokolow, Cornell Voltage, Cornell Voltage-Duration, Lewis [34,36,37]. The Romhilt–Estes score was included in the ECG score described below, by virtue of its peculiar structure, addressing a number of morphologic abnormalities beyond voltage amplitude increase [34].

In order to quantify and compare the magnitude of ECG alteration in each study patient, we constructed a simple score based on 9 qualitatively different criteria: 1 — presence of abnormal cardiac rhythm (atrial fibrillation, atrial flutter, supraventricular tachycardia); 2 — prolonged QRS duration (≥100 ms) [32,38]; 3 — Romhilt–Estes score ≥ 5 suggesting LVH [34]; 4 — presence of fascicular block (in particular left anterior hemiblock (LAHB), left bundle-branch block (LBBB), right bundle branch block (RBBB) alone or in association to LAFB or LBBB [7,10]; 5 — ST segment/T wave abnormalities, defined as asymmetrical inversion of the T wave ≥ 0.1 mV deep in two or more leads except aVr, V1, V2; ST segment depression ≥ 0.1 mV at 0.08 s from the j point [3,7,10,32,39], or giant negative T waves > 10 mm deep [40]; 6 — convex ST-T segment elevation ≥ 0.2 mV [39]; 7 — prolonged QT interval corrected for cardiac frequency (QTc, measured in the six precordial leads, considering as normal limits 440 ms for men and 460 ms for women) [32,41]; 8 — presence of pathological Q waves (defined as Q waves > 0.04 s wide and 3 mm deep, or more than 1/3 of the following R wave in at least two consecutive leads with the exception of aVR) [7,10,50,42–44]; 9 — absence of normal Q wave in leads I-aVL and V5–V6 [32,45].

By summing the number of parameters in each individual, the 257 HCM study patients were divided into four groups as follows: — *group 1*: normal ECG (0 criteria); — *group 2*: mildly abnormal ECG (1–3 criteria); — *group 3*: moderately abnormal ECG (4–6 criteria); — *group 4*: markedly abnormal ECG (7–9 criteria).

2.3. Echocardiography

Standard echocardiographic studies were performed in the left lateral supine decubitus with commercially available instruments according to current guidelines [11]]. Maximum end-diastolic LV wall thickness was taken as the dimension of greatest magnitude at any site within the LV wall. Subaortic obstruction was defined as mechanical impedance to outflow due to systolic anterior motion (SAM) mid-systolic mitral-septal contact, and was graded semi-quantitatively, as previously described [3,6]. Peak instantaneous LV outflow gradient (LVOTG) was measured at rest (and with Valsalva maneuver) in the left lateral position with continuous-wave Doppler interrogation in the apical 5-chamber view, taking care to avoid contamination of the waveform by the mitral regurgitation jet [3,6]. LV outflow obstruction, due to mitral valve systolic anterior motion and mitral-septal contact, was identified by a peak instantaneous outflow gradient 30 mm HG. Mitral regurgitation was graded as none or trivial (0), mild (1+), moderate (2+), severe (3+) [3,6]. Left atrial volume was measured at end-systole using the biplane area-length method [46]. The baseline atrial volume calculated at the time of patient enrolment was used for all analyses. Left atrium was considered dilatated when A-P diameter was > 40 mm.

2.4. Cardiac magnetic resonance

CMR examinations were performed using commercially available scanners (Avanto, Siemens Medical System and Intera 1.5 T Philips) in conjunction with a phased-array body coil and electrocardiogram gating. There were executed images for the study of 1) Cine-MR and 2) delay enhancement.

1) Cine-MR images of the LV were obtained using a steady state free precession (SSFP, repetition time ms/echo time ms 2.6/1.3; flip angle, 60; field of view, 286 × 340 m^2, matrix, 256 × 304; section thickness, 5–8 mm). The Cine-MR sequences of the LV were obtained in the four-chamber, three chamber, two-chamber and short-axis view from base to apex, obtaining 12–14 sections of 5 mm with gap of 50% or 12–14 sections of 8 mm no gap. Endocardial and pericardial borders were outlined on the short axis cine images in order to calculate end-diastolic and end-systolic volumes, LV ejection fraction (EF), stroke volume, left myocardial mass, using standard ventricular analysis software (Leonardo, Siemens and Viewform, Philips); all images were analyzed by an experienced investigator (a cardiologist with experience in CMR) at each center, blinded to the results of echocardiography.

