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ORIGINAL RESEARCH

Automated Quantification of Abnormal QRS Peaks From High-Resolution ECGs Predicts Late Ventricular Arrhythmias in Hypertrophic Cardiomyopathy: A 5-Year Prospective Multicenter Study

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BACKGROUND: Patients with hypertrophic cardiomyopathy (HCM) are at risk of ventricular arrhythmia (VA) attributed to abnormal electrical activation arising from myocardial fibrosis and myocyte disarray. We sought to quantify intra-QRS peaks (QRSp) in high-resolution ECGs as a measure of abnormal activation to predict late VA in patients with HCM.

METHODS AND RESULTS: Prospectively enrolled patients with HCM (n=143, age 53±14 years) with prophylactic implantable cardioverter-defibrillators had 3-minute, high-resolution (1024 Hz), digital 12-lead ECGs recorded during intrinsic rhythm. For each precordial lead, QRSp was defined as the total number of peaks detected in the QRS complex that deviated from a smoothing filtered version of the QRS. The VA end point was appropriate implantable cardioverter-defibrillator therapy during 5-year prospective follow-up. After 5 years, 21 (16%) patients had VA. Patients who were VA positive had greater QRSp (6.0 [4.0–7.0] versus 4.0 [2.0–5.0]; $P<0.01$) and lower left ventricular ejection fraction (57±11 versus 62±9; $P=0.038$) compared with patients who were VA negative, but had similar established HCM risk metrics. Receiver operating characteristic analysis revealed that QRSp discriminated VA (area under the curve=0.76; $P<0.001$), with a QRSp ≥4 achieving 91% sensitivity and 39% specificity. The annual VA rate was greater in patients with QRSp ≥4 versus QRSp <4 (4.4% versus 0.98%; $P=0.012$). In multivariable Cox regression, age <50 years (hazard ratio [HR], 2.53; $P=0.009$) and QRSp (HR per QRS peak, 1.41; $P=0.009$) predicted VA after adjusting for established HCM risk metrics. In patients aged <50 years, the annual VA rate was 0.0% for QRSp <4 compared with 6.9% for QRSp ≥4 ($P=0.012$).

CONCLUSIONS: QRSp predicted VA in patients with HCM who were eligible for an implantable cardioverter-defibrillator after adjusting for established HCM risk metrics, such that each additional QRS peak increases VA risk by 40%. QRSp <4 was associated with a <1% annual VA risk in all patients, and no VA risk among those aged <50 years. This novel ECG metric may improve patient selection for prophylactic implantable cardioverter-defibrillator therapy by identifying those with low VA risk. These findings require further validation in a lower risk HCM cohort.

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Key Words: hypertrophic cardiomyopathy ■ myocardial disarray ■ QRS fractionation ■ risk stratification ■ sudden cardiac death ■ ventricular arrhythmias

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CLINICAL PERSPECTIVE

What Is New?

- Abnormal low-amplitude, automatically quantified intra-QRS peaks (QRSp) provide a novel metric of conduction heterogeneity, which is a prerequisite for re-entrant ventricular arrhythmia (VA).
- In patients with hypertrophic cardiomyopathy (HCM) with American College of Cardiology/American Heart Association guideline-directed prophylactic implantable cardioverter-defibrillators, QRSp predicts late VA after adjusting for established HCM risk metrics such that each additional QRSp peak increases VA risk by 40% for 5 years.
- The presence of QRSp ≥4 was associated with an annual VA rate of 4.4%, whereas a QRSp <4 identified a low-risk group with a <1% annual VA rate.
- Among patients with HCM aged <50 years, QRSp was particularly effective at discriminating risk such that the annual event rates for those with QRSp <4 and QRSp ≥4 were 0.0% and 6.9%, respectively.

What Are the Clinical Implications?

- QRSp identifies low-risk patients with HCM with an annual VA rate of <1%, which may refine patient selection for prophylactic implantable cardioverter-defibrillator therapy among those with American College of Cardiology/American Heart Association guideline indications.
- QRSp may be particularly effective in identifying very-low-risk patients with HCM among those aged <50 years.
- These findings require validation in a larger cohort of unselected, low-risk patients with HCM and may guide prophylactic implantable cardioverter-defibrillator therapy.

Nonstandard Abbreviations and Acronyms

ACC	American College of Cardiology
AHA	American Heart Association
ESC	European Society of Cardiology
fQRS	fragmented QRS
gQRS	global QRS average
HCM	hypertrophic cardiomyopathy
LGE	late gadolinium enhancement
lQRS	local QRS average
QRSd	QRS duration
QRSp	intra-QRS peaks
QRSp max	maximum QRSp in V1 to V6
SCD	sudden cardiac death
V1p to V6p	QRSp of precordial leads V1 to V6
VA	ventricular arrhythmia

Prophylactic implantable cardioverter-defibrillators (ICDs) have significantly reduced the incidence of sudden cardiac death (SCD) in high-risk patients with hypertrophic cardiomyopathy (HCM).[1] However, patient selection for prophylactic ICD therapy remains challenging and requires risk-stratification schema to accurately assess the dynamic and heterogeneous nature of their abnormal myocardial substrate.[2] The current American College of Cardiology (ACC)/American Heart Association (AHA) risk markers and European Society of Cardiology (ESC) risk score attempt to risk stratify patients with HCM based on high-risk clinical, ECG, and imaging parameters,[3,4] but these schema do not consider ECG-based QRS metrics.[5] Crucial to the formation of arrhythmogenic substrate in HCM is the presence of slow, heterogeneous electrical conduction, which can promote re-entrant ventricular arrhythmia (VA) as seen in other forms of cardiomyopathy.[2] ECG markers of abnormal conduction include prolonged QRS duration (QRSd) and fragmented QRS (fQRS) on a standard 12-lead ECG.[6] However, prolonged QRSd has limited specificity in identifying regional VA substrate because it is also dependent on global ventricular activation time.[7] In the case of fQRS, the presence of visually apparent, large intra-QRS deflections on a standard 12-lead ECG has been associated with localized conduction abnormalities[8] and predicts VA in patients with heart disease, including HCM.[6] However, fQRS has also been reported in patients without structural or electrical heart disease.[9] Moreover, fQRS does not consider smaller amplitude QRS deflections and requires manual classification as present or absent, which may limit its precision and reliability.

High-resolution ECG recordings with signal averaging offer the advantage of detecting abnormal, low-amplitude components in the QRS that may not be considered with fQRS. We developed and validated a novel high-resolution ECG technique that automatically quantifies low-amplitude, intra-QRS peaks, known as QRSp, that are not part of the smoothing filtered QRS waveform.[10] We previously reported that QRSp was a significant predictor of VA in patients with ischemic and dilated cardiomyopathy who are ICD eligible.[11] The aim of the present study was to determine the prognostic utility of QRSp for future VA events in patients with HCM.

METHODS

The authors declare that all supporting data are available in the article and its supplemental files.

Study Population

Patients diagnosed with HCM aged >18 years (see Data S1) who were treated with a prophylactic ICD according to contemporary ACC/AHA practice guidelines[12] were prospectively enrolled between 2009 and 2017. All patients had at least 1 of the following ACC/AHA risk markers and enhanced risk markers for SCD[12,13] at the time of ICD implantation: family history of SCD in ≥1 first-degree relative presumably caused by HCM, left ventricular (LV) wall thickness ≥30 mm, unexplained syncope in the previous 5 years, nonsustained ventricular tachycardia ≥3 beats at a rate of ≥120 bpm on Holter, abnormal blood pressure response to exercise, LV ejection fraction (LVEF) <50%, LV apical aneurysm, or cardiac magnetic resonance (CMR) late gadolinium enhancement (LGE) >15% of LV mass (or visually estimated to be extensive). Patients with secondary prevention ICDs for aborted sudden death or sustained VA were excluded. The study was approved by the Research Ethics Board of each participating institution, and all patients provided informed written consent.

Quantification of QRSp

Following ICD implantation, high-resolution, low-noise, digital 12-lead ECGs were recorded for 3 minutes during native QRS rhythm using a 12-lead Holter monitor (CardioMem CM 3000-12BT, Getemed Inc.) at a sampling rate of 1024 Hz (see Data S1). QRSp was automatically quantified for each precordial lead (V1–V6) using custom software developed in MATLAB (version 2012b, MathWorks) as previously described.[10] In brief, QRSp for each lead represented the total number of abnormal QRS deflections that deviated from a smoothed QRS template of that lead.

Before QRSp detection, each lead was preprocessed to reduce noise and exclude irregular beats (eg, noisy, paced, fused, or ectopic beats) as described in Data S1. The first 100 consecutive, nonexcluded QRS complexes in the 3-minute recording were used to quantify QRSp. For each lead, QRSp was assessed in consecutive 10-beat windows incremented by a single beat from the first to the last of the 100 preprocessed QRS complexes.

In each 10-beat window, abnormal QRS peaks were distinguished from normal QRS peaks by comparing the following 2 different filtered versions of the QRS complex (see Data S1): (1) a smoothed moving average filtered 100-beat global QRS average (gQRS) and (2) a no-smoothed 10-beat local QRS average (lQRS). The smoothed gQRS complex contained the major components of the depolarizing wavefront, and all of its local maxima and minima were considered to be normal QRS peaks. However, the nonsmoothed lQRS retained minor perturbations that may relate to localized conduction abnormalities in addition to the major components of the depolarizing wavefront. Thus, peaks detected on the lQRS that were not present on the gQRS were considered to be abnormal as illustrated in Figure 1. The QRSp for a 10-beat window was calculated as the total number of abnormal peaks identified in that window.

