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Title: Advanced echocardiography and clinical surrogates to risk stratify and manage patients with structural heart disease
Issue Date: 2016-04-28
Part II

Echocardiographic deformation imaging
Chapter 7

Fragmented QRS and QTc duration relate to malignant ventricular tachyarrhythmias and sudden cardiac death in patients with hypertrophic cardiomyopathy

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ABSTRACT

Objectives
QRS fragmentation (fQRS) and prolonged QTc interval on surface ECG are prognostic in various cardiomyopathies, other than hypertrophic cardiomyopathy (HCM). The association between fQRS and prolonged QTc duration with occurrence of ventricular tachyarrhythmias or sudden cardiac death (VTA/SCD) in patients with HCM was explored.

Methods and Results
195 clinical HCM patients were studied. QTc duration was derived applying Bazett’s formula; fQRS was defined as presence of various RSR’ patterns, R or S notching and/or >1 additional R wave in any non-aVR lead in patients without pacing or (in) complete bundle branch block. The endpoints comprised SCD, ECG documented sustained VTA (tachycardia or fibrillation) or appropriate implantable cardioverter defibrillator (ICD) therapies [anti-tachycardia pacing (ATP) or shock] for VTA in ICD recipients [n=58 (30%)]. QT prolonging drugs recipients were excluded. After a median follow-up of 5.7 years (IQR 2.7-9.1), 26 (13%) patients experienced VTA or SCD. Patients with fQRS in ≥3 territories (inferior, lateral, septal and/or anterior) (p=0.004) or QTc ≥460 ms (p=0.009) had worse cumulative survival free of VTA/SCD than patients with fQRS in <3 territories or QTc <460 ms. fQRS in ≥3 territories (β 4.5, p=0.020, 95%CI 1.41-14.1) and QTc ≥460 ms (β 2.7, p=0.037, 95%CI 1.12-6.33) were independently associated with VTA/SCD. Likelihood ratio test indicated assessment of fQRS and QTc on top of conventional SCD risk factors provides incremental predictive value for VTA/SCD (p=0.035).

Conclusions
Both fQRS in ≥3 territories and QTc duration are associated with VTA/SCD in HCM patients, independently of and incremental to conventional SCD risk factors.
INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is characterized by cellular hypertrophy, interstitial fibrosis and myofiber disarray that increase the risk of (arrhythmic) sudden cardiac death (SCD). These ultra-structural alterations may account for abnormalities in left ventricular (LV) electrical activation, including depolarization and repolarization, reflected on surface electrocardiography (ECG). Abnormal ECG findings, although non-specific, are found in between 75% and 95% of HCM patients. Recently the severity of ECG abnormalities in HCM patients were linked to the presence and extent of phenotypic expression as evaluated by cardiac magnetic resonance (CMR) imaging, including LV mass, hypertrophy and scarring (fibrosis). However, whether ECG abnormalities might relate to electrical instability and be useful for stratification of HCM patients at risk for ventricular tachyarrhythmia (VTA) or SCD remains poorly explored.

Fragmentation of the QRS complex (fQRS) on surface ECG (comprising various RSR\(^-\) patterns of QRS morphology) represents a depolarization abnormality that has been related to presence of myocardial fibrosis. Moreover, the presence of fQRS is an independent predictor of VTA and/or mortality in patients with ischemic and non-ischemic cardiomyopathies, has been associated with reduced event-free survival in patients with Brugada syndrome and is a diagnostic marker in arrhythmogenic right ventricular dysplasia. Its potential clinical prognostic value in patients with HCM, however, is poorly studied. In addition, congenital or acquired QT prolongation on ECG is a well-known repolarization abnormality implying increased risk of VTA and SCD. Heart rate corrected QT (QTc) prolongation is not infrequent in HCM patients, but limited data exist on its clinical significance.

Therefore the aim of this study was to explore the association of both fQRS and QTc duration with the occurrence of malignant VTA or SCD in HCM patients.