The LV mass was indexed to body surface area (BSA). LV mass index was considered normal when < 82 g/m^2 for men and < 62 g/m^2 for women, mildly increased when < 81 for men, < 91 g/m^2 and < 69 g/m^2 for women, and markedly increased when > 91 g/m^2 for men and > 69 g/m^2 for women [22]. Maximum end-diastolic LV wall thickness was taken as the dimension of greatest magnitude at any site within the LV wall. The American Heart Association 16-segment model for the LV was used to analyze wall thickness, contractile function, and delay enhancement for segment [47]. The true apex (segment 17) was analyzed on the four chambers or two chambers view of the LV.

2) The presence of late gadolinium enhancement (LGE) was assessed by visual inspection 5–7 min after intravenous injection of a dose of 0.2 mmol/Kg of body weight bolus of gadopentetate dimeglumine (Gadovist; Shering) at 1 mL/s with a breath-held segmented inversion recovery sequence (inversion time 220 to 270 ms, adjusted manually in each patient) to null the signal of the normal myocardium, acquired in the same views as the cine images (flip angle, 25°; field of view, 276 × 340 mm^2; matrix, 135 × 256; section thickness, 8 mm). LGE was considered present in areas with signal intensity exceeding > 6 SD that of normal myocardium signal, as generally recommended [48]. The same segment model used to analyze wall thickness in the Cine-MR images [47], was used to semi-quantitatively assess the extent and distribution of LGE, based on the number of segments involved [47,49].

2.5. Statistical analysis

Data were expressed as mean ± SD. For the comparison of 2 and more than 2 normally distributed variables, we employed the Student t test and 1-way analysis of variance (ANOVA). The chi-square test was utilized to compare non-continuous variables expressed as proportions; however, the Fisher exact test was employed when 1 or more cells in the comparison table had an expected frequency of < 5. All p values were considered significant when < 0.05.

3. Results

3.1. Study population

The study cohort comprised 257 HCM patients with a maximum LV wall thickness of 22 ± 6 mm; mean age was 49 ± 16 years; 70% were male. Most (90%) were in NHYA functional classes I or II at enrolment and 39% had evidence of dynamic LV outflow obstruction at rest (Table 1).

3.2. General ECG findings

Overall, 6% of patients (n = 16) had a normal ECG, 38% (n = 97) had abnormalities highly suggestive for HCM (such as giant negative t waves, Romhilt–Estes score ≥ 5 and/or presence of pathological Q wave), and the remaining 56% (n = 144) had non-specific abnormalities (Fig. 1; Fig. 2). Most patients (n = 249; 97%) were in sinus rhythm at enrolment, although 8 (3%) were in AF; of note, an abnormal atriogram was common (72%), and mostly comprised negative portion of the P wave in lead V1 ≥ 0.1 mV in depth and ≥ 0.04 s in duration [5,10]. The PR interval was prolonged in 23 patients (9%) with a maximum PR interval of 280 ms.

Intraventricular conduction abnormalities (QRS duration ≥ 100 ms) were present in 44% patients, with LAHB morphology in 57 patients (22%), LBBB in 24 (9%) and RBBB in 16 (6%); 5 additional patients (2%) presented LAHB and RBBB combined. A prolonged QTc interval (> 440 ms for men and > 460 in women) was present in 89 patients (35%) (Table 2). Repolarization abnormalities were present in 47% of patients: specifically, 30% (n = 77) had both ST-T depression and T wave inversion, 7% (n = 18) had only ST-T depression and 10%

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Table 1
Clinical, ECG and CMR findings in 257 patients with HCM.

	Total population	Normal ECG (0 criteria)	Mildly abnormal ECG (1–3 criteria)	Moderately abnormal ECG (4–6 criteria)	Markedly abnormal ECG 7–9 criteria	p value
No. of patients	257	16	96	129	16	
Sex (M)	182 (70%)	8 (50%)	72 (75%)	91 (70%)	11 (69%)	0.24
Age (years)	49 ± 16	49.9 ± 13.1	48.9 ± 14.7	48.7 ± 16.9	52.5 ± 18.4	0.54
Family history of HCM	96 (38%)	8 (50%)	40 (42%)	39 (30%)	9 (56%)	0.069
LVOT obstruction at rest ≥ 30 mm Hg	100 (39%)	8 (50%)	42 (44%)	46 (36%)	4 (25%)	0.3
≥ Moderate mitral regurgitation	67 (26%)	3 (19%)	22 (23%)	37 (29%)	5 (31%)	0.65
AF history	73 (28%)	3 (19%)	22 (23%)	42 (33%)	6 (38%)	0.27
NYHA class	I: 139 (54%)	I: 11 (69%)	I: 54 (56%)	I: 63 (49%)	I: 11 (69%)	0.22
	II: 92 (36%)	II: 3 (19%)	II: 35 (37%)	II: 49 (38%)	II. 5 (31%)	0.48
	III–IV: 26 (10%)	III–IV: 2 (12%)	III–IV: 7 (7%)	III–IV: 17 (13%)	III–IV: 0 (0%)	0.34
CMR						
Left atrial dilatation (>40 cc/m^2)	141 (55%)	6 (38%)	53 (55%)	71 (55%)	11 (69%)	0.36
Mass index (g/m^2)	101.6 ± 43.2	70.9 ± 18.6	92.3 ± 35.3	110.8 ± 44.7	107.1 ± 55.1	<0.0001
Maximal wall thickness (mm)	21.8 ± 5.7	17.3 ± 3.1	21.2 ± 5.7	22.8 ± 5.7	21.3 ± 5.4	0.001
With LGE	188 (73%)	6 (38%)	66 (73%)	102 (83%)	14 (93%)	0.0012
LV EF	67% ± 12%	69% ± 9%	70% ± 10%	65% ± 12%	60% ± 14%	0.001
Diffuse hypertrophy	134 (52%)	0 (0%)	42 (44%)	82 (64%)	10 (63%)	<0.0001
Localized hypertrophy	123 (48%)	16 (100%)	54 (56%)	47 (36%)	6 (38%)	<0.0001
Apical hypertrophy	31 (12%)	0 (0%)	8 (8%)	20 (16%)	3 (19%)	0.13