QRSp for each precordial lead (V1p–V6p) was computed as the greatest QRSp value found in >5% of all 10-beat windows, an empirically derived threshold used to reduce the chances of a spurious result.

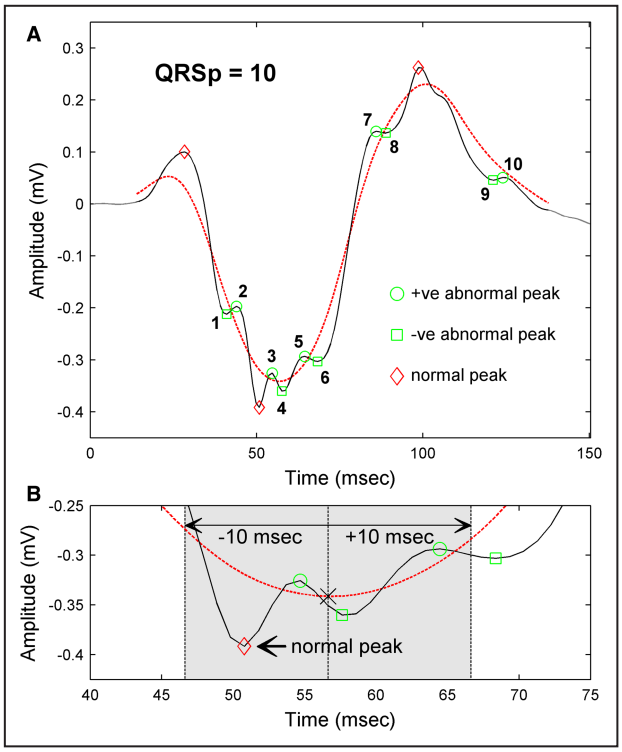

Figure 1. Quantification of QRSp.
A, Illustration of the QRSp method applied to lead V5 of a representative patient. A total of 5 positive (green circles) and 5 negative (green squares) abnormal QRS peaks are identified on the lQRS (solid black line denoting the unfiltered 10-beat QRS signal average) after identifying 3 normal peaks (red diamonds) using the smoothed gQRS (dashed red line denoting the smoothing filtered 100-beat QRS signal average). The number of positive and negative abnormal peaks is summed to produce a QRSp score of 10. **B**, Illustrative example of normal QRS peak classification using a magnified view of the same QRS complex as in **A**. A negative normal peak is identified on the smoothed gQRS (black x). The most negative normal peak on the lQRS within ±10 milliseconds of the gQRS peak (shaded area) is classified as normal. gQRS indicates global QRS average; lQRS, local QRS average; and QRSp, intra-QRS peaks.

QRSp max and QRSp mean were calculated for each patient as the maximum and mean of their 6 precordial lead QRSp values, respectively. Noise was assessed for each lead by computing the average ST-segment root mean square noise value of all 100 beats.[10]

Assessment of Traditional ECG Parameters

Native PR interval, QTc interval, QRSd, presence of left bundle-branch block, and presence of fQRS[14,15] were assessed by a trained observer blinded to VA outcomes from a 10-second printout of the 12-lead Holter recording using standard clinical ECG settings (25 mm/s, 10 mm/mV, 500 Hz sampling rate, 0.01–150 Hz bandpass filter).

Clinical Demographics and SCD Risk Variables

To reflect the most current patient risk profile, clinical demographics were collected at the time of QRSp assessment rather than ICD implant. SCD risk variables were similarly recorded at the time of QRSp assessment, aside from blood pressure response to exercise and nonsustained ventricular tachycardia on Holter, which were typically only assessed before ICD implant. LV wall thickness, LVEF, LV apical aneurysm, and left atrial diameter were assessed according to standard methods from a transthoracic echocardiogram or CMR study performed (for clinical indications) within 1 year before the 12-lead Holter study, with CMR parameters being preferred if available. Continuous-wave Doppler was used to estimate the peak instantaneous LV outflow tract gradient at rest and with Valsalva maneuver. When available, LGE percentage was assessed from a clinical LGE CMR study performed within 1 year before the 12-lead Holter study as previously described.[16] The ESC quantitative risk score was calculated, as described by O'Mahony et al,[3] to predict SCD event rates for 5 years from the time of the QRSp assessment. The 5-year risk scores were categorized into 3 predefined subsets for ICD recommendation: low (<4%; no ICD indicated), intermediate (4%–6%; ICD can be considered), and high risk (≥6%; ICD recommended).

Long-Term Clinical Outcomes

Prophylactic ICD programming was standardized as follows: ventricular tachycardia detection zone at >180 bpm to deliver antitachycardia pacing followed by cardioversion shock and ventricular fibrillation detection zone at >230 bpm to deliver defibrillation shock. Prolonged VA duration was programmed for each detection zone to avoid ICD therapy for nonsustained VA. Supraventricular tachycardia discriminators, bradycardia pacing, and dual-chamber pacing to reduce the LV outflow tract gradient was left to the discretion of the attending physician. Patients were followed prospectively after the 12-lead Holter study in the ICD clinic every 6 months for 5 years to evaluate the primary clinical outcome of VA, defined as appropriate ICD therapy (shock or antitachycardia pacing). All ICD therapies were adjudicated by the consensus of 2 experts (V.S.C. and P.C.). Patients with <6 months of follow-up who did not reach the primary outcome were excluded from the analysis.

Statistical Analysis

Continuous variables are presented as mean±SD or median and interquartile range (25th–75th percentile) where appropriate. The Student *t* test or Mann–Whitney *U* test was used for unpaired comparisons of patients with and without VA events. Categorical variables are presented as frequency or percentage and were compared by χ^2 or Fisher exact test where appropriate. Correlations were assessed using the Pearson correlation coefficient. Age was assessed as a continuous variable and as a dichotomous variable of <50 years (selected based on the median of our cohort [54 years; interquartile range, 45–62 years] and the high prevalence of SCD in younger patients).[1]

Receiver operating characteristic curves were constructed for QRSp mean and QRSp max as predictors of VA. An optimal cut point was chosen as the point with the highest Youden index with at least a 90% sensitivity for VA. The area under the receiver operating characteristic curve and 95% CI were compared between QRSp mean and QRSp max using the DeLong test. Sensitivity and specificity characteristics (with 95% CI) at the optimal QRSp mean and QRSp max cut points were compared using the NcNemar test, whereas negative and positive predictive values (with 95% CI) were compared using a weighted generalized score statistic.

Univariable and multivariable Cox regression analyses were used to assess the predictive value of QRSp max and other candidate covariates for VA. The QRSp max metric was chosen a priori as it provided an aggregate evaluation of abnormal QRS peaks among all precordial leads and had better performance for identifying VA than QRSp mean. Regression results are presented as the hazard ratio (HR) and 95% CI. The multivariable models included covariates with a univariable significance level of $P<0.15$ and the established HCM risk metrics. Multicollinearity between potential predictor variables was considered to be present if the variance inflation factor for any variable was >3. Model discrimination was assessed using the Harrell C statistic. All assumptions of the Cox proportional hazards regression model were verified. VA-free survival was determined for QRSp and age groups

using Kaplan–Meier analysis and compared with the log-rank test.

We previously demonstrated QRSp max to have excellent intraobserver and interobserver reliability for static measurements from the same window (intraclass correlation coefficients of 0.97 and 0.99, respectively).[11] To determine the temporal stability of the QRSp assessment, QRSp max from 20 randomly selected patients was compared using repeated-measures ANOVA between 3 different time points 8 hours apart. Measurement reliability was assessed by computing the coefficient of variation and the intraclass correlation coefficient.

All statistical analyses were performed using MATLAB (version 8.0, MathWorks) and SPSS (version 20.0, SPSS Inc.). A 2-sided $P<0.05$ was considered statistically significant except when multiple comparisons were made among a related family of QRSp variables (V1p, V2p, V3p, V4p, V5p, V6p, QRSp mean, and QRSp max), in which case a Bonferroni-corrected significance level of $P<0.00625$ was used to control for potential experiment-wise error.

RESULTS

Patient Population

A total of 143 consecutive patients were enrolled and completed the 12-lead Holter recording. Of the patients, 9 with <6 months of follow-up were excluded from the analysis. The baseline clinical characteristics of the remaining 134 patients are presented in Table 1. The study cohort was predominately men (68%) with a mean age of 53±14 years. HCM ACC/AHA risk factors and ESC risk scores for SCD are presented in Table 2. Because LGE CMR data were only available in 84 (63%) patients, LGE CMR >15% of LV mass was excluded as a risk factor in subsequent analysis. After excluding LGE CMR >15% of LV mass, the mean number of ACC/AHA risk factors was 1.7±0.8, with 59% of patients having >1 risk factor. The mean ESC risk score was 4.6%±2.7% with 48%, 33%, and 19% of patients being classified as low, intermediate, and high risk, respectively. Among patients who underwent genetic testing (79%), 35% were gene positive for a pathogenic or likely pathogenic variant in a sarcomeric gene. No pathogenic or likely pathogenic variants in genes encoding HCM mimics were identified.