METHODS

Patient population

Clinical HCM patients enrolled in an ongoing echocardiographic and clinical registry at our department were included in this analysis if ECG was present within one year before or after the baseline echocardiographic exam and subjects were ≥18 year-old (n=323). Clinical HCM was defined as a non-dilated LV with a maximal wall thickness of ≥15 mm on echocardiography in patients without systemic or alternative explanations for the magnitude of LV hypertrophy. Patients with ventricular pacing (n=20) or (in)complete bundle branch block (BBB) at baseline ECG were
excluded. In particular, RSR’ pattern in lead V1 and/or V2 with QRS duration ≥110 or ≥120 ms and S wave of greater duration than R wave or greater than 40 ms in leads I and V6 was defined as incomplete right BBB (n=11) and complete right BBB (n=19), respectively. Left BBB (n= 12) was defined as a QRS duration ≥120 ms with RSR’ pattern in leads I, aVL, V5 and V6. In addition, patients taking QTc prolonging medications were excluded (n=20). Finally, patients without clinical follow-up within the last 3 years (n=46) were also excluded from further analysis.

Extensive baseline evaluation including medical history, demographics, medications, ECG and echocardiography was performed in all patients and data were prospectively collected at the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, the Netherlands) and retrospectively analyzed. According to guidelines, the SCD risk profile of the patients was determined based on the following clinical and echocardiographic parameters: secondary prevention implantable cardioverter defibrillator (ICD) indication, maximal LV wall thickness ≥30 mm, family history of SCD (≥ one 1st to 3th degree relative), unexplained syncope and, as additional risk factor, documented non-sustained ventricular tachycardia (≥3 beats at ≥120 bpm) prior to device implantation. Blood pressure response during exercise testing was not systematically available and therefore not included as a conventional SCD risk factor.

Patients were followed-up at the out-patient clinic or through contact with the general practitioners in order to evaluate the occurrence of cardiac events. The Ethical Committee of the Leiden University Medical Center approved this retrospective study and waived the need for written informed consent.

**ECG analysis**

Routine 12-lead ECG (settings: 0.05-300 Hz filter range, AC filter 50 Hz, paper speed 25 mm/s and voltage 10 mm/mV) was performed and stored digitally for off-line analysis, using a dedicated software (Siemens/Dräger Mega Care ECG Management System). QT interval and heart rate were automatically provided by the software. Heart rate corrected QT (QTc) duration was calculated applying Bazett’s formula [QTc=QT/√(60/heart rate)]. Detection of fQRS was performed manually. As shown in Figure 1, QRS fragmentation comprises presence of various RSR’ patterns, notching in the R or S wave or presence of >1 additional R in ≥2 beats of a non-aVR lead. fQRS was allocated to a territory when present in ≥2 contiguous leads of the inferior (II, III, aVF), lateral (I, aVL, V6), septal (V1,V2) or anterior (V3,V4,V5) regions. Assessment of fQRS required consensus of 2 independent observers, blinded for the study endpoint.
Standard 2-dimensional transthoracic echocardiography was performed with the patient in left lateral decubitus position using commercially available ultrasound machines (System-5, Vivid-7 and E9, GE-Vingmed, Milwaukee, WI) equipped with a 3.5 MHz transducer. ECG-triggered standard 2-dimensional gray-scale and color-Doppler images were acquired in cine-loop format and transferred to a workstation for off-line analysis (EchoPAC version 112, GE Medical Systems, Horten, Norway). Cardiac chamber quantification was performed in accordance with current recommendations.\(^ {23} \) Maximal LV wall thickness was assessed at end-diastole on the basal, mid or apical short-axis LV view. Simpson`s biplane method was applied to assess LV volumes that were indexed to body surface area and additionally used to calculate LV ejection fraction. Systolic anterior mitral leaflet motion was evaluated on M-mode acquisition in parasternal long-axis LV view. Mitral regurgitation was

**Figure 7.1**
Baseline electrocardiographic abnormalities: QRS fragmentation and QTc prolongation. Panel A: QRS fragmentation includes various RSR` patterns, notched R wave, notched S wave or presence of >1 additional R wave (fragmentation) in ≥2 beats per lead. (In)complete bundle branch block patients are excluded (see text for details). Panel B: Hypertrophic cardiomyopathy (HCM) patient with QTc prolongation. Of note, QRS fragmentation is also present in lead III (S notching). Panel C: QTc prolongation and extensive QRS fragmentation in the inferior (II,III,aVF), lateral (I,V6,aVL) and anterior (V3,V4,V5) territories in a HCM patient. ATP: antitachycardia pacing. QTc: heart rate corrected QT duration, VF: ventricular fibrillation, VT: ventricular tachycardia.