Abbreviations: HCM: hypertrophic cardiomyopathy, CMR: cardiac magnetic resonance, LGE: late gadolinium enhancement, AF: atrial fibrillation, LV: left ventricle, EF: ejection fraction, LVOT: left ventricular outflow tract.

(n = 26) had only T wave inversion; among 37% of patients with T wave inversion 8% (n = 20) had giant negative T waves. Convex ST-T segment elevation was present in 93 patients (36%). Finally, 135 patients (53%) of the study patients had pathological Q waves in the inferior (n = 39, 29%), lateral (n = 78, 58%) or inferolateral leads (n = 18, 13%), whereas absence of physiological Q waves in leads I-aVL and V5–V6 was seen in 61% (Table 2; Fig. 2). Of note, patients with pathological Q waves were younger than those without (45 ± 16 vs 52 ± 16 years, p = 0.002).

3.3. Comparison of ECG criteria for LV hypertrophy

We calculated the accuracy of 5 ECG criteria for LV hypertrophy in identifying extreme LV mass increase at CMR (>69 g/m^2 for females and >91 for males), including Romhilt–Estes, Sokolow, Cornell Voltage, Cornell Voltage-Duration, Lewis. When compared to the other scores, the Romhilt–Estes showed the best positive predictive value (72%) and the second highest accuracy (66%), although sensitivity was relatively low. Conversely, Sokolow and Cornell Voltage were the most sensitive (Table 3).

3.4. Classes of ECG score

When the 9 pre-specified criteria were analyzed and computed, the average score for the study cohort was 3.7 ± 1.6. Of note, 16 patients (6%) had completely normal ECG, 96 (38%) had only mildly abnormal tracings (1–3 criteria), whereas 129 (50%) had moderately abnormal (4–6 criteria) and 16 (6%) had markedly abnormal ECG (7–9 criteria). There was no significant difference in the number of criteria based on gender, age (<40 and ≥40 years), symptomatic status or presence of LV obstruction (Table 1).

With regard to the conventional risk factors for sudden death, none of the 16 patients with normal ECG had a history of resuscitated cardiac arrest or maximum LV wall thickness ≥30 mm, recurrent NSVT, syncope or abnormal blood pressure response to exercise, while 6 patients (38%) had a family history of sudden death and 8 (50%) had dynamic LVOT obstruction at rest ≥ 30 mm Hg. Overall, only 3 of the 16 patients (19%) had 2 or more risk factors suggesting a moderate or high-risk profile.

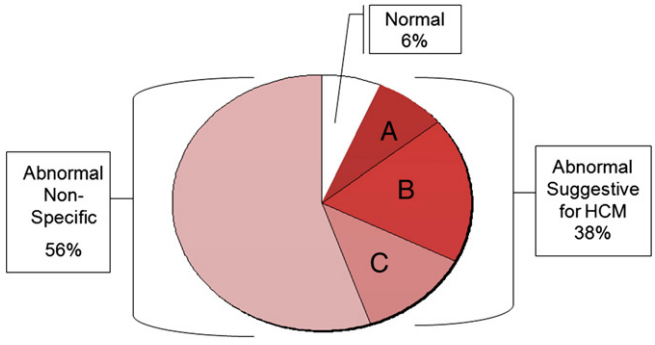

Fig. 1. Prevalence of ECG patterns in a cohort of 257 patients with HCM.A — patients with giant T waves (8%); B — inferolateral Q waves, positive Romhilt–Estes point score, repolarization abnormalities (18%); C — inferolateral Q wave and positive Romhilt–Estes point score (12%).