QRSp Assessment and Relationship to LV

QRSp was measurable with high signal:noise for all precordial leads (see Data S2). The QRSp characteristics are presented in Table 3. All precordial leads had a median QRSp of 2.0 (V1p, 2.0 [0.0–2.0]; V2p, 2.0 [0.0–3.0]; V3p, 2.0 [0.0–3.0]; V4p, 2.0 [0.0–3.0]; V5p, 2.0 [0.0–4.0]; V6p, 2.0 [0.0–4.0]), but no strong correlations were observed between the QRSp values of the individual leads ($r<0.6$). Median QRSp max and QRSp mean values were 4.0 (3.0–6.0) and 1.6 (1.0–2.5), respectively. QRSp max demonstrated excellent temporal stability when it was measured serially at 3 different time points in 20 patients (Table S1), such that it was not statistically different between the time points (5.2±2.4, 5.3±2.5, and 5.0±2.2; $P=0.16$), with a low coefficient of variation (10.4%) and a high intraclass correlation coefficient (0.95). There was a moderate correlation between QRSp and QRSd (QRSp mean, $r=0.65$ [$P<0.01$]; QRSp max, $r=0.62$ [$P<0.01$]; Figure S1). There was a weak negative correlation between QRSp and LVEF (QRSp mean, $r=-0.36$ [$P<0.01$]; QRSp max, $r=-0.31$ [$P<0.01$]), but no correlation with maximum LV wall thickness. In the subgroup of 84 patients with LGE CMR studies, QRSp was greater in those with extensive LV LGE than in those without (QRSp mean, 2.2 [1.3–2.7] versus 1.3 [1.0–1.7; $P=0.001$]; QRSp max, 4.0 [3.0–6.0] versus 3.5 [2.0–4.0; $P=0.001$]).

Relationship of Clinical Variables and QRSp to Ventricular Arrhythmias

Following the 12-lead Holter recording, patients were followed prospectively for a median of 60 months (60–60 months), and 21 (16%) experienced the primary clinical outcome of VA after a median of 23 months (18–31 months). Among the 134 patients, 3 (2%) had a heart transplant, 2 (1%) had a nonarrhythmic death, 2 (1%) were lost to follow-up, and 1 (1%) had their ICD explanted before completing the 5-year follow-up. Among the 21 patients who experienced a VA event during prospective follow-up after their 12-lead Holter study, 14 patients had monomorphic ventricular tachycardia (mean heart rate, 200±42 bpm), and 7 had polymorphic ventricular tachycardia or ventricular fibrillation (mean heart rate, 278±68 bpm). The VA events were successfully treated via ICD shock and antitachycardia pacing in 9 and 12 patients, respectively.

Baseline clinical characteristics, SCD risk variables, and ECG characteristics are compared between patients who were VA positive and VA negative in Tables 1, 2, and 3, respectively. Among clinical characteristics, patients who were VA positive had lower LVEF (57±11 versus 62±9%; $P=0.038$) and a trend toward being aged <50 years (57 versus 35%; $P=0.060$). Among established HCM risk metrics and ECG metrics, there were no observed differences.

Among the QRSp metrics (Table 3, Figure 2), patients who were VA positive had a greater QRSp mean (2.5 [1.7–3.0] versus 1.5 [1.0–2.3]; $P=0.002$) and QRSp max (6.0 [4.0–7.0] versus 4.0 [2.0–5.0]; $P<0.001$) than patients who were VA negative. In contrast, fQRS (68% versus 60%; $P=0.575$) and QRSd (116±31 versus 105±26; $P=0.120$) were not statistically different between patients who were VA positive and VA negative.

Table 1. Clinical Demographics in Patients Who Were VA Negative and VA Positive

	All patients (N=134)	VA negative (N=113)	VA positive (N=21)	*P* value
Age, y	52±13	53±13	48±15	0.115
Age <50 y	52 (39)	40 (35)	12 (57)	0.060
Male sex	91 (68)	77 (68)	14 (68)	0.894
LVEF, %	61±9	62±9	57±11	0.038
Max LV thickness, mm	20±6	20±6	21±6	0.738
Left atrial diameter, mm	44±6	44±6	44±7	0.945
Max LVOT gradient (rest/Valsalva), mm Hg	7.0 (2.0–17.0)	8.0 (2.0–19.0)	5.0 (2.0–8.0)	0.115
Comorbidities				
Coronary artery disease	3 (2)	3 (3)	0 (0)	1.000
History of AF	35 (26)	29 (26)	6 (29)	0.781
Prior cointerventions*				
Surgical myectomy	10 (8)	9 (8)	1 (5)	1.000
Alcohol septal ablation	1 (1)	1 (1)	0 (0)	1.000
Medications				
β-blocker	110 (82)	95 (84)	15 (71)	0.212
Class I antiarrhythmic drugs	10 (8)	9 (8)	1 (5)	1.000
Class III antiarrhythmic drugs	17 (13)	14 (12)	3 (14)	0.731
Sotalol	4 (3)	3 (3)	1 (5)	0.602
Amiodarone	13 (10)	11 (10)	2 (10)	1.000
Calcium channel blockers	23 (17)	19 (17)	4 (19)	0.759
ACE-I/ARB	36 (27)	31 (27)	5 (24)	0.731
Diuretic	25 (19)	22 (20)	3 (14)	0.764

Data are provided as mean±SD, median (interquartile range), or number (percentage).

ACE-I/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; AF, atrial fibrillation; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; and VA, ventricular arrhythmia.

*Performed in prior 10 years.

Receiver Operating Characteristic Analysis of QRSp

Receiver operating characteristic analysis was used to evaluate the performance characteristics of the QRSp summary metrics, QRSp max and QRSp mean, for discriminating VA (Figure 2). The area under the curve (95% CI) for identifying VA was greater for QRSp max (0.76 [0.66–0.86]; *P*<0.001) than for QRSp mean (0.71 [0.60–0.82]; *P*=0.002), although the difference was not statistically significant (*P*=0.152). The optimal cut points with >90% sensitivity for identifying VA were determined to be QRSp max ≥4 and QRSp mean ≥1.08 (Figure 2). QRSp max ≥4 compared with QRSp mean ≥1.08 achieved greater specificity (39% [30%–48%] versus 29% [21%–38%]; *P*=0.027), with no statistical difference in sensitivity (91% [73%–99%] versus 95% [81%–100%]; *P*=1.00), positive predictive value (22% [14%–31%] versus 20% [13%–29%]; *P*=0.785), or negative predictive value (96% [87%–99%] versus 97% [88%–100%]; *P*=0.748) for identifying VA. QRSp max was thus selected for use in the subsequent survival analyses. The clinical characteristics, established HCM risk metrics, and ECG characteristics of patients with QRSp max <4 versus QRSp max ≥4 are presented in Tables S2 through S4, respectively. Compared with patients with QRSp max <4, patients with QRSp max ≥4 had lower LVEF (60±10 versus 64±8; *P*=0.025), more LV apical aneurysms (10% versus 0%; *P*=0.027), larger left atrial diameter (45±6 versus 42±7; *P*=0.025), longer PR interval (191±43 versus 169±33; *P*=0.004), longer QRSd (114±29 versus 93±16; *P*<0.001), lesser use of class I antiarrhythmic drugs (3% versus 15%; *P*=0.032), and greater use of class III antiarrhythmic drugs (18% versus 2%; *P*=0.008). There was also a trend toward patients with QRSp max ≥4 having more ACC/AHA risk factors (1.8±0.9 versus 1.6±0.7; *P*=0.077) and >1 risk factor (65% versus 48%; *P*=0.06) and being in a higher ESC risk score category (low/intermediate/high: 41%/38%/22% versus 61%/24%/15%; *P*=0.058).

Survival Analysis

Relevant clinical characteristics, established HCM risk metrics, and ECG metrics were evaluated with Cox regression analysis (Table 4). Univariable predictors of VA

Table 2. HCM ACC/AHA Risk Factors and ESC Risk Score for SCD in Patients Who Were VA Negative and VA Positive

	All patients (N=134)	VA negative (N=113)	VA positive (N=21)	*P* value
ACC/AHA risk factors				
History of syncope*	38 (28)	30 (27)	8 (38)	0.281
History of NSVT†	85 (63)	71 (63)	14 (68)	0.738
Family history of SCD‡	39 (29)	35 (31)	4 (19)	0.269
LV wall thickness ≥30 mm	25 (19)	22 (20)	3 (14)	0.764
Abnormal BP response to exercise§,‖	24 (18)	22 (22)	2 (11)	0.358
LVEF <50%	13 (10)	10 (9)	3 (14)	0.429
LV apical aneurysm	9 (7)	7 (6)	2 (10)	0.632
No. of ACC/AHA risk factors	1.7±0.8	1.7±0.8	1.7±0.9	0.882
>1 ACC/AHA risk factor	79 (59)	66 (58)	13 (62)	0.765
ESC risk score	4.6±2.7	4.5±2.6	5.2±3.1	0.156
ESC risk score category				0.535
Low, <4% for 5 y	64 (48)	56 (50)	8 (38)	
Intermediate, 4%–6% for 5 y	44 (33)	35 (31)	9 (43)	
High, ≥6% for 5 y	26 (19)	22 (20)	4 (19)	

Data are provided as mean±SD or number (percentage).