**Echocardiography**

Standard 2-dimensional transthoracic echocardiography was performed with the patient in left lateral decubitus position using commercially available ultrasound machines (System-5, Vivid-7 and E9, GE-Vingmed, Milwaukee, WI) equipped with a 3.5 MHz transducer. ECG-triggered standard 2-dimensional gray-scale and color-Doppler images were acquired in cine-loop format and transferred to a workstation for off-line analysis (EchoPAC version 112, GE Medical Systems, Horten, Norway). Cardiac chamber quantification was performed in accordance with current recommendations.\(^ {23} \) Maximal LV wall thickness was assessed at end-diastole on the basal, mid or apical short-axis LV view. Simpson`s biplane method was applied to assess LV volumes that were indexed to body surface area and additionally used to calculate LV ejection fraction. Systolic anterior mitral leaflet motion was evaluated on M-mode acquisition in parasternal long-axis LV view. Mitral regurgitation was
semi-quantitatively graded as trivial (grade 1), mild (grade 2), moderate (grade 3) or severe (grade 4), according to current recommendations.\textsuperscript{24} Finally, presence of intraventricular or LV outflow tract gradient at rest was evaluated by pulsed-wave Doppler on the apical long-axis view and peak gradient was measured on continuous wave Doppler recordings.

**ICD implantation and settings**

Transvenous approach was used for implantation of all defibrillator devices (Boston Scientific [Natick, MA, USA, formerly CPI, Guidant (St Paul, MN, USA)], Biotronik (Berlin, Germany), St Jude Medical/Ventritex (St Paul, MN, USA) and Medtronic (Minneapolis, MN, USA). The antitachycardia modus was set in all devices using 3 consecutive zones with slightly varying limits per manufacturer: a monitor zone (150-155 to 185-190 bpm), an antitachycardia pacing (ATP) shock zone (185-190 to 205-210 bpm), and an initial shock zone (≥205-210 bpm). In the monitor zone no therapy was programmed, unless during follow-up VTA was detected. An initial attempt to terminate arrhythmias by two ATP bursts was programmed in the ATP-shock zone, however, defibrillator shocks were fired if arrhythmia persisted. Shocks were the initial therapy for VTA with higher rate than the ATP shock zone. ICD device interrogation was regularly performed every 3 to 6 months after implantation.

**Study endpoint**

The primary endpoint of the study included occurrence of malignant VTA or SCD, whichever occurred first. VTA was defined as sustained ventricular tachycardia or fibrillation documented on ECG or by appropriate ICD therapies (shock/ATP) for VTA in patients with an ICD. SCD was defined as (unexpected) death of a HCM patient inside or outside a hospital due to any cardiac cause within 1 hour of onset of symptoms (if documented).\textsuperscript{25} Deaths and cause of death were assessed by evaluating the official Dutch National Survival Registry, patients’ clinical files and by direct communication with general practitioners.

**Statistical analysis**

According to distribution, continuous data were expressed as mean ± standard deviation or median ± interquartile range and compared between groups by Student-T test and Mann-Whitney U test, respectively. Categorical data were presented as percentages and compared with χ\textsuperscript{2} or Fisher-exact test, as appropriate. A receiver operating curve (ROC) was constructed to derive a cut-off value for QTc with cut-point maximizing sum of sensitivity and specificity for prediction of the study endpoint. The cumulative survival free of VTA/SCD was evaluated
with Kaplan-Meier curve analysis. Patients were dichotomized according to the QTc duration cut-off and presence of fQRS in <3 vs ≥3 territories, and compared by log-rank test. Sensitivity, specificity, positive and negative predictive value for the study endpoint of these dichotomized ECG criteria were calculated. Among the various clinical, ECG and echocardiographic variables, the independent correlates of VTA/SCD were evaluated with multivariate Cox proportional hazard ratios. Variables showing a p-value <0.05 in univariate analysis were entered in multivariate Cox regression analysis. Finally, the likelihood ratio test was applied to explore the incremental value of QTc duration and fQRS on top of conventional SCD risk factors to predict the occurrence of VTA/SCD. Statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, Illinois). All tests were two-sided and a p-value of <0.05 was considered statistically significant.

RESULTS

Patient population
A total of 195 HCM patients (mean age 52 ± 13 years, 61% male) were included. Baseline clinical, echocardiographic characteristics and SCD risk profile are summarized in Table 1. The overall HCM population had a median LV wall thickness of 21 mm (IQR: 18-24 mm), small ventricular cavity and preserved LV ejection fraction. Only a minority of patients (n=58, 30%) had an ICD at baseline, of which 13 (22%) were for secondary prevention reasons (survived sustained VTA).