3.5. CMR findings

LV mass index in the 257 HCM patient cohort was 101 ± 43 g/m^2, and was greater in males than females (106 ± 43 vs. 90 ± 39 g/m^2, respectively; p<0.001). LV mass index was normal (≤81 g/m^2 for men and ≤61 g/m^2 for women) in 61 patients (24%), mildly increased (>81 and ≤91 g/m^2 for men and >61 g/m^2 and ≤69 g/m^2 for women) in 48 patients (19%), and markedly increased (>91 g/m^2 for men and >69 g/m^2 for women) in 148 patients (57%). Maximum LV wall thickness was 22 ± 6 mm, generally localized to the interventricular septum; 31 patients (12%) had apical hypertrophy (isolated or associated with other hypertrophic segments). Severe focal hypertrophy (max LV wall thickness ≥ 30 mm) was observed in 31 patients, localized to the basal or mid anteroseptal segments. Overall 188 (73%) patients had evidence of myocardial fibrosis as reflected by LGE (Table 1), ranging from 2 to 60 cc. Of note, in 74 patients (29%) LGE involved one localized segment of left ventricle, while in the remaining patients (183, 71%) LGE involved more than one segment, ranging from two to multiple and diffuse areas of LV.

Of note, younger patients (<40 years; n = 72) showed significantly greater LV mass index and LV maximum wall thickness compared to those >40 years (n = 182; 118.64 ± 57.1 vs 92.8 ± 33.2 g/m^2, p<0.001 and 24.4 ± 7.3 mm vs 20.7 ± 4.6 mm, p<0.001, respectively). Conversely, prevalence of LGE was similar in the two groups (77% vs 76% p = 0.66).

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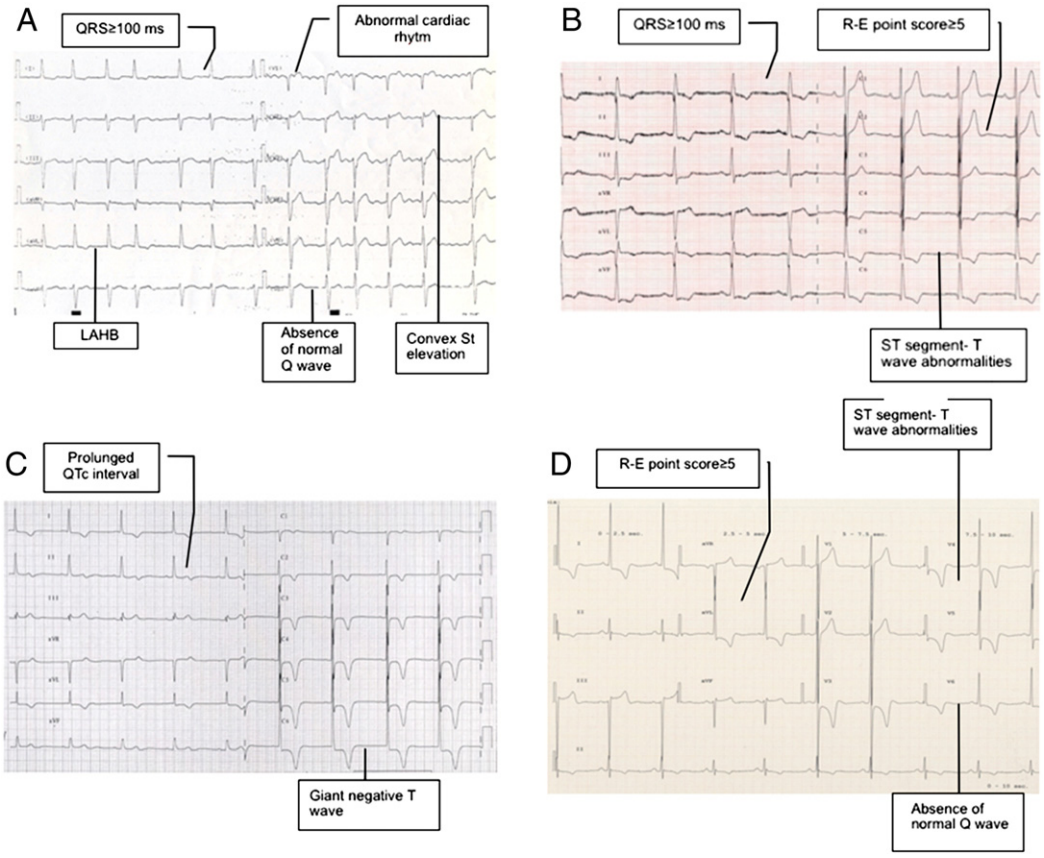