ACC indicates American College of Cardiology; AHA, American Heart Association; BP, blood pressure; ESC, European Society of Cardiology; HCM, hypertrophic cardiomyopathy; LV, left ventricular; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; SCD, sudden cardiac death; and VA, ventricular arrhythmia.

*Loss of consciousness without a known causal factor in the previous 5 years.

†A total of ≥3 consecutive ventricular beats at a rate of ≥120 bpm lasting for <30 seconds on ambulatory ECG.

‡SCD in ≥1 first-degree relatives.

§Flat response (increase in systolic BP during whole exercise period of <25 mm Hg compared with resting systolic BP) or hypotensive response (initial increase in systolic BP with a subsequent fall by peak exercise of >10 mm Hg from baseline or the peak BP value).

‖BP response to exercise was not assessed in 14 patients (N=120).

(*P*<0.15) included the following (HR [95% CI]): age (per 5 years, 0.86 [0.74–1.01]; *P*=0.068), age <50 years (2.45 [1.03–5.81]; *P*=0.042), LVEF (per 5%, 0.8 [0.65–0.99]; *P*=0.036), QRSd (per 10 milliseconds, 1.11 [0.98–1.27]; *P*=0.108), QTc (per 10 milliseconds, 1.10 [0.98–1.23]; *P*=0.103), and QRSp max (per QRS peak, 1.27 [1.11–1.45]; *P*=0.001). QRSp max was evaluated in 2 separate models adjusted for age <50 years, LVEF, QRSd, QTc, and either >1 ACC/AHA risk factor or ESC risk score ≥4%. In the model including >1 ACC/AHA risk factor, QRSp max (per QRS peak, 1.41 [1.09–1.82]; *P*=0.009) and age <50 years (3.29 [1.31–8.30]; *P*=0.011) were the only significant predictors of VA (C statistic=0.78). In the model including ESC risk score ≥4%, QRSp max (per QRS peak, 1.40 [1.08–1.81]; *P*=0.010) and age <50 years (3.10 [1.23–7.83]; *P*=0.017) were the only significant predictors of VA (C statistic=0.77). When QRSp max was excluded from the models containing >1 ACC/AHA risk factor and ESC risk score ≥4%, the C statistics fell to 0.70 and 0.71, respectively. Similar results were observed when the models were adjusted for age as a continuous rather than a dichotomous variable (Table S5). Multicollinearity was not observed (variance inflation factor <3) between any of the variables included in the multivariable models, and there was no correlation between QRSp max and age (*r*=0.08; *P*=0.363).

Kaplan–Meier event-free survival curves for QRSp max ≥4 and age <50 years are presented in Figure 3. After 5 years of follow-up, patients with QRSp max <4 had greater freedom from VA compared with patients with QRSp max ≥4 (total events, 2/46 versus 19/88; annual event rate, 0.98% versus 4.4%; *P*=0.012). Patients aged ≥50 years also had greater freedom from VA compared with patients aged <50 years (total events, 9/82 versus 12/52; annual event rate, 2.3% versus 4.8%; *P*=0.036). The cohort was then divided into the following 4 groups to assess the predictive ability of QRSp in young and old patients: QRSp <4/age <50 (N=16), QRSp <4/age ≥50 (N=30), QRSp ≥4/age <50 (N=36), and QRSp ≥4/age ≥50 (N=52). Kaplan–Meier analysis of these categories revealed patients with QRSp <4/age <50 (*P*=0.012), QRSp <4/age ≥50 (*P*=0.009), and QRSp ≥4/age ≥50 (*P*=0.010) to have greater freedom from VA than patients with QRSp ≥4/age <50 (total events, 0/16, 2/30, 7/52, and 12/36, respectively; annual event rates of 0.0%, 1.5%, 2.8%, and 6.9%, respectively). There was no difference in survival outcomes between any of the other categories. Figure 4A and 4B illustrate QRSp in 2 patients aged <50 years with and without a VA event, respectively.; Figure 4C and 4D illustrate 2 patients aged ≥50 years with and without a VA event, respectively.

Table 3. ECG Characteristics in Patients Who Were VA Negative and VA Positive

	All patients (N=134)	VA negative (N=113)	VA positive (N=21)	*P* value
Baseline heart rate, bpm	62±12	61±11	65±12	0.210
PR interval, milliseconds*	183±41	181±39	194±51	0.196
QRSd, milliseconds	107±27	105±26	116±31	0.120
LBBB	15 (11)	11 (10)	4 (19)	0.254
QTc interval, milliseconds	447±33	445±33	459±29	0.072
fQRS	82 (61)	68 (60)	14 (68)	0.575
QRSp				
V1p	2.0 (0.0–2.0)	2.0 (0.0–2.0)	2.0 (2.0–4.0)	0.046
V2p	2.0 (0.0–3.0)	2.0 (0.0–2.0)	2.0 (2.0–4.0)	0.072
V3p	2.0 (0.0–3.0)	2.0 (0.0–2.0)	3.0 (2.0–4.0)	0.002†
V4p	2.0 (0.0–3.0)	2.0 (0.0–2.0)	2.0 (0.0–5.0)	0.145
V5p	2.0 (0.0–4.0)	2.0 (0.0–4.0)	3.0 (2.0–4.0)	0.074
V6p	2.0 (0.0–4.0)	2.0 (0.0–4.0)	3.0 (1.0–5.0)	0.071
QRSp max	4.0 (3.0–6.0)	4.0 (2.0–5.0)	6.0 (4.0–7.0)	<0.001†
QRSp mean	1.6 (1.0–2.5)	1.5 (1.0–2.3)	2.5 (1.7–3.0)	0.002†

Data are provided as mean±SD, median (interquartile range), or number (percentage).
fQRS indicated fragmented QRS; LBBB, left bundle-branch block; QRSd, QRS duration; QRSp, intra-QRS peaks; QRSp max, maximum QRSp in V1 to V6; QRSp mean, average QRSp of V1 to V6; V1p to V6p, QRSp values of leads V1 to V6; and VA, ventricular arrhythmia.
*PR interval could not be assessed in 7 patients with atrial arrhythmias (N=127).
†QRSp variables below Bonferroni-corrected significance level (*P*<0.00625).

Stratification of patients to low and high VA risk categories using QRSp max ≥4 was compared with stratification by >1 ACC/AHA risk factor and an ESC risk score ≥4%. Compared with the >1 ACC/AHA risk factor, QRSp max ≥4 reclassified 13 patients as low risk and 16 patients as high risk. Among the 21 patients with VA, QRSp max ≥4 identified 7 as high risk who would have been classified as low risk, and 1 as low risk who would have been classified as high risk by >1 ACC/AHA risk factor (event net reclassification improvement=29%). Compared with ESC risk score ≥4%, QRSp max ≥4 reclassified 14 patients as low risk and 17 patients as high risk. Among the 21 patients with VA, QRSp max ≥4 identified 7 as high risk who would have been classified as low risk, and 1 as low risk who would have been classified as high risk by ESC risk score ≥4% (event net reclassification improvement=29%).

DISCUSSION

In this prospective study of high-risk patients with HCM with prophylactic ICDs, we evaluated the prognostic utility of low-amplitude, QRSp, quantified automatically from high-resolution ECGs, as a measure of conduction heterogeneity and arrhythmogenicity. The main study findings are as follows: (1) QRSp predicted VA after adjusting for established HCM risk metrics, such that each additional QRS peak increased VA risk by 40%; (2) QRSp max ≥4 was associated with an annual VA rate of 4.4% during the 5-year follow-up, whereas a QRSp max <4 identified a low-risk group with an annual VA rate of only 0.98%; and (3) patients with QRSp max ≥4 had structural remodeling, including lower LVEF, more LV apical aneurysms, and larger left atrial diameter. QRSp was particularly effective in discriminating VA risk in patients aged <50 years, such that these younger patients with QRSp max ≥4 had an annual VA rate of 6.9% compared with 0.0% in those with QRSp max <4. In our previous report of ICD-eligible patients with ischemic and dilated cardiomyopathy, those with a QRSp max ≥4 had an annual VA rate of 23%, whereas patients with QRSp max <4 had no VA during 2 years of follow-up.[11] Together, these 2 studies support the robust prognostic utility of QRSp for VA in a variety of cardiomyopathy subtypes.

