ST-segment depression as a risk factor in hypertrophic cardiomyopathy


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Aims
From the spectrum of electrocardiogram (ECG) changes that may occur in hypertrophic cardiomyopathy (HCM), there is no criterion reported to be useful for risk stratification. We sought to determine whether there was a relationship between the resting ECG findings and prognosis in patients with HCM.

Methods
We retrospectively analysed data on 173 consecutive patients admitted to our centre with a diagnosis of HCM. The 12-lead ECGs were assessed for underlying rhythm, PR interval, QRS voltages, QRS width, corrected QT interval, ST-segment deviation, T-wave inversion, and left atrial enlargement (LAE). During a mean follow-up of 50 months, 6.4% of patients had a combined endpoint [sudden death or appropriate implantable cardioverter-defibrillator (ICD) therapy]. The frequency of the combined endpoint was greater in patients with syncope, non-sustained ventricular tachycardia, maximal left ventricular (LV) wall thickness /C21 30 mm, and ST-segment depression in the high lateral leads (all *P* < 0.05). Other ECG findings (LV hypertrophy, LAE, abnormal Q wave, abnormal ST-T changes, and underlying rhythm), family history of sudden death, and LV outflow obstruction were not related to the combined endpoint. The results of our multivariate analysis demonstrated that ST-segment depression in the high lateral leads (OR: 20.0, 95% CI: 12.7–27.5; *P* = 0.0001) and syncope (OR: 19.0, 95% CI: 11.7–26.9; *P* = 0.0001) were the predictors of sudden death or appropriate ICD therapy in patients with HCM.

Conclusion
The results of this study indicated that, in addition to generally accepted risk factors, ST-segment depression in the high lateral leads could be of prognostic significance in HCM patients.

Keywords
Risk stratification • Hypertrophic cardiomyopathy • Electrocardiography • Prognosis

Introduction
Hypertrophic cardiomyopathy (HCM) is a relatively common genetic disease (1:500) and is the most common cause of sudden cardiac death (SCD) in young people, including trained athletes.1–3 The identification of this high-risk subset of subjects has been a perennial major clinical challenge. Several non-invasive clinical features have been recognized as the major risk factors of SCD in HCM, including age, family history, syncope, and arrhythmias.4–10

The 12-lead electrocardiogram (ECG) has traditionally been an integral part of the non-invasive evaluation of patients with HCM.11–15 From the spectrum of ECG changes likely to occur in HCM, no criterion has hitherto been reported to be of value for risk stratification. We, therefore, sought to determine whether there was a relationship between the resting ECG findings and prognosis in patients with HCM.

Methods
Patient selection
We retrospectively analysed data on 173 consecutive patients admitted to our hospital from October 1998 to December 2007 with diagnosis of HCM. The patients were excluded if: (i) their ECG tracings were obtained with poor technical quality, (ii) they had
paced ventricular rhythm, or (iii) they had significant missing echo and ambulatory ECG (AECG) data in their files. The study was approved by our institution’s Ethics Committee. Each patient underwent clinical and physical examinations, 12-lead ECG, 24 h AECG, and transthoracic two-dimensional (2D) echocardiography. The functional status was classified according to the New York Heart Association classification. Exercise stress testing was performed in selected cases at the discretion of the treating physicians. The diagnosis of HCM was suspected on the basis of clinical and ECG findings and was confirmed via trans thoracic echocardiography as the presence of a hypertrophied and non-dilated left ventricle (LV) in the absence of another cardiac or systemic disease capable of producing the magnitude of LV hypertrophy (LVH) evident in that patient.16

**Electrocardiography**

For the purpose of this investigation, ECG recordings obtained at or nearest to the time of the initial diagnostic echocardiographic study were analysed. Electrocardiography was performed in a routine fashion in the supine position during quiet respiration and recorded at a paper speed of 25 mm/s and amplification of 10 mm/mV. Amplitude measurements were made from 10 consecutive complexes to minimize beat-to-beat variation produced by respiration. The following parameters were obtained: PR interval, QRS width, QRS voltages, QT interval, RR interval, and corrected QT interval (Bazett’s formula). Left atrial enlargement was diagnosed if the product of the depth and duration of the negative portion of the P-wave in lead V1 was ≥0.04 mm-s. Left or right bundle branch block was classified according to international criteria.17 The degree of LVH was assessed using the point score system of Romhilt-Estes.18 Q or QS waves were considered abnormal if they were ≥0.04 s in duration or ≥3 mm in depth in at least two leads, except aVR.19 Repolarization abnormalities were defined by ST-segment elevation or depression ≥0.1 mV above or below the baseline at 0.08 s after the J point and T-wave inversion >0.1 mV, except aVR and V1–V2 leads.20 All the ECGs were evaluated by two independent observers, who were blinded to the combined endpoint.