Fig. 2. ECG criteria employed in the study.The nine different ECG criteria used to construct the score for ECG analysis (as described in Materials and methods section): 1 — abnormal cardiac rhythm; 2 — QRS ≥ 100 ms; 3 — Romhilt–Estes (R–E) point score ≥ 5; 4 — left anterior hemiblock (LAHB), left bundle-branch block (LBBB), right bundle branch block (RBBB) alone or in association to LAFB; 5 — ST segment/T wave abnormalities; 6 — convex ST-T segment elevation ≥ 0.2 mV; 7 — prolonged QTc; 8 — pathological Q waves; 9 — absence of normal Q wave in leads D I-aVL and V5–V6.

Table 2
Prevalence of ECG abnormalities.

ECG results	Total population	%
	No. pt 257	
1 Abnormalities of cardiac rhythm		
Atrial fibrillation	8	3%
2 QRS duration > 90 ms		
100 ≤ QRS duration < 120 ms	76	30%
QRS duration ≥ 120 ms	29	11%
3 bundle-branch block		
LAHB	57	22%
LBBB	24	9%
RBBB	16	6%
4 LV hypertrophy criteria		
Romhilt–Estes point score ≥ 5	155	60%
5 Prolonged QTc interval		
QT corrected ≥ 440 ms for men	68/182	37%
QT corrected ≥ 460 ms for women	18/75	24%
6 Repolarization abnormalities		
Both ST segment depression and negative T wave	77	30%
Only ST segment depression	18	7%
Only negative T wave (≤ 10 mm and ≥ 10 mm)	26	10%
Only negative T wave ≥ 10 mm	20	8%
7 ST convex segment elevation ≥ 2 mm in V1-V2 leads	93	36%
8 Pathological Q waves	135	53%
9 Absent Q waves in leads D1, aVl and V5–V6	156	61%

Abbreviations/symbols:

LAHB: left anterior fascicular block
LBBB: left bundle-branch block
RBBB: right bundle-branch block
LV: left ventricle.

3.6. Relation of ECG morphology to CMR findings

In the subset of patients with normal ECG, the CMR phenotype was milder compared to the other subgroups. The value of LV mass index, according to the definition specified in methods, was normal in most patients with normal ECG (mean value 76.8 ± 18.4 g/m^2 in males and 63.8 ± 18.8 g/m^2 in females), and progressively increased with each class of ECG score (Table 1, Fig. 3A). Likewise, maximum LV wall thickness was only 17 ± 3 mm in patients with normal ECG, and increased progressively with each score class, to 22 and 21 mm, respectively, in the two upper classes of ECG score ($p = 0.001$) (Table 1, Fig. 3B). Of note, none of patients with normal ECG had severe focal hypertrophy ≥ 30 mm, or apical hypertrophy (Table 1). Likewise, the prevalence and extent of LGE increased significantly with the ECG score: LGE was present only in 37% of normal ECG patients, compared to 83% of patients with moderately and 93% with markedly abnormal ECG (overall $p = 0.0012$) (Table 1, Fig. 3C).

When specific ECG features were analyzed, patients with pathological Q waves ($n = 103$, 40%) showed greater prevalence of LGE (80% vs 69%; $p = 0.05$) compared to those without. In addition, the 20 patients with giant negative T waves (8%), had greater degrees of hypertrophy compared to those without (LV mass index 120 ± 53 g/m^2 vs 99 ± 42 g/m^2, respectively, $p = 0.03$), and more often involved the LV apex (50% vs. 9%, respectively, $p = 0.0004$). Finally, a positive Romhilt–Estes point score ($n = 155$, 60%) was associated with marked increase in LV mass index (111 ± 48.6 g/m^2; compared to 86 ± 25 g/m^2 in those with a negative score; $p < 0.001$), and increased prevalence of LGE (78% vs 66%, respectively; $p = 0.025$). Conversely we observed no correlation between QTc prolongation and prevalence of LGE (83% among patients with vs. 73% without QTc prolongation, $p = 0.08$).

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Table 3
Accuracy of different ECG LV hypertrophy scores in the identification of severe LV hypertrophy by CMR. For each score [34,36,37], we calculated the accuracy in identifying extreme LV mass increase at CMR (i.e. >69 g/m^2 for females and >91 for males, [22]).