Prior Studies on Abnormal Conduction and QRS Signals in HCM

The arrhythmogenic myocardial substrate in HCM arises from a combination of myocyte disarray, gap-junction remodeling, and interstitial/replacement fibrosis, which provide structural and functional barriers to rapid, uniform ventricular activation.[2] The resulting slow, zig-zag conduction gives rise to local, fractionated intracardiac electrograms. Saumarez et

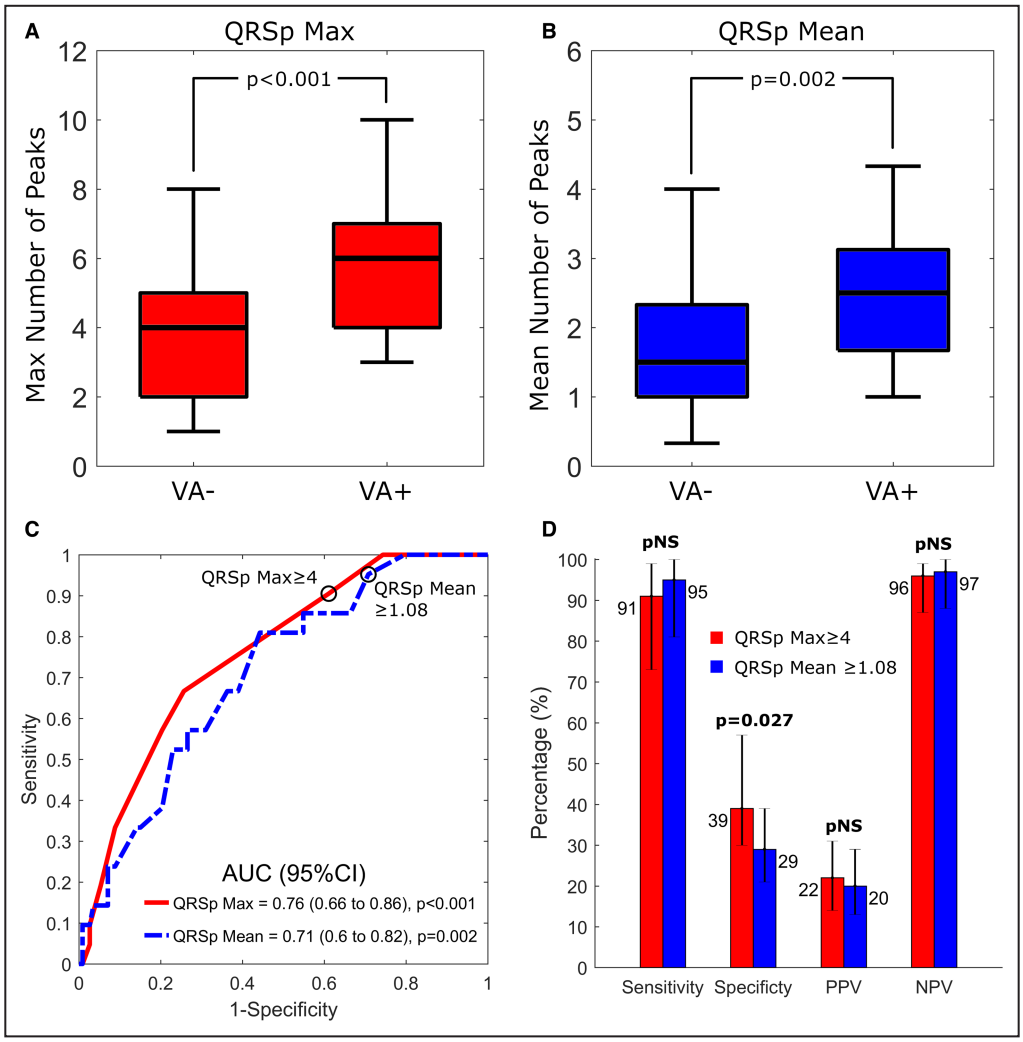

Figure 2. Performance of QRSp max and QRSp mean in predicting arrhythmic events.
Box plots comparing (**A**) QRSp max and (**B**) QRSp mean between patients with and without VA events. **C**, Receiver operating characteristic curves for QRSp max (red solid line) and QRSp mean (blue dashed line) as a predictor of VA events for 5 years. Black circles highlight the sensitivity and 1-specificity obtained by using a QRSp max cut point ≥4 and a QRSp mean cut point ≥1.08. **D**, Bar graphs comparing the prognostic performance of the QRSp max and QRSp mean cut points for identifying patients with VA events for 5 years. QRSp mean is the average QRSp of V1 to V6. AUC indicates area under the curve; NPV, negative predictive value; PPV, positive predictive value; QRSp, intra-QRS peaks; QRSp max, maximum QRSp in V1 to V6; and VA, ventricular arrhythmia.

al[17] performed invasive electrophysiology studies in high-risk patients with HCM and demonstrated fractionated bipolar electrograms along the right ventricular septum that became more fractionated with shorter ventricular extra-stimuli-induced conduction slowing. Noninvasive assessment of conduction slowing and heterogeneity in HCM has also been reported using fQRS. Kang et al[18] found fQRS in 40% of patients with HCM, which did predict VA, including nonsustained VA. The presence of fQRS in HCM has been associated with histologic myocardial fibrosis[19,20] with a sensitivity and specificity similar to that of CMR LGE.[19]

QRSp and VA Risk in HCM

QRSp was a strong predictor of future VA in high-risk patients with HCM. A QRSp max cutoff of ≥4 had a sensitivity of 91%, specificity of 39%, positive predictive value of 22%, and a negative predictive value of 96% in identifying patients at risk of VA during a 5-year follow-up. Patients with QRSp max ≥4 had lower LVEF, more LV apical aneurysms, and larger left atrial diameters. These structural abnormalities are associated with more extensive ventricular fibrosis in HCM,[21–23] which may lead to greater conduction heterogeneity, higher QRSp, and a propensity for VA.[3,24] Patients

Table 4. Cox Regression Analysis for the Prediction of VA Events (N=134)

	Univariable analysis		Multivariable model 1*		Multivariable model 2†	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, per 5 y	0.86 (0.74–1.01)	0.068	…	…	…	…
Age <50 y	2.45 (1.03–5.81)	0.042	3.29 (1.31–8.30)	0.011	3.10 (1.23–7.83)	0.017
Male sex	0.94 (0.38–2.33)	0.897	…	…	…	…
LVEF, per 5%	0.80 (0.65–0.99)	0.036	0.86 (0.68–1.09)	0.203	0.86 (0.69–1.08)	0.192
History of syncope	1.58 (0.66–3.82)	0.306	…	…	…	…
History of NSVT	1.15 (0.46–2.85)	0.764	…	…	…	…
Family history of SCD	0.60 (0.20–1.79)	0.361	…	…	…	…
Septal thickness ≥30 mm	0.71 (0.21–2.40)	0.578	…	…	…	…
Abnormal BP response to exercise§	0.46 (0.11–2.00)	0.302	…	…	…	…
LVEF <50%	1.67 (0.49–5.67)	0.411	…	…	…	…
Apical aneurysm	1.63 (0.38–7.02)	0.509	…	…	…	…
No. of ACC/AHA risk factors	0.99 (0.58–1.70)	0.974	…	…	…	…
>1 ACC/AHA risk factor	1.17 (0.48–2.82)	0.728	0.99 (0.39–2.53)	0.990	…	…
ESC risk score	1.10 (0.95–1.26)	0.201	…	…	…	…
ESC risk score ≥4%	1.54 (0.64–3.71)	0.340	…	…	1.52 (0.60–3.86)	0.378
QRSd, per 10 milliseconds	1.11 (0.98–1.27)	0.108	0.89 (0.71–1.11)	0.298	0.89 (0.72–1.12)	0.319
QTc interval, per 10 milliseconds	1.10 (0.98–1.23)	0.103	1.03 (0.90–1.19)	0.673	1.04 (0.90–1.20)	0.607
fQRS	1.31 (0.53–3.24)	0.565	…	…	…	…
QRSp max	1.27 (1.11–1.45)	0.001	1.41 (1.09–1.82)	0.009	1.40 (1.08–1.81)	0.010

ACC indicates American College of Cardiology; AHA, American Heart Association; BP, blood pressure; ESC, European Society of Cardiology; fQRS, fragmented QRS; HR, hazard ratio; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; QRSd, QRS duration; QRSp, intra-QRS peaks; QRSp max, maximum QRSp in V1 to V6; SCD, sudden cardiac death; and VA, ventricular arrhythmia.

*Model 1: C statistic=0.78

†Model 2: C statistic=0.77.

§BP response to exercise was not assessed in 17 patients (N=110).

with QRSp max ≥4 also had greater PR interval, QRSd >120 milliseconds, and left bundle-branch block, a finding consistent with more infra-Hisian conduction disease. Although there was a modest correlation between QRSp and QRSd (r=0.62), QRSd was not a predictor of VA in HCM, suggesting that regional conduction heterogeneity in the myocardium may play a greater role in arrhythmogenesis than more global His-Purkinje conduction slowing. Antiarrhythmic drugs are known to modulate myocardial substrate, QRSd, and ultimately VA risk.[25] Among our study patients, 21% were taking class I or III antiarrhythmic drugs to manage atrial fibrillation or high LV outflow tract gradients. In those with QRSp max ≥4, class III drugs were used more commonly, whereas class I drugs were less common. It is possible that conduction slowing from class III drugs contributed to greater QRSp, but despite antiarrhythmic drug therapy, VA events were still higher in patients with QRSp max ≥4.