**Ambulatory electrocardiography**

Ambulatory ECG recordings were obtained using the VISTA Holter Analysis System (VISTA, Novacor, France). Non-sustained ventricular tachycardia (NSVT) and non-sustained supraventricular tachycardia were defined as three or more consecutive premature complexes with a heart rate of >100 bpm. In each case, the arrhythmias were verified by an experienced observer, who was blinded to the combined endpoint.

**Echocardiography**

The echocardiographic studies were performed using a Vivid 7 echocardiograph (General Electric, USA). Greatest thickness measured at any site in the LV wall was considered the maximal thickness.2 Left ventricular outflow tract obstruction under basal conditions was considered present when a peak gradient ≥30 mmHg was identified by Doppler echocardiography.21

**Definitions**

The combined endpoint was defined as a composite of SCD, aborted SCD, or appropriate implantable cardioverter-defibrillator (ICD) therapy for ventricular tachycardia/ fibrillation (VT/VF). Sudden cardiac death was defined as unexpected collapse occurring <1 h from the onset of symptoms in a patient who had previously experienced a relatively stable or uneventful clinical course. Unwitnessed death was also classified as sudden if it occurred unexpectedly (e.g. at night, in a patient without prior severe symptoms). In addition, potentially lethal cardiovascular events in which patients either were successfully reanimated from cardiac arrest or received appropriate ICD therapy were regarded as equivalents of SCD in the present data analysis.22 Based on previous studies, a family history of SCD was defined as the presence of at least one HCM-related sudden death in a first-degree relative aged <40 years.23

**Statistical analysis**

The continuous data are presented as mean ± SD and ranged when appropriate. The continuous variables were compared using Student’s t-test in case of a normal distribution. Otherwise, the non-parametric test of Mann–Whitney U was used. The χ² analysis was utilized for the categorical data and the Fisher exact test for a cell count less than five. A binary logistic regression analysis with a forward selection method was employed to find the potential predictors of SCD or appropriate ICD therapy in patients with HCM. All the parameters that showed a P-value<0.1 during the bivariable correlation were included in our binary logistic regression analysis model. The Hosmer–Lemeshow statistics were used to confirm model fitness for the data. A P-value <0.05 was considered statistically significant. The software SPSS (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis.

**Results**

From a total of 190 subjects with HCM, 5 were excluded for this analysis because they had paced rhythms (making the ECG uninterpretable) and 12 due to significant missing data in their files. The study group consisted of 173 patients who fulfilled the inclusion criteria. During a mean follow-up of 50 months (range 24–114), 5 patients died suddenly and 6 received an appropriate ICD therapy for VT/VF for a total of 11 (6.4%) patients with a combined endpoint.

**Clinical characteristics**

The clinical characteristics of the patients with and without the combined endpoint are summarized in Table 1. There were 86 (49.7%) males and 87 (50.3%) females. The mean age at the time of the evaluation was 42 ± 18 years (range 10–78). One hundred and fifty-four (89%) patients were in sinus rhythm, whereas the remaining 19 (11%) were in atrial fibrillation (3 paroxysmal and 16 chronic). Of the HCM patients investigated in this study, 9% had a family history of premature SCD and 5% exhibiting a ‘malignant’ family history (presence of at least two affected first-degree relatives).