Primary prevention ICD implantation was performed, in accordance to current guidelines, if ≥1 conventional SCD risk factor(s) was present (n=43).21 ICD implantation in patients without SCD risk factors was performed in one patient with total atrio-ventricular conduction block and in one patient due to induction of ventricular fibrillation during electrophysiological study. Few patients (n=16) had prior septal alcohol ablation for symptomatic drug refractory LV obstruction.

Study endpoint
A total of 26 out of 195 patients (13.3%) experienced VTA/SCD after a median follow-up of 5.7 years (IQR 2.7-9.1). In particular 10 out of 137 patients without ICD (7%) reached the endpoint, consisting of sustained ventricular tachycardia (n=4), ventricular fibrillation (n=2) and SCD (n=4). Of note, at that time point these patients did not fulfill criteria for primary prevention ICD implantation. Additionally in 16 out of 58 baseline ICD recipients (28%) appropriate ICD therapy occurred with a total of 9 ATP and 7 shocks.
Data on fQRS and for QTc duration on ECG are listed in Table 2. Mean QTc duration in the overall study population was 427 ± 28 ms. QTc duration ≥460 ms comprised highest sum of sensitivity (31%) and specificity (89%) for prediction of the study endpoint (area under curve 0.61 on ROC analysis). Significant QTc prolongation ≥460 ms was noted in a total of 26 out of 195 HCM patients (13%). The vast majority of HCM patients (n=181, 93%) displayed a fQRS in at least one ECG
lead with a median of 4 leads affected per patient. A total of 145 patients (75%) exhibited a fQRS in ≥1 ECG territory. Leads III, aVF and aVL were the most affected in 69%, 62% and 52% of cases, respectively. Leads V4, V3 and V1 were the least affected in only 13%, 16% and 21% of patients, respectively. fQRS was most commonly observed in the inferior territory (61%), followed by the lateral (31%), anterior (13%) and septal territories (11%). Presence of fQRS in ≥3 territories was noted in 15 out of 195 (8%) of patients.

**Table 7.2**
Baseline electrocardiographic characteristics of the overall patient population and divided according to the study endpoint.

<table>
<thead>
<tr>
<th>QRS</th>
<th>Overall (n 195)</th>
<th>No VTA/SCD (n 169)</th>
<th>VTA/SCD (n 26)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration, ms</td>
<td>97 ± 12</td>
<td>97 ± 12</td>
<td>99 ± 13</td>
<td>0.30</td>
</tr>
<tr>
<td>Fragmentation, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 1 lead</td>
<td>181 (93)</td>
<td>156 (92)</td>
<td>25 (96)</td>
<td>0.70</td>
</tr>
<tr>
<td>Inferior territory</td>
<td>118 (61)</td>
<td>101 (60)</td>
<td>17 (65)</td>
<td>0.56</td>
</tr>
<tr>
<td>Lead II</td>
<td>85 (44)</td>
<td>73 (43)</td>
<td>12 (46)</td>
<td>0.78</td>
</tr>
<tr>
<td>Lead III</td>
<td>135 (69)</td>
<td>114 (67)</td>
<td>21 (81)</td>
<td>0.17</td>
</tr>
<tr>
<td>Lead aVF</td>
<td>121 (62)</td>
<td>105 (62)</td>
<td>16 (62)</td>
<td>0.95</td>
</tr>
<tr>
<td>Lateral territory</td>
<td>60 (31)</td>
<td>48 (28)</td>
<td>12 (46)</td>
<td>0.07</td>
</tr>
<tr>
<td>Lead I</td>
<td>50 (26)</td>
<td>40 (24)</td>
<td>10 (38)</td>
<td>0.11</td>
</tr>
<tr>
<td>Lead aVL</td>
<td>102 (52)</td>
<td>86 (51)</td>
<td>16 (62)</td>
<td>0.31</td>
</tr>
<tr>
<td>Lead V6</td>
<td>55 (28)</td>
<td>47 (28)</td>
<td>8 (31)</td>
<td>0.76</td>
</tr>
<tr>
<td>Septal territory</td>
<td>22 (11)</td>
<td>17 (10)</td>
<td>5 (19)</td>
<td>0.17</td>
</tr>
<tr>
<td>Lead V1</td>
<td>41 (21)</td>
<td>85 (21)</td>
<td>6 (23)</td>
<td>0.78</td>
</tr>
<tr>
<td>Lead V2</td>
<td>42 (25)</td>
<td>36 (21)</td>
<td>6 (23)</td>
<td>0.84</td>
</tr>
<tr>
<td>Anterior territory</td>
<td>22 (13)</td>
<td>16 (9)</td>
<td>6 (23)</td>
<td>0.04</td>
</tr>
<tr>
<td>Lead V3</td>
<td>32 (16)</td>
<td>28 (17)</td>
<td>4 (15)</td>
<td>1.00</td>
</tr>
<tr>
<td>Lead V4</td>
<td>26 (13)</td>
<td>21 (12)</td>
<td>5 (19)</td>
<td>0.34</td>
</tr>
<tr>
<td>Lead V5</td>
<td>42 (25)</td>
<td>33 (20)</td>
<td>9 (35)</td>
<td>0.08</td>
</tr>
<tr>
<td>Number of leads</td>
<td>4 (2-5)</td>
<td>4 (2-5)</td>
<td>4 (3-6)</td>
<td>0.53</td>
</tr>
<tr>
<td>≥ 3 territories</td>
<td>15 (8)</td>
<td>10 (6)</td>
<td>5 (19)</td>
<td>0.02</td>
</tr>
<tr>
<td>QTc Duration, ms</td>
<td>427 ± 28</td>
<td>425 ± 25</td>
<td>440 ± 34</td>
<td>0.01</td>
</tr>
<tr>
<td>≥460 ms, n (%)</td>
<td>26 (13)</td>
<td>18 (11)</td>
<td>8 (31)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