A frequency-domain, signal-averaged ECG analysis by Kulakowski et al[25] also demonstrated abnormal QRS potentials in patients with HCM and VA, but more commonly in the initial portion of the QRS complex. Unlike the terminal QRS, the initial QRS arises from activation of the interventricular septum, where a predilection for abnormal substrate in HCM may produce these early QRS potentials.[25] In contrast, our time-domain analysis with QRSp showed no correlation with maximum LV wall thickness, including the interventricular septum. In our study, fQRS was not predictive of VA, unlike the study by Kang et al,[18] which may be explained by differences in the study populations and clinical end points. Higher risk patients with ICDs, LV dysfunction, and QRS prolongation were excluded in their study, whereas our study patients all had prophylactic ICDs, and a few had LVEF <50% (10%) and QRSd >120 milliseconds (27%). Kang et al[18] included nonsustained ventricular tachycardia in the definition of VA, but in our study, only appropriate ICD therapy (shock or antitachycardia pacing) was included as the primary end point, which is more clinically relevant. In contrast to fQRS, the intra-QRS signals counted by

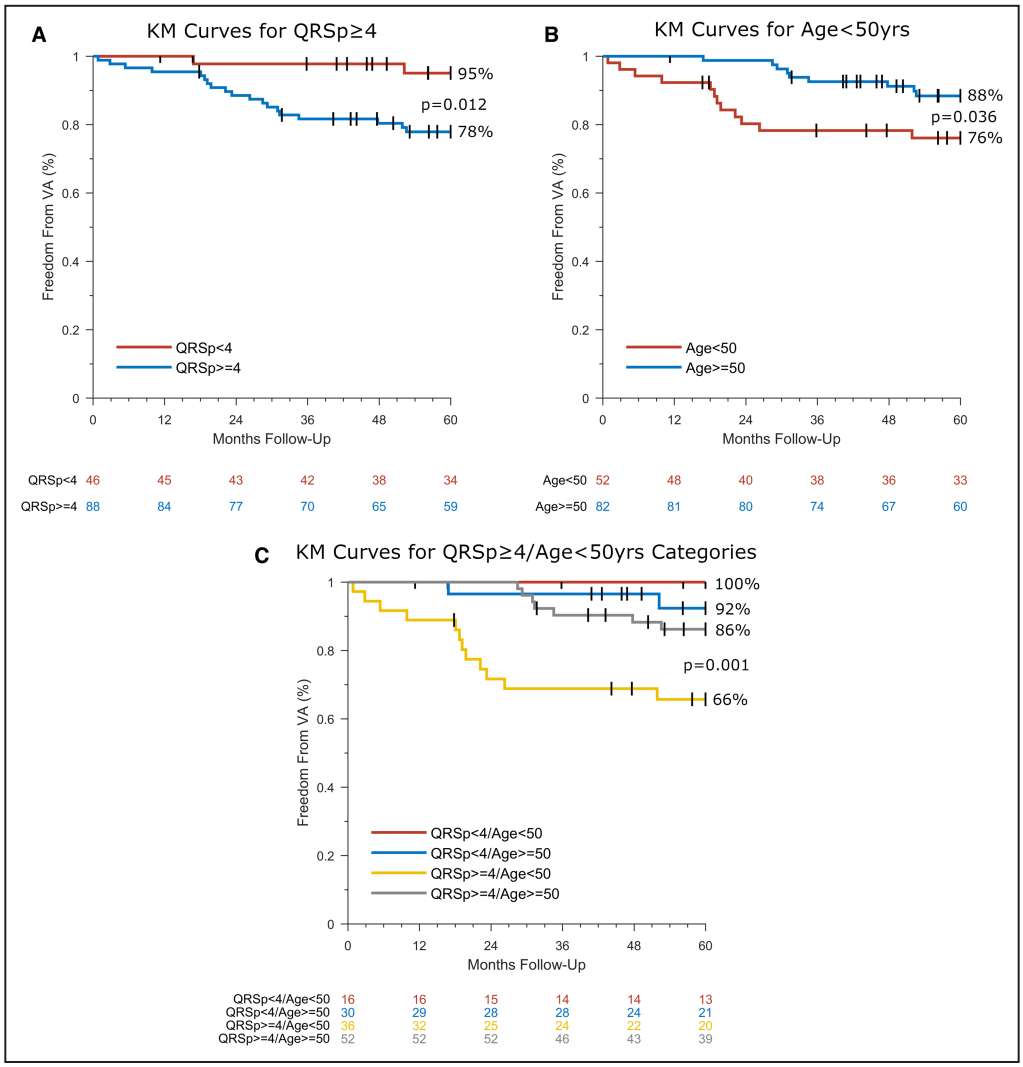

Figure 3. KM survival curves for VA events.
KM survival curves for VA events stratified by (**A**) QRSp ≥4, (**B**) age <50 years, and (**C**) the combined QRSp ≥4 and age <50 years classifications. KM indicates Kaplan–Meier; QRSp, intra-QRS peaks; and VA, ventricular arrhythmia.

QRSp were typically lower in amplitude and detectable using signal averaging of high-resolution ECG recordings.[26] These higher fidelity signal features may allow QRSp to more accurately quantify arrhythmogenic ventricular activation.[27]

Clinical Implications

Appropriate patient selection for prophylactic ICDs remains 1 of the most challenging issues in the management of HCM. The current ACC/AHA and ESC risk metrics have modest accuracy in predicting SCD owing to the high prevalence of appointed risk factors (≈45% of the population) and the low incidence of SCD (<1% per year).[5] Therefore, measures to improve risk stratification will more effectively direct prophylactic ICD therapy and reduce their long-term morbidity.[5] QRSp provides an automated, objective measure of conduction heterogeneity and its time-domain measure of QRS fragmentation is intuitive. It can be measured from the 12-lead ECG during intrinsic rhythm, making it a practical tool for VA risk assessment. In our HCM cohort with prophylactic ICDs, QRSp max ≥4 identified a very-high-risk subgroup (annual VA rate, 4.4%) who may require closer ICD follow-up and possibly early antiarrhythmic drug therapy to prevent VA. In contrast, QRSp max <4 identified a low-risk group with an annual VA rate of <1%, whereas patients aged <50 years with QRSp max <4 had no VA events during the 5-year follow-up. SCD in HCM is reported to be more common in young patients,[28] and VA risk decreases with older age according to the ESC risk

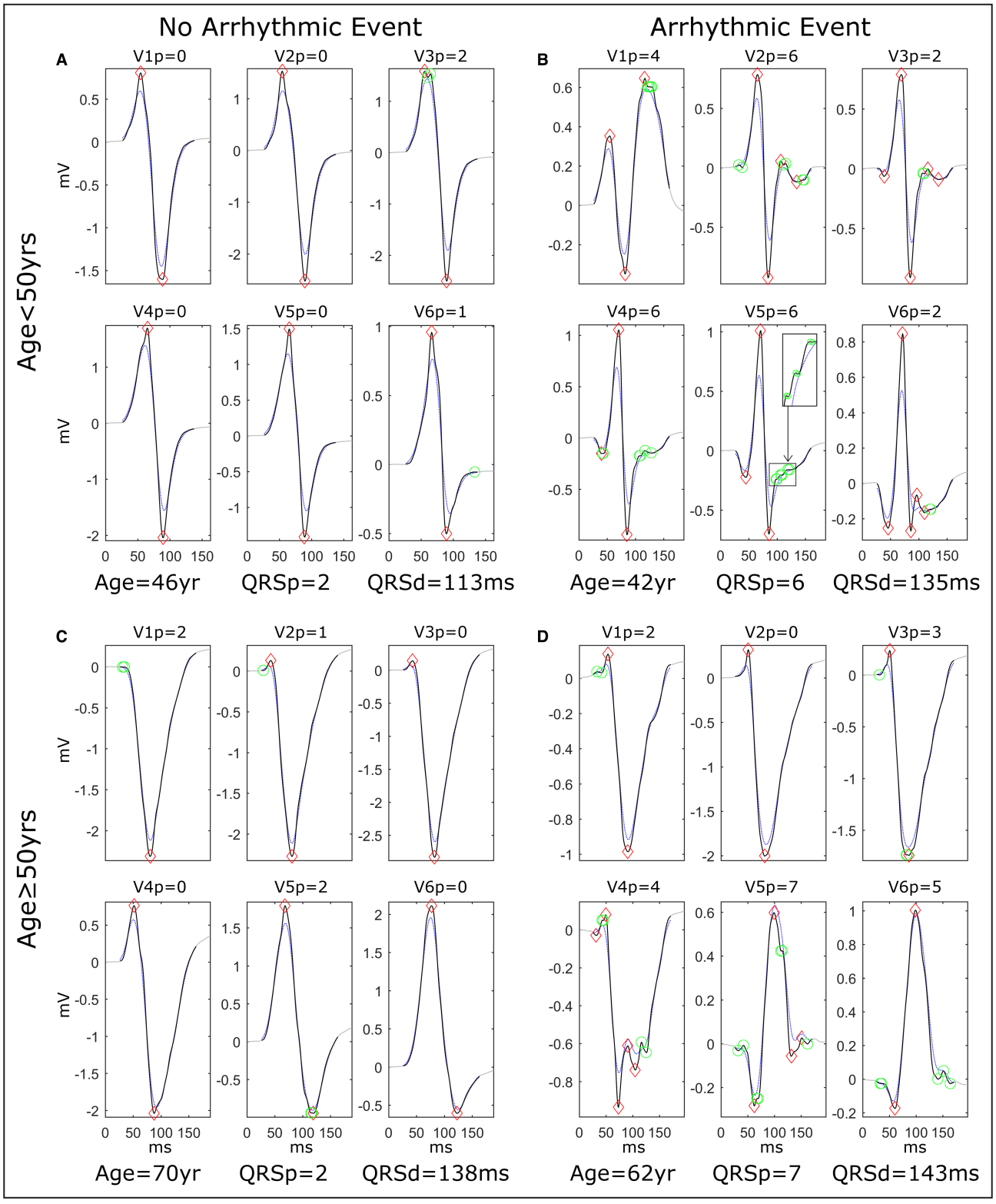

Figure 4. Examples of QRSp in patients aged <50 and ≥50 years with and without VA events.
QRSp results for a single 10-beat window from (**A**) a younger patient (aged <50 years) with no VA event, (**B**) a younger patient (aged <50 years) with a VA event, (**C**) an older patient (aged ≥50 years) with no VA event, and (**D**) an older patient (aged ≥50 years) with a VA event. Irrespective of their age, the patients with VA events have greater individual precordial lead QRSp values (V1p–V6p) and maximum QRSp in V1 to V6 than those without VA events. Solid black lines indicate the local QRS average (ie, the unfiltered 10-beat QRS signal average), and dashed blue lines indicate the global QRS average (ie, the smoothing filtered 100-beat QRS signal average). Normal peaks are annotated with red diamonds, and abnormal peaks are annotated with green circles. QRSd indicates QRS duration; QRSp, intra-QRS peaks; V1p to V6p, QRSp values of leads V1 to V6; and VA, ventricular arrhythmia.

score.[3] Thus, QRSp may identify very-low-risk patients aged <50 years, where prophylactic ICD therapy could be deferred for 5 years. However, these findings require validation in a larger, unselected cohort of lower risk patients with HCM without ICDs to refine prophylactic ICD use.