	Romhilt–Estes score	Sokolow score	Cornell Voltage score	Cornell Voltage-Duration score	Lewis score
Sensitivity (%)	71%	90%	80%	81%	76%
Specificity (%)	59%	52%	61%	45%	48%
Accuracy (%)	66%	63%	67%	55%	56%
Positive predictive value (%)	72%	45%	48%	36%	37%
Negative predictive value (%)	59%	92%	87%	86%	83%
Prevalence of LVH with each score (%)	59%	30%	31%	27%	29%

LV = left ventricle.
LVH = LV hypertrophy.
CMR = cardiac magnetic resonance.

3.7. CMR findings according to ECG score

When the four classes of ECG score were assessed with regard to CMR findings, we observed a direct relationship between severity of ECG abnormalities and HCM phenotype expressed as LV mass index, maximum LV wall thickness and presence of LGE (Fig. 3). Specifically, mean LV mass was 70.9 ± 18.6 g/m^2 among patients with normal ECG, compared to 107.1 ± 55.1 g/m^2 among those with markedly abnormal ECG ($p<0.001$). Furthermore, the extension of LGE was different in the four groups of ECG score: patients with normal ECG generally had localized LGE (a single segment was involved in 5 of 6 patients, or 83%). Among 16 patients with normal ECG, 6 exhibited areas of LGE on CMR (38%), a significantly lower proportion compared to the other ECG groups (Table 1). Specifically, 5 of the 6 patients only had limited areas of LGE localized to a single segment at the basal septal level, and the remaining patient had moderate LGE involving 4 segments at the basal anteroseptal and inferior level. Conversely, patients with moderately and markedly altered ECG generally had diffuse LGE (>3 segments in 78% and 93% respectively; $p<0.001$ compared to normal ECG).

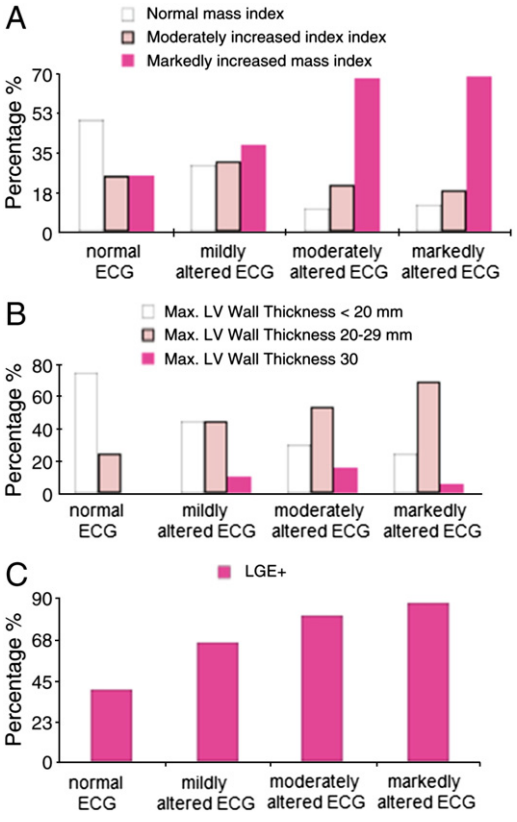

Fig. 3. Prevalence of different HCM phenotypes according to ECG score.A — Distribution of LV mass index values based on class of ECG score. B — distribution of maximum LV wall thickness values based on class of ECG score. C — presence of LGE based on class of ECG score.

In spite of this evident trend, individual variability was great, and included patients with severe CMR phenotypes despite normal ECG, as well as very mild phenotypes despite markedly abnormal ECG. Clear discordance between ECG and CMR findings were observed in 87 (34%) patients, including 46 (18%) with markedly abnormal ECG in the presence of mild hypertrophy at CMR (Fig. 4C), and 41 (16%) with mildly abnormal ECG but striking phenotype and severe hypertrophy (Fig. 4B). On the other side, substantial concordance between ECG and CMR findings was found in 170 patients (66%), including 71 (28%) with mild ECG and CMR findings (Fig. 4D), and 99 (39%) with severe ECG and CMR alterations (Fig. 4A). Overall, a normal ECG proved to have a 96% negative predictive accuracy for markedly increased LV mass; conversely, a markedly abnormal ECG was highly specific for a severe CMR phenotype (Table 4).

4. Discussion

The principal finding of the present study is that the severity of ECG abnormalities in HCM patients is directly related to the degree of phenotypic expression, as characterized by CMR. In a consecutive HCM cohort of 257 patients, we observed a clear trend linking the extent of ECG derangement to both the degree of hypertrophy (in terms of LV mass and LV wall thickness), and the prevalence of myocardial fibrosis expressed as LGE. On one hand, severe HCM phenotypes were generally associated with marked ECG alteration, so that a score equal or greater than 7 among 9 different abnormalities showed very high sensitivity for severe degrees of LVH. Conversely, mild LVH was generally associated with lesser ECG abnormalities, including totally normal tracings.