QTc: heart rate corrected QT duration, SCD: sudden cardiac death, VTA: ventricular tachyarrhythmia, * p value for comparison of no VTA/SCD versus VTA/SCD group.
HCM patients with versus without study endpoint

The patient population was dichotomized based on the occurrence (n=26, 13.3%) or absence (n=169, 86.7%) of the study endpoint (VTA/SCD). These 2 groups showed similar clinical and conventional echocardiographic characteristics, as summarized in Table 1. Patients with VTA/SCD, however, showed higher baseline HCM SCD risk profile, evidenced by higher prevalence of non-sustained ventricular tachycardia (50% versus 24%, p=0.006) and prior unexplained syncope (31% versus 5%, p<0.001).

Concerning baseline ECG characteristics (Table 2), mean QTc duration was longer in patients with VTA/SCD versus patients without (440 ± 34 ms versus 425 ± 25 ms, p=0.01) and a higher percentage of patients with VTA/SCD showed a QTc duration ≥460 ms as compared to their counterparts (31% versus 11%, p=0.01; Figure 2). No significant difference between patients with versus without VTA/SCD was observed for the presence of fQRS in any individual lead, the median number of leads with fQRS, nor the territory affected by fQRS, except for the anterior territory (23% versus 9%, p=0.04). Interestingly, the prevalence of fQRS in ≥3 territories was higher in subjects with VTA/SCD (19% versus 6%, p=0.03; Figure 2).

Figure 7.2

QTc duration, fQRS and the study endpoint

The cumulative survival free of VTA/SCD was worse in patients with a QTc duration ≥460 vs <460 ms (p=0.009) or fQRS in ≥3 vs <3 territories (p=0.004). (Figure 3). As shown in Table 3, presence of QTc ≥460 ms has a positive predictive value for
occurrence of VTA/SCD of 31%, comparable to 33% if presence of fQRS ≥3 territories. When both ECG criteria co-exist in one patient, a high positive predictive value of 75% is noted, yielding low sensitivity, however. As shown in Table 4, QTc duration ≥460 ms, fQRS in ≥3 territories, non-sustained ventricular tachycardia and unexplained syncope were univariate correlates of VTA/SCD. Of note, other conventional SCD risk factors, secondary prevention ICD indication and prior septal alcohol ablation were not significantly associated with the study endpoint. In the multivariate analysis, both QTc duration ≥460 ms and fQRS in ≥3 territories remained independently related to VTA/SCD, in addition to non-sustained ventricular tachycardia and unexplained syncope (Table 4).

Moreover, excluding secondary prevention ICD recipients (n=13), likelihood ratio test indicated that assessment of both ECG parameters, QTc duration ≥460 ms and fQRS in ≥3 territories, provided incremental value over conventional SCD risk factors to predict occurrence of VTA/SCD (p=0.035; Figure 4).