Limitations

First, the detection of low-amplitude, intra-QRS signals is susceptible to noise. Adequate ECG recording setup and preprocessing were performed to reduce noise and exclude ectopic/fusion beats. Second, the detection of low-amplitude QRS peaks using our time-domain analysis may also be affected by the duration of QRS averaging, such that a longer averaging window may lead to the underdetection of QRS peaks if they are phasic with respiratory chest wall movement, whereas a smaller window may not average out spurious peaks.[10] A 10-beat averaging window was validated to be sufficiently long in a prior report using simulated QRS peaks and noise,[10] so the same averaging window was used in the present study. Third, CMR LGE-detected fibrosis is a strong predictor of VA in HCM[1] but was not included in the multivariable modeling with QRSp because 37% of patients had not undergone CMR assessment of LGE. Further studies are required to evaluate the relationship of QRSp with CMR LGE and whether QRSp provides functional assessments of CMR LGE. Fourth, VA substrate in HCM may evolve, and QRSp at 1 time point will not assess dynamic substrate that may itself increase VA risk. Longitudinal studies evaluating the temporal evolution of QRSp may further improve VA risk assessment in HCM. Finally, our study was modest in size, with a limited number of VA events during the 5-year follow-up, and only high-risk patients with HCM were included with guideline indications for prophylactic ICD. Future studies in a larger cohort of lower risk patients with HCM are warranted to confirm our findings.

CONCLUSIONS

In patients with HCM with prophylactic ICDs, automated quantification of abnormal, low-amplitude, QRSp predicted VA during a 5-year follow-up after adjusting for established HCM risk metrics in which each additional QRS peak increased VA risk by 40%. Patients with a QRSp max ≥4 had a 4.4% annual VA risk, whereas QRSp max <4 was associated with a <1% annual VA risk in all patients, and no VA risk in those aged <50 years. QRSp provides a robust measure of conduction heterogeneity in HCM, such that fewer QRS peaks identify low-risk patients with less VA substrate. These findings require validation in a larger cohort of lower risk patients and may help to improve patient selection for prophylactic ICD therapy.

ARTICLE INFORMATION

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Disclosures

AS and VC are authors of QRSp intellectual property (US patent: US 10,111,598 B2) owned by the University Health Network, Canada.

Supplemental Material

Data S1–S2
Tables S1–S5
Figure S1
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SUPPLEMENTAL MATERIAL

Data S1. SUPPLEMENTAL METHODS

HCM Diagnosis and Imaging

Hypertrophic cardiomyopathy (HCM) was defined by echocardiography or cardiac magnetic resonance (CMR) imaging according to current practice guidelines,[29] as unexplained hypertrophy with left ventricular (LV) wall thickness >15 mm or LV wall thickness >13 mm in first-degree family members of patients with unequivocal HCM.

All patients underwent comprehensive 2-dimensional transthoracic echo evaluation and studies were interpreted by an experience cardiologist. LV wall thickness was measured in end-diastole in accordance with current guidelines.[30] All myocardial segments were interrogated, and the measurements reported were from the thickest segment identified. CMR studies were performed using 1.5-T (Magnetom Avanto or Avanto Fit; Siemens Healthineers, Erlangen, Germany) or 3-T (Magnetom Skyra or Skyra Fit; Siemens Healthineers) scanners with commercially available cardiac surface coils. Breath-hold retrospectively gated cine steady-state free-procession images were acquired in long-axis planes (single-slice two-chamber, four-chamber, stacked three-chamber) and short-axis slices from the atrioventricular groove to the apex to cover the entire LV volume (slice thickness 6–8 mm, interslice gap 0–2 mm, temporal resolution 30–40 ms). Late gadolinium enhanced imaging was performed 12 to 15 min following intravenous administration of a gadolinium-based contrast agent (gadobutrol [Gadovist] or gadopentetate dimeglumine [Magnevist]; Bayer Healthcare, Berlin, Germany) at a dose of 0.15 to 0.2 mmol/kg body weight with a two-dimensional breath-hold inversion-recovery gradient-recalled echo sequence acquired in multiple imaging planes, including a short-axis stack (slice thickness 6–8 mm, interslice gap 0–2 mm).

ECG Acquisition

Following ICD implantation, high-resolution, digital 12-lead ECGs were recorded for 3 minutes during native QRS rhythm using a 12-lead Holter monitor (CardioMem CM 3000-12BT, Getemed Inc.) at a sampling rate of 1024Hz (0.05-120Hz analogue bandwidth, ±6 mV voltage range, 12-bit digital resolution, 2.9μV least significant bit). To minimize ECG noise, patients were required to lie still in the supine position with their hands at their sides for the duration of the recording. The precordial leads were specifically selected for QRSp analysis because each is an independent unipolar recording unlike the six limb leads which are derived from only two independent lead pairs (i.e. leads I and II).

ECG Preprocessing

Prior to QRSp quantification each lead was pre-processed as follows. First, a low noise-QRS template was manually defined on the overlayed digital 12-lead ECG by a trained observer blinded to ventricular arrhythmia (VA) outcomes. Using the peak of the R-wave as a fiducial point, each QRS complex in the 3-minute recording was roughly aligned to the QRS template, and further refined by identifying the cross-correlation with the QRS template for each point in a window from 25ms before to 25ms after the initial alignment position. The point which produced the greatest average cross-correlation across all leads was chosen as the final point of alignment. To eliminate non-sinus beats, complexes that were <90% similar to the morphology of the template complex were excluded.[31] Second, to eliminate noisy beats, QRS complexes with a ST segment root mean square noise value >10μV were excluded, which minimizes false QRS peak detection as previously shown.[10] Third, the ECG was denoised using a 150Hz bidirectional low pass filter (4th order Butterworth) to attenuate high frequency noise,[8] and then cubic spline corrected to remove baseline wander.[32]

gQRS and lQRS Construction and QRS Peak Classification

For each lead, QRSp was assessed in consecutive 10-beat windows incremented by a single beat from the first to the last of the 100 pre-processed QRS complexes. We have previously demonstrated that a ten 10-beat window provides sufficient signal averaging to reduce noise, while a longer 100-beat window actually reduces QRS peak detection.[2] The smaller window is more sensitive to transient peaks that may be dependent on chest wall excursions and changing precordial lead QRS amplitude during cyclic respiration.

For each 10-beat window, normal and abnormal QRS peaks were classified by comparing two different filtered versions of the QRS complex: (a) a smoothed global QRS average (gQRS) and (b) a non-smoothed local QRS average (lQRS). The gQRS was generated by applying a 15-point bidirectional moving average filter to the ECG and then signal averaging all 100 filtered QRS complexes. This produces a smoothed QRS complex with low frequency contours that portrays the major components of the depolarizing wavefront. Thus, all local maxima and minima in the gQRS are considered to be normal QRS peaks. In contrast, the lQRS was generated by signal averaging 10 consecutive QRS complexes within the 10-beat window without applying the additional moving average filter that was used to construct the gQRS. Since the lQRS is not smoothed like the gQRS, it not only contains the major components of the depolarizing wavefront but also retains minor perturbations that may relate to more localized conduction abnormalities. Accordingly, the local maxima and minima in the lQRS include both normal and abnormal QRS peaks. As illustrated in Figure 1, for a 10-beat window, the peaks on the lQRS corresponding, within 10ms, to those on the gQRS were classified as normal, while those not corresponding to gQRS peaks were considered abnormal.

Data S2. SUPPLEMENTAL RESULTS

Relationship of QRSp to root mean squared ST segment (RMS-ST) noise

The mean RMS-ST noise level was 1.05±0.37μV for V1, 0.95±0.27μV for V2, 0.96±0.26μV for V3, 0.99±0.28μV for V4, 1.00±0.33μV for V5, and 1.01±0.34μV for V6. This was similar to the noise levels observed in our prior study of ischemic and dilated cardiomyopathy patients. [5] There was no correlation between the RMS-ST noise level and QRSp of each precordial lead (V1: r=0.09, p=0.32; V2: r=0.08, p=0.35; V3: r=0.07, p=0.41; V4: r=0.09, p=0.31; V5: r=-0.07, p=0.41; V6: r=0.08, p=0.38). Thus, noise did not significantly contribute to the low-amplitude QRSp signal.