**Electrocardiographic characteristics**

**Twelve-lead electrocardiography**

The electrocardiographic characteristics of the patients with and without the combined endpoint are summarized in Table 2. The probability of reaching the combined endpoint was similar irrespective of abnormal ST-segment depression in any lead (6.7% vs. 5.7%; P = 0.80). When the patients with ST depression were categorized according to the location of ST-segment depression, 7.0% had ST depression in the right precordial leads (V1–V3), 62% had ST depression in the left precordial leads (V4–V6), 14.5% in the inferior leads (II, III, and aVF), and 14% in the high lateral leads (I and aVL). Interestingly, there was a significant difference in the combined endpoints between
the patients with and without ST-segment depression in the high lateral leads (21% vs. 4%, respectively; \( P = 0.002 \)). Similar observations were not observed in the ST-segment depression of the other locations. The ST-segment depression in the high lateral leads was not associated with the ST-segment depression in the inferior or right precordial leads, whereas the ST-segment depression in the lateral precordial leads was a common association (63%). A typical example of high-risk ECG is illustrated in Figure 1.

**Ambulatory electrocardiography**

A comparison of the AECG findings and prognosis is depicted in Table 3. The mean premature ventricular complex count was significantly higher in the patients with the combined endpoint than that in those without (1994 ± 866 vs. 293 ± 95, \( P = 0.01 \)). Seventy-two percent of the patients had no episode of NSVT, 13.4% had one episode, 2.2% had two episodes, and 12.4% had three or more episodes of NSVT. The likelihood of identifying the HCM patients with the combined endpoints increased when a higher frequency of NSVT in AECG was detected (2.9% in the no-episode group vs. 7.7% in the one-episode group vs. 50% in the two- or more-episode group; \( P = 0.0001 \)).

**Arrhythmias**

The ICDs were implanted for secondary prevention (aborted SCD) in four patients and for primary prevention in 29 patients. Six patients (four patients from secondary prevention group and two patients from primary prevention group) had received appropriate ICD therapies for VT/VF. Of the 33 patients who had ICD,
21 (64%) experienced sustained supraventricular tachycardia (SVT). Sustained SVT, however, was not a predictor of subsequent appropriate ICD therapy for life-threatening ventricular tachyarhythmias ($P = 0.64$).

### Echocardiographic characteristics

A comparison of the echo data between the patients with the combined endpoint and those who survived free from events is shown in Table 4. Among the different echocardiographic parameters evaluated in this study, the maximal LV wall thickness was the only parameter significantly associated with the combined endpoint ($32.0 \pm 6.7$ vs. $24.0 \pm 6.2$, $P = 0.0001$).

### Multivariate analysis

Of the multiple clinical, electrocardiographic, and echocardiographic variables that were examined, only two were identified by the multivariate logistic regression analysis as the significant predictors of subsequent SCD or appropriate ICD therapy in the patients with HCM: ST-segment depression in the high lateral leads (OR: 20.0, 95% CI: 12.7–27.5; $P = 0.0001$) and syncope (OR: 19.3, 95% CI: 11.7–26.9; $P = 0.0001$).

### Discussion

The main finding of this study is that, in addition to well-known risk factors, ST-segment depression in the high lateral leads can also predict an unfavourable outcome for the patients with HCM. The 12-lead ECG has traditionally been an integral part of the non-invasive evaluation of HCM patients.\textsuperscript{11 – 15} Although the ECG pattern has frequently been used to make inferences regarding the phenotypic expression of HCM,\textsuperscript{15,24,25} there is no generally accepted ECG criterion to identify subsets of patients predisposed to SCD.\textsuperscript{10,16,26} Furthermore, there is now enhanced interest in identifying the non-invasive markers of SCD risk,\textsuperscript{10,16,26} given the recent efficacy of ICDs for the secondary and primary prevention of SCD.\textsuperscript{26} The fact that LV wall thickness assessed via echocardiography has recently been used to estimate the prognosis in HCM means that...
this is an appropriate time to revisit the clinical significance of the 12-lead ECG in this disease. We, consequently, sought to answer this question in our cohort of HCM.