Of note, LV mass index in patients with a normal ECG was only 70.9 ± 18.6 g/m^2, compared to 107.1 ± 55.1 g/m^2 among those with markedly abnormal tracings ($p<0.001$). A similar relationship was found with regard to maximum LV wall thickness, averaging 17 mm in patients with normal ECG, as compared to 22 and 21 mm, respectively, in patients with moderately and markedly abnormal ECG ($p=0.001$). Indeed, it is interesting to note that a positive Romhilt–Estes point score (n = 155, 60%) was associated with marked increase in LV mass index (111 ± 48.6 g/m^2: compared to 86 ± 25 g/m^2 in those with a negative score; $p<0.001$). Conversely, none of patients with normal ECG had extreme focal hypertrophy ≥30 mm. Finally, the assessment of LGE, considered a reflection of intramyocardial fibrosis in HCM hearts, was significantly more prevalent and extensive in the two patients subgroups with moderately and markedly abnormal ECG (i.e. 83% and 93%, respectively, in patients with ECG scores of 4–6 and 7–9), compared to those with normal ECG (37,5%; $p=0.0012$). Intriguingly, these findings were particularly evident in younger patients, in whom the most striking manifestations of HCM

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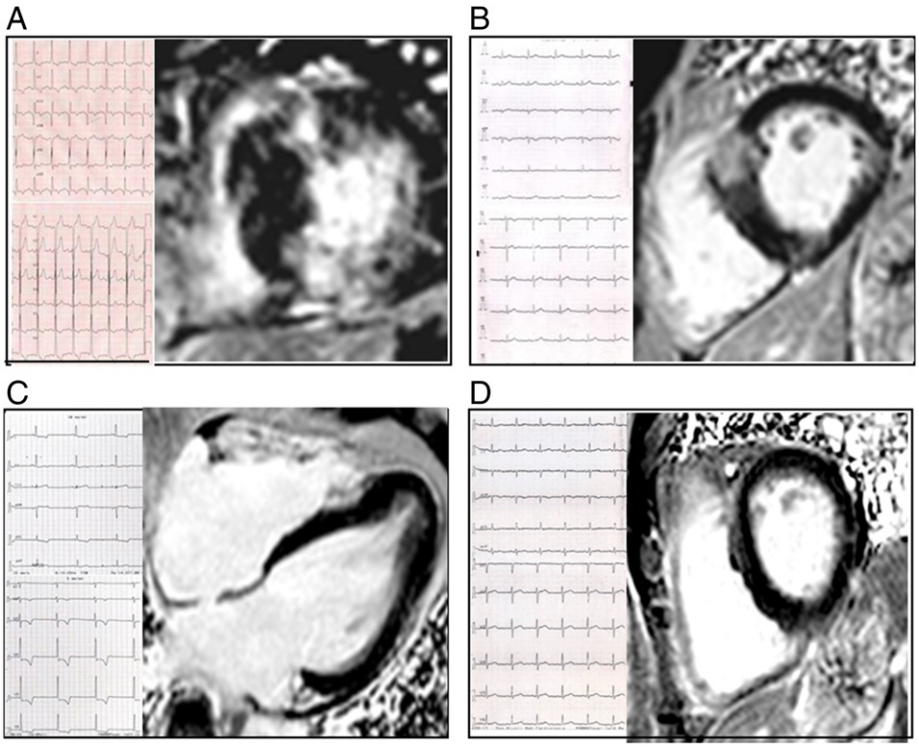

Fig. 4. Examples of concordance and discordance of ECG and CMR phenotypes. A — markedly abnormal ECG in a patient with severe LVH and extensive LGE; B — normal ECG in a patient with severe LVH and significant LGE; C — markedly abnormal ECG in a patient with mild LVH and no LGE; D — normal ECG in a patient with mild LVH and no LGE. Abbreviations: LV = left ventricle, VS = ventricular septum, asterisk = LGE.

were observed, including greater LV mass index and LV maximum wall thickness values.