Figure 7.3
Cumulative survival free of ventricular tachyarrhythmia or sudden cardiac death according to novel electrocardiographic criteria. fQRS: presence of QRS fragmentation, QTc: heart rate corrected QT duration.

Table 7.3
Sensitivity, specificity, positive and negative predictive value of novel ECG criteria for prediction of ventricular tachyarrhythmia or sudden cardiac death.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc ≥460 ms</td>
<td>31</td>
<td>89</td>
<td>89</td>
<td>31</td>
</tr>
<tr>
<td>fQRS ≥3 territories</td>
<td>19</td>
<td>94</td>
<td>88</td>
<td>33</td>
</tr>
<tr>
<td>QTc ≥460 ms AND fQRS ≥3 territories</td>
<td>12</td>
<td>99</td>
<td>80</td>
<td>75</td>
</tr>
</tbody>
</table>

fQRS: presence of QRS fragmentation, NPV: negative predictive value, PPV: positive predictive value.
DISCUSSION

The main findings of this study are 1) fQRS in ≥3 territories and QTc prolongation ≥460 ms are easily identifiable surface ECG markers which are prevalent in 8% and 13% respectively of clinical HCM patients without (in)complete bundle branch

Figure 7.4
Likelihood ratio test to predict occurrence of ventricular tachyarrhythmia or sudden cardiac death. Excluding secondary prevention ICD recipients (n=13), assessment of the novel electrocardiographic (ECG) criteria on top of conventional sudden cardiac death (SCD) risk factors (see main text for details) in the remaining HCM patients yields incremental value to predict occurrence of ventricular tachyarrhythmia or sudden cardiac death. fQRS: QRS fragmentation, QTc: heart rate corrected QT duration.

Table 7.4
Univariate and multivariate Cox regression analysis for the study endpoint.

<table>
<thead>
<tr>
<th></th>
<th>univariate</th>
<th>multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>p value</td>
</tr>
<tr>
<td>Age, years</td>
<td>1.0</td>
<td>0.638</td>
</tr>
<tr>
<td>Male gender</td>
<td>2.0</td>
<td>0.140</td>
</tr>
<tr>
<td>β-blocker use</td>
<td>1.1</td>
<td>0.807</td>
</tr>
<tr>
<td>LVEF, per %</td>
<td>0.96</td>
<td>0.081</td>
</tr>
<tr>
<td>Max wall thickness ≥ 30 mm</td>
<td>3.6</td>
<td>0.209</td>
</tr>
<tr>
<td>Family Hx SCD</td>
<td>1.4</td>
<td>0.397</td>
</tr>
<tr>
<td>Non-sustained VT</td>
<td>2.5</td>
<td>0.019</td>
</tr>
<tr>
<td>Unexplained syncope</td>
<td>5.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary prevention ICD</td>
<td>1.7</td>
<td>0.217</td>
</tr>
<tr>
<td>fQRS ≥3 territories</td>
<td>4.0</td>
<td>0.008</td>
</tr>
<tr>
<td>QTc ≥460 ms</td>
<td>2.9</td>
<td>0.013</td>
</tr>
</tbody>
</table>

CI: confidence interval, fQRS: presence of QRS fragmentation, HR: hazard ratio, other abbreviations: see table 1 and 2
block and 2) both parameters are independently associated with VTA and SCD in this HCM population (with almost 50% at relatively low-risk), showing incremental predictive value over conventional SCD risk factors for primary prevention.

Most HCM patients have a benign course reflected by a 1% annual risk of presumed arrhythmic SCD in non-selected cases.\textsuperscript{1} Identification of the subset of HCM patients at high-risk for SCD, however, remains a clinical challenge. Various SCD risk factors, including personal history of cardiac arrest, massive LV hypertrophy, family history of SCD, presence of non-sustained ventricular tachycardia and unexplained syncope have been identified.\textsuperscript{21} Although ICD therapy in HCM patients at high risk for SCD based on these risk factors undoubtly remains a treatment cornerstone, the robustness of evidence supporting these risk factors is variable and in particular risk factors for primary prevention are limited by low positive predictive value (between 10% and 20%).\textsuperscript{21, 26} Therefore improvement of risk prediction in HCM remains an unmet clinical need.\textsuperscript{27} Although the vast majority of HCM patients show abnormal ECG findings, no specific ECG abnormality has been validated for risk stratification so far.\textsuperscript{3, 28, 29} This study indicated that the presence of fQRS in ≥3 territories or QTc ≥460 ms on baseline ECG were independently associated with VTA or SCD.