We performed the current retrospective analysis to assess the clinical utility of the standard 12-lead ECG in the risk stratification of patients with HCM. To the best of our knowledge, this study is the first of this kind to show that ST-segment depression in the high lateral leads is a predictor of SCD in addition to the other generally accepted risk factors. Precordial ST-segment depression is common in HCM patients (62%). Unlike these changes, which do not have a prognostic implication, ST-segment depression in leads I and aVL is less common (14%) but appears to have implications in prognosis: it was found in 5 of the 11 patients with the combined endpoint (45%) and 19 of 162 without the combined endpoint (12%). In addition, our data demonstrated that the risk of SCD or appropriate ICD therapy was 20 times higher in the patients with this ECG abnormality compared with those without and this finding may identify high-risk patients better than NSVT in AECG and history of syncope. Interestingly, we found no significant difference in the clinical and echocardiographic features of the 24 individuals with, compared with those without, ST-segment depression in leads I and aVL (Table 5).

The exact mechanism linking this observation to the higher risk of SCD is unknown. An interesting study by Maron et al. showed that certain electrocardiographic patterns reflected particular patterns of LVH on the 2D echocardiogram. They found that ST-T abnormalities were more prevalent in the patients with the involvement of substantial portions of both the ventricular septum and anterolateral LV free wall than in those with the isolated involvement of the anterior septum, posterior septum, or apical region. Therefore, ST-segment depression in the high lateral leads may reflect the extent or particular location of LVH in patients with HCM. It is deserving of note that the relation of LVH distribution and its particular location to prognosis has not been assessed yet. Unfortunately, a dearth of data precluded the determination of the exact location or extent of hypertrophy in our patients with and without cardiac events. There was no association between the severity of LVH (maximum wall thickness in echo) and the presence of ST-segment depression in the high lateral leads.

Table 4 Comparison of echocardiographic findings at diagnosis in hypertrophic cardiomyopathy patients with and without combined endpoint

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Combined + (n = 11)</th>
<th>Combined – (n = 162)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral regurgitation (moderate/severe, %)</td>
<td>45.5/9.0</td>
<td>36.0/8.7</td>
<td>0.80</td>
</tr>
<tr>
<td>Systolic anterior motion (%)</td>
<td>72.7</td>
<td>72.0</td>
<td>0.95</td>
</tr>
<tr>
<td>LVOT gradient ≥ 30 mmHg (%)</td>
<td>24.5</td>
<td>27.0</td>
<td>0.87</td>
</tr>
<tr>
<td>LV end-diastolic dimension (mean ± SD, mm)</td>
<td>41.5 ± 5.7</td>
<td>40.4 ± 7.6</td>
<td>0.57</td>
</tr>
<tr>
<td>LV end-systolic dimension (mean ± SD, mm)</td>
<td>23.6 ± 6.0</td>
<td>26.1 ± 7.8</td>
<td>0.38</td>
</tr>
<tr>
<td>LV ejection fraction (mean ± SD, mm)</td>
<td>56.0 ± 10</td>
<td>57.3 ± 9.4</td>
<td>0.84</td>
</tr>
<tr>
<td>Left atrial dimension (mean ± SD, mm)</td>
<td>44.4 ± 5.7</td>
<td>44.0 ± 8.2</td>
<td>0.87</td>
</tr>
<tr>
<td>Maximal LV wall thickness (mean ± SD, mm)</td>
<td>32.0 ± 6.7</td>
<td>24.0 ± 6.2</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Combined+, patients with combine endpoint; combined _, patients without combined endpoint; LV, left ventricle; LVOT, left ventricular outflow tract.

Table 5 Comparison of clinical and echocardiographic features of the hypertrophic cardiomyopathy patients with and without ST-segment depression in high lateral leads