As a result of these findings, a normal ECG proved to have a 96% negative predictive accuracy for extreme LV mass increase, a known predictor of adverse outcome in HCM (Table 4). This concept may prove very important for the risk stratification of patients with HCM, because is well now that some aspects as extreme focal hypertrophy, greatly augmented LV mass index and presence of wide area of LGE are associated with substantial risk of adverse events, and adverse prognosis [22, 27–31]. Ultimately, it is plausible to hypothesize that severe ECG abnormalities may represent predictors of outcome in HCM. Specifically, patients in the most severe class of ECG score showed a cluster of clinical features, such as increased maximum LV wall thickness, LV mass index and LGE, associated with adverse outcome in this disease. Conversely, patients with mildly abnormal or normal ECG have a substantially more favorable profile, consistent with the recent study by McLeod et al. [11] depicting a relatively benign prognosis in HCM individuals with normal tracings. Therefore, it is a sound working hypothesis that the long-neglected ECG may represent an important tool for long-term risk stratification in HCM; large multicenter studies are required to investigate this issue, not only with regard to an ECG score, but also to single, specific abnormalities which may ported increased risk, such as QTc and QRS prolongation or pathologic Q waves [10–15].

Table 4
Specificity, sensitivity and predictive accuracy of the ECG score for markedly increased LV mass index (>91 g/m^2 for men and >69 g/m^2 for women, [22] in the text).

	Specificity	Sensibility	Positive PV	Negative PV
Normal ECG (%)	60	60	8	96
Mildly abnormal ECG (%)	68	50	41	76
Markedly abnormal ECG (%)	86	50	30	93

PV = predictive value; LV = left ventricle.

The nine criteria chosen in the present study were intended to reflect different morpho-functional features of the ECG, in order to construct a score that might be fairly exhaustive in gauging its overall degree of abnormality. As such, all main types of ECG abnormalities have been included. That said, it would not have been practical, or feasible to address several fine details such as, for example, P wave abnormalities or prolongation of intrinsecoid deflection. Of note, P wave abnormalities are very common in HCM patients, as an expression of atrial dilatation, potentially reflecting important pathophysiologic features such as diastolic dysfunction and increased LV filling pressures [2]; while the prolongation of intrinsecoid deflection is an expression of myocardial activation delay due to LV hypertrophy [32]. Although not included as such, however, both features are included in the Romhilt-Estes model, and are therefore represented in our overall ECG score.

With regard to specific ECG morphologies, we identified, three different subgroups among our HCM patients: the first comprised 6% of patients who had a with normal ECG; the second, comprising 38%, with abnormalities which may raise the specific suspicion of HCM (such Romhilt Estes point score≥5 [34], giant negative T wave [40] or pathological Q wave [7,10,50,42–45]), and the last, including 56% of the total cohort, with nonspecific abnormalities of the ECG, which do not suggest the presence of an HCM phenotype, but represent "red flags" useful in identifying individuals deserving further investigation. Among the classic ECG abnormalities considered suggestive for HCM, both a Romhilt Estes score≥5 and a pathological Q wave were associated with greater LV mass index and LV maximum wall thickness values; furthermore, Q waves were associated with increased prevalence of LGE, although specificity was low (80% vs 69% in patients without Q waves; p=0.05). Finally, patients with giant negative T waves generally showed markedly increased LV mass index compared (with an average of 120 g/m^2) which, not unexpectedly, was frequently localized to the apical septum and apex of the LV.

These data point to the ECG as a powerful screening tool for severe HCM phenotypes, potentially associated with increased arrhythmic risk [23,31]. In such perspective, there are several clinical considerations

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to be made, with potential implications for management. First of all, while the ECG may be less than optimal for ruling out HCM in large populations, this widely available technique represents a very cost-effective tool to exclude severe disease expression. In the general population, the likelihood of a false negative ECG failing to identify HCM patients appears mostly confined to mild phenotypes, which are recognized to be at substantially lower risk [11]. Therefore, these findings support the role of the ECG as a valuable initial screening tool in order to prioritize referral to echocardiography and imaging techniques such as CMR, particularly in those settings where access is limited. In addition, regular ECG screening may allow frequent and more affordable follow-up evaluation in HCM family members with negative phenotype at initial echocardiographic screening. Indeed, the appearance of new ECG abnormalities, sometimes occurring abruptly over short periods of time, generally precede overt LVH and represent sensitive indicators of HCM phenotype development, particularly in young patients. The same strategy can be envisaged in athletes or individuals with mild LVH which is not diagnostic for HCM but requires monitoring over time. In each of these scenarios, the use of automated ECG software and simple scores, such as that employed in the present study, may be of help in order to increase sensitivity, as has been successfully experimented for in other diseases [50–52].

In conclusion, the number and severity of ECG abnormalities were directly related to phenotypic expression of HCM as revealed by CMR. A normal ECG showed very high negative predictive value for severe LVH and LGE, suggesting potential implications for long-term follow-up of HCM patients and family members. The significant minority of HCM patients with normal ECG findings, although rarely characterized by high risk profiles, continues to represent a diagnostic challenge for screening. A simple score for quantification of ECG abnormalities in HCM patients is proposed.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [53].

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