\textbf{fQRS in HCM}

In ischemic and non-ischemic dilated cardiomyopathy patients, fQRS has been related to fibrosis and represents a strong prognostic marker for VTA and/or mortality.\textsuperscript{6-8, 30}

The origin of fQRS on ECG in HCM patients is poorly studied. Recently, in a study including 82 HCM patients, detection of fQRS was reported to predict presence of fibrosis identified on DE-CMR, yielding a positive and negative predictive value of 86% and 68% respectively.\textsuperscript{31} In addition, the ECG lead territory displaying fQRS correlated with the myocardial region where fibrosis was detected. In this study 75% of HCM patients displayed fQRS in ≥1 ECG territory, with the inferior territory most often affected. These findings are in line with previous reports, indicating presence of fibrosis on DE-CMR in up to 80% of HCM patients, with small amounts of fibrosis often detected in the inferior region at the conjunction with the right ventricle.\textsuperscript{32, 33} However, apart from local fibrosis (scar), it should be considered that fQRS in HCM may also stem from tissue heterogeneity such as myofiber disarray, interstitial (diffuse) fibrosis or functional rather than structural (scar) modulation of conduction, as suggested in other channelopathies (such as Brugada syndrome).\textsuperscript{9} Therefore fQRS in HCM patients may not necessarily relate focal fibrosis, as assessed by DE-CMR imaging.
The potential clinical value of fQRS on ECG in HCM to predict malignant VTA or SCD was suggested previously.\textsuperscript{34} Recently, a study involving 179 HCM subjects showed that presence of paced ventricular ECG fractionation during electrophysiologic testing was predictive of SCD.\textsuperscript{35} Only one study so far by Kang et al., comprising 167 relatively low-risk HCM patients without BBB (no ICD recipients, but presence of $\geq 1$ conventional SCD risk factors in 42%), reported that presence of fQRS (in particular in the inferior leads) on surface ECG independently of conventional SCD risk factors related to occurrence of VTA/SCD during follow-up.\textsuperscript{11} The present study demonstrated that fQRS in $\geq 3$ territories in HCM was independently associated with a nearly 5-fold increased risk for VTA or SCD, suggesting that the extent of fibrosis rather than its presence is related to adverse cardiac outcome, in line with previous reports in HCM patients using delayed-enhancement CMR (DE-CMR) to identify fibrosis.\textsuperscript{33, 36} The fact that presence of $\geq 3$ territories was required to relate to VTA/SCD in our study compared to $\geq 1$ territory (in particular the inferior territory) in the report of Kang et al., might also be attributed to the use of more sensitive ECG settings by default in our centre, which allows for more sensitive detection of fQRS (0.05-300 Hz vs. 0.15-100 Hz filter range).\textsuperscript{11} Similar to our report, Kang et al. also pointed out higher predictive value for VTA/SCD when adding fQRS to conventional SCD risk factors.\textsuperscript{11}

fQRS in HCM patients, likely representing (local or diffuse) fibrosis and/or tissue heterogeneity, may reflect the vulnerable structural substrate that is a prerequisite for occurrence of re-entry VTA that occurs if appropriate triggers coincide.

**QTc in HCM**

The QT interval, comprising the interval between QRS onset and end of the T wave, mainly reflects myocardial repolarization. QTc prolongation in HCM patients is consistently reported.\textsuperscript{14, 15, 19, 20} In our large cohort of 195 HCM subjects, QTc prolongation defined as a duration $\geq 460$ ms had a prevalence of 13%. In HCM patients QTc prolongation has been, although weakly, related to extent of LV maximal wall thickness, LV outflow tract obstruction, underlying causative mutation (potentially affecting sodium or potassium ion channels related to depolarization and repolarization) and even sympathetic tone differences.\textsuperscript{4, 14, 15, 20, 37} Furthermore, the presence of fibrosis, myofiber disarray and/or (microvascular) ischemia might be other determinants of QTc in this patient population.