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>With STd in I and aVL (n = 24)</th>
<th>Without STd in I and aVL (n = 149)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD, years)</td>
<td>43.8 ± 15.7</td>
<td>41.5 ± 17.0</td>
<td>0.30</td>
</tr>
<tr>
<td>Male (%)</td>
<td>46.0</td>
<td>50.0</td>
<td>0.70</td>
</tr>
<tr>
<td>History of syncope (%)</td>
<td>16.7</td>
<td>29.7</td>
<td>0.20</td>
</tr>
<tr>
<td>Family history of premature SCD (%)</td>
<td>8.3</td>
<td>9.3</td>
<td>0.90</td>
</tr>
<tr>
<td>NYHA functional class III and IV (%)</td>
<td>16.7</td>
<td>20.6</td>
<td>0.30</td>
</tr>
<tr>
<td>LVOT gradient ≥ 30 mmHg (%)</td>
<td>56.0</td>
<td>57.0</td>
<td>0.70</td>
</tr>
<tr>
<td>LV ejection fraction (mean ± SD, mm)</td>
<td>55.0 ± 8.4</td>
<td>57.0 ± 9.6</td>
<td>0.27</td>
</tr>
<tr>
<td>Left atrial dimension (mean ± SD, mm)</td>
<td>46.0 ± 7.0</td>
<td>44.0 ± 8.0</td>
<td>0.25</td>
</tr>
<tr>
<td>Maximal LV wall thickness (mean ± SD, mm)</td>
<td>25.0 ± 6.0</td>
<td>24.0 ± 7.0</td>
<td>0.55</td>
</tr>
<tr>
<td>Follow-up period (mean ± SD, months)</td>
<td>52 ± 24</td>
<td>49.0 ± 23</td>
<td>0.52</td>
</tr>
</tbody>
</table>

STd, ST-segment depression; SCD, sudden cardiac death; NYHA, New York Heart Association; LVOT, left ventricular outflow tract; LV, left ventricle.
lateral leads in our cohort of HCM patients. Moreover, extreme LVH was not a predictor of the combined endpoint in our multivariate analysis. A limitation of the current definition of extreme LVH in HCM studies is that a single measurement of maximum LV wall thickness, although reproducible and practical for clinical purposes, does not accurately reflect the total burden of hypertrophy and its distribution in individual patients and thus represents only a crude estimate of the morphologic severity of HCM. Indeed, several pathophysiologic substrates coexisting in the hypertrophied myocardium, including disarray, fibrosis, and ischemia, are possibly more relevant than the degree of LVH itself in determining HCM-related risk and ideally require a comprehensive assessment in each patient. A severe reduction and transmural maldistribution of the myocardial blood flow, which have been clearly demonstrated in HCM patients with massive hypertrophy, are strongly predictive of an adverse long-term outcome, irrespective of individual maximum LV wall thickness values. It is likely that ST-segment depression in the high lateral leads reflects a severe reduction in the myocardial blood flow or other pathophysiologic substrates such as extensive disarray or fibrosis.

Currently available studies report controversial results regarding resting ECG findings and prognosis in HCM. McKenna et al. reported that a comparison of resting ECGs at the time of diagnosis in the living patients and those who died did not show any significant difference. A univariate analysis of the ECG data between survivors and non-survivors in a study by Pelliccia et al. disclosed that patients who subsequently died had, at the time of diagnosis, higher frequencies of AF, atrioventricular block, and intraventricular conduction delay. The multivariate analysis, however, failed to identify independent ECG risk factors for death. The study of Montgomery et al. also showed that diverse ECG patterns did not predict HCM-related death. Lazzeri et al. evaluated electrophysiological abnormalities underlying the increased arrhythmogenicity of LVH in patients with HCM. They found that QT interval, QT dispersion, and T-wave complexity could not distinguish patients with hypertensive LVH from those with HCM, indicating that ECG data were affected more by the presence of LVH than by its type. Nonetheless, Bayrak et al. reported that baseline QT dispersion significantly increased in HCM patients who died suddenly or in patients who had clinical evidence of worsening heart failure symptoms at long-term follow-up.

Similar to several published studies, a family history of SCD was not a predictor of prognosis in the current HCM population. There are several problems in identifying an adverse family history of SCD and its use as a risk factor for SCD. Reliance was placed on the history that a direct pedigree analysis with a cardiovascular evaluation of relatives or genetic testing is usually feasible. By history, it is often not possible to determine the precise number of affected relatives or the precise cause of death. These factors may contribute to the low positive predictive accuracy of a family history of SCD in the current study and previous publications.

Study limitations

The results of this study should be interpreted in the light of certain limitations. First, the retrospective nature of the study may have introduced selection bias. The second limitation is related to the limited number (7%) of exercise testing performed in this study. However, the significance of abnormal systolic blood pressure has not been substantiated in all studies.

Conclusions

The results of this study indicated that, in addition to generally accepted risk factors, ST-segment depression in the high lateral leads could be of prognostic significance in HCM patients.

Conflict of interest: none declared.

References