QTc duration has prognostic value in predicting occurrence of VTA or SCD in patients with congenital or acquired long QT.\textsuperscript{12, 13} In the present study a QTc duration $\geq 460$ ms was significantly associated with a nearly 3-fold increased risk for VTA or SCD. QTc duration $\geq 460$ ms was independently associated with VTA/SCD and was incremental to conventional SCD risk factors in predicting its occurrence.\textsuperscript{21}
Recently Gray et al., in a group of 164 high-risk HCM patients, all ICD recipients, showed that QTc duration ≥439 ms independently of presence of conventional risk factors predicts appropriate ICD therapies, yielding a more than 3-fold risk increase.\textsuperscript{20} QTc prolongation, comparable to numbers reported in our lower risk profile HCM patients, was 2 times more frequent in patients that received versus did not experience appropriate ICD therapy, up to 79\% versus 40\% respectively.\textsuperscript{20} Longer QTc duration in patients with history of SCD or SCD during follow-up was also noted in a study by Baranowski et al., including a group of 26 HCM subjects.\textsuperscript{18} Sherrid et al. in a study involving 330 HCM ICD recipients did not find a significant difference in QTc duration between subjects with appropriate versus no ICD discharge.\textsuperscript{29} However, this study did not exclude QTc duration confounders such as intake of QTc prolonging drugs or bundle branch block, had shorter follow-up time compared to our study and to that of Gray et al., and focused on high-risk HCM patients with ICD only.\textsuperscript{20} A QTc duration ≥480 ms in a subgroup analysis of 90 out of 479 HCM patients was not able to discriminate between subjects with and without appropriate ICD discharge, but again involved exclusively high-risk HCM patients without excluding patients with BBB.\textsuperscript{14}

The exact mechanism of VTA or SCD in HCM patients with prolonged QTc remains speculative, but may involve early after depolarizations due to prolonged ventricular repolarization which can lead to re-entry and provoke torsades de pointes. Another potential mechanism is depolarization abnormality, including fQRS, offering a substrate for maintaining the re-entry circuit after initiation of torsades de pointes.\textsuperscript{38}

**Clinical implications**

The current study suggests that surface ECG may be of clinical value for management and decision-making in selected HCM patients. Conventional SCD risk factors have only moderate PPV about 10 to 20\%, particularly when applied for primary prevention.\textsuperscript{39} We indicated that PPV of both novel ECG criteria for VTA/SCD is above 30\% and is of incremental predictive value when applied in primary prevention HCM patients. Therefore presence of fQRS or QTc prolongation in fact might serve as an easy to obtain additional SCD risk marker on top of conventional risk parameters and help to optimize selection of candidates for prophylactic ICD implantation. Nevertheless, appropriate ICD therapy does not entirely correspond to SCD events and thus further prospective validation in larger HCM patient cohorts is needed to confirm these findings. In addition, given the prognostic impact of QTc duration in HCM patients, the current study underlines the clinical importance of measuring QTc duration in HCM patients and suggests a restrictive approach when considering administration of drugs that may prolong QTc duration.
or careful monitoring of QTc duration if drug initiation is deemed to be necessary in this population.

Limitations

Some limitations to this study need consideration. First, high ECG filter settings allow high sensitivity to detect ECG abnormalities but imply a risk of over-diagnosing fQRS which cannot be excluded in the current study. Second, although a potential mechanistic link between fQRS and myocardial fibrosis (as assessed by DE-CMR) has been previously suggested in HCM patients, this evaluation was not performed in this study cohort due to absence of systematic CMR data at the time of ECG. Although validation of equating true fractionation with a local conduction abnormality such as r-prime is lacking, the definition of QRS fragmentation applied in present analysis is similar to the study of Das et al, demonstrating the link between scar due to myocardial infarction and fQRS in patients with coronary artery disease. Third, our findings were observed in a relatively low-risk HCM population (only 30% ICD recipients and 48% without family history of SCD) in the absence of BBB or QTc prolonging drugs and therefore can-not be extrapolated to other subsets of HCM patients. Four, appropriate ICD therapy should not be regarded as a full surrogate of SCD as it tends to overestimate historical mortality in HCM. Fifth, the absolute number of events was typically low despite a moderately sized HCM study cohort. Finally, as ICD recipients have continued rhythm monitoring, the occurrence of VTA events is potentially biased in favor of these patients. Due to these limitations, this study should be regarded as hypothesis generating.

CONCLUSION

Extensive QRS fragmentation and QTc prolongation in clinical HCM patients are independently associated with VTA and/or SCD in this cohort of HCM patients (48% at relatively low-risk). Both parameters are incremental to conventional SCD risk factors. These findings suggest that baseline ECG, widely available at low cost, might be valuable for risk-stratification and management of HCM patients.
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