Table S1. Temporal Variability and Reliability of QRSp (N=20)

QRSp Max1 (Baseline)	QRSp Max2 (Baseline+8h)	QRSp Max3 (Baseline+16h)	Average Difference*	Maximum Difference†	ANOVA p-value‡	CoV (%)	ICC (95% CI)
5.20±2.42	5.25±2.51	4.95±2.19	-0.17±0.41	0.65±0.65	0.16	10.4	0.95 (0.90-0.98)

CI – confidence interval; CoV – coefficient of variation; ICC – intraclass correlation coefficient

*Mean(QRSp Max2-QRSp Max1, QRSp Max3-QRSp Max1, QRSp Max3-QRSp Max2)

†Max(QRSp1,QRSp2,QRSp3) – Min(QRSp1,QRSp2,QRSp3)

‡Repeated measures ANOVA

Table S2. Clinical Demographics in patients with QRSp Max<4 vs. QRSp Max≥4

	All Patients (N=134)	QRSp Max<4 (N=46)	QRSp Max≥4 (N=88)	P
Age, yrs	52±13	53±15	52±12	0.760
Age <50yrs	52 (39)	16 (35)	36 (41)	0.490
Male, n (%)	91 (68)	27 (59)	64 (73)	0.099
LVEF, %	61±9	64±8	60±10	**0.025**
Max LV Thickness, mm	20±6	20±7	20±6	0.809
LA diameter, mm	44±6	42±7	45±6	**0.025**
Max LVOT gradient (Rest/Valsalva), mmHg	7.0 (2.0-17.0)	8.5 (2.0-23.0)	6.0 (2.0-12.2)	0.133
Co-morbidities				
Coronary Artery Disease, n (%)	3 (2)	1 (2)	2 (2)	1.000
History of AF, n (%)	35 (26)	11 (24)	24 (27)	0.674
Prior Co-interventions*				
Surgical Myectomy, n (%)	10 (8)	2 (4)	8 (9)	0.493
Alcohol Septal Ablation, n (%)	1 (1)	0 (0)	1 (1)	1.000
Medications				
Beta-blocker, n (%)	110 (82)	39 (85)	71 (81)	0.557
Class I anti-arrhythmic, n (%)	10 (8)	7 (15)	3 (3)	**0.032**
Class III anti-arrhythmic drugs, n (%)	17 (13)	1 (2)	16 (18)	**0.008**
Sotalol, n(%)	4 (3)	0 (0)	4 (5)	0.298
Amiodarone, n(%)	13 (10)	1 (2)	12 (14)	**0.035**
Calcium channel blockers, n (%)	23 (17)	7 (15)	16 (18)	0.666
ACE-I/ARB, n (%)	36 (27)	10 (22)	26 (30)	0.333
Diuretic, n (%)	25 (19)	9 (20)	16 (18)	0.845

ACE-I/ARB – angiotensin converting enzyme inhibitor / angiotensin II receptor blocker; AF – atrial fibrillation; LA – left atrial; LV – left ventricular; LVEF – left ventricular ejection fraction; LVOT – left ventricular outflow tract; VA – ventricular tachyarrhythmia

*Performed within prior 10 years

Table S3. HCM ACC/AHA Risk Factors and ESC Risk Score for SCD in patients with QRSp<4 vs. QRSp≥4

	All Patients (N=134)	QRSp Max<4 (N=46)	QRSp Max≥4 (N=88)	P
ACC/AHA Risk Factors, n (%)				
History of Syncope*	38 (28)	12 (26)	26 (30)	0.673
History of NSVT†	85 (63)	25 (54)	60 (68)	0.114
Family history of SCD‡	39 (29)	14 (30)	25 (28)	0.806
LV Wall Thickness ≥30mm	25 (19)	9 (20)	16 (18)	0.845
Abnormal BP response to exercise§||	24 (18)	9 (21)	15 (19)	0.774
LVEF <50%	13 (10)	3 (7)	10 (11)	0.541
LV Apical Aneurysm	9 (7)	0 (0)	9 (10)	**0.027**
# of ACC/AHA Risk Factors	1.7±0.8	1.6±0.7	1.8±0.9	0.077
>1 ACC/AHA Risk Factor, n (%)	79 (59)	22 (48)	57 (65)	0.058
ESC Risk Score, %	4.6±2.7	4.1±2.7	4.8±2.7	0.119
ESC Risk Score Category, n (%)				0.088
Low (<4% over 5yrs)	64 (48)	28 (61)	36 (41)	
Intermediate (4-6% over 5yrs)	44 (33)	11 (24)	33 (38)	
High (≥6% over 5yrs)	26 (19)	7 (15)	19 (22)	

ACC/AHA – American College of Cardiology/American Heart Association; BP – blood pressure; ESC – European Society of Cardiology; HCM – hypertrophic cardiomyopathy; LV – left ventricular; LVEF – left ventricular ejection fraction; NSVT – non-sustained ventricular tachycardia; SCD – sudden cardiac death; VA – ventricular arrythmia

* Loss of consciousness without a known causal factor in the previous 5 years

† ≥3 consecutive ventricular beats at a rate of ≥120 bpm lasting for <30 sec on ambulatory ECG

‡ SCD in ≥1 first degree relatives

§ Flat response (increase in systolic BP during whole exercise period of <25mmHg compared with resting systolic BP) **OR** hypotensive response (initial increase in systolic BP with a subsequent fall by peak exercise of >10mmHg from baseline or the peak BP value)

|| BP response to exercise was not assessed in 14 patients (N=120)

Table S4. ECG Characteristics in patients with QRSp Max<4 vs. QRSp Max≥4

	All Patients (N=134)	QRSp Max<4 (N=46)	QRSp Max≥4 (N=88)	P
Baseline heart rate, bpm	62±12	62±11	62±12	0.453
PR interval, ms*	183±41	169±33	191±43	**0.004**
QRSd, ms	107±27	93±16	114±29	**<0.001**
LBBB, n (%)	15 (11)	1 (2)	14 (16)	**0.019**
QTc interval, ms	447±33	441±32	451±33	0.098
fQRS, n (%)	82 (61)	24 (52)	58 (66)	0.121

LBBB – left bundle branch block; QRSd – QRS duration;
*PR interval could not be assessed in 7 patients with atrial arrhythmias (N=127)

Table S5. Cox Regression Analysis for Prediction of VA Events Including Age as a Continuous Variable in Multivariable Models (N=134)

	Univariable Analysis		Multivariable Model #3*		Multivariable Model #4†	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age (per 5yrs)	**0.86 (0.74-1.01)**	**0.068**	**0.96 (0.92-0.99)**	**0.019**	**0.96 (0.92-0.99)**	**0.020**
Age <50yrs	**2.45 (1.03-5.81)**	**0.042**	-	-	-	-
Male Sex	0.94 (0.38-2.33)	0.897	-	-	-	-
LVEF (per 5%)	**0.80 (0.65-0.99)**	**0.036**	0.87 (0.68-1.11)	0.254	0.86 (0.68-1.09)	0.208
History of Syncope	1.58 (0.66-3.82)	0.306	-	-	-	-
History of NSVT	1.15 (0.46-2.85)	0.764	-	-	-	-
Family history of SCD	0.60 (0.20-1.79)	0.361	-	-	-	-
Septal Thickness ≥30mm	0.71 (0.21-2.40)	0.578	-	-	-	-
Abnormal BP response to exercise‡	0.46 (0.11-2.00)	0.302	-	-	-	-
LVEF<50%	1.67 (0.49-5.67)	0.411	-	-	-	-
LV Apical Aneurysm	1.63 (0.38-7.02)	0.509	-	-	-	-
# of ACC/AHA Risk Factors	0.99 (0.58-1.70)	0.974	-	-	-	-
>1 ACC/AHA Risk Factor	1.17 (0.48-2.82)	0.728	1.09 (0.43-2.81)	0.853	-	-
ESC Risk Score	1.10 (0.95-1.26)	0.201	-	-	-	-
ESC Risk Score ≥4%	1.54 (0.64-3.71)	0.340	-	-	1.78 (0.70-4.52)	0.225
QRSd (per 10ms)	1.11 (0.98-1.27)	0.108	0.89 (0.70-1.13)	0.322	0.9 (0.71-1.13)	0.349
QTc Interval (per 10ms)	1.10 (0.98-1.23)	0.103	1.01 (0.88-1.17)	0.845	1.02 (0.89-1.19)	0.743
fQRS	1.31 (0.53-3.24)	0.565	-	-	-	-
QRSp Max	**1.27 (1.11-1.45)**	**0.001**	**1.42 (1.10-1.84)**	**0.008**	**1.42 (1.10-1.84)**	**0.007**

ACC/AHA – American College of Cardiology/American Heart Association; BP – blood pressure; CI – confidence interval; ESC – European Society of Cardiology; HCM – hypertrophic cardiomyopathy; HR – hazard ratio; LVEF – left ventricular ejection fraction; NSVT – non-sustained ventricular tachycardia; SCD – sudden cardiac death; VA – ventricular tachyarrhythmias

*Model #1: C-statistic = 0.76

†Model #2: C-statistic = 0.77

‡ Blood pressure response to exercise was not assessed in 17 patients (N=110)

Figure S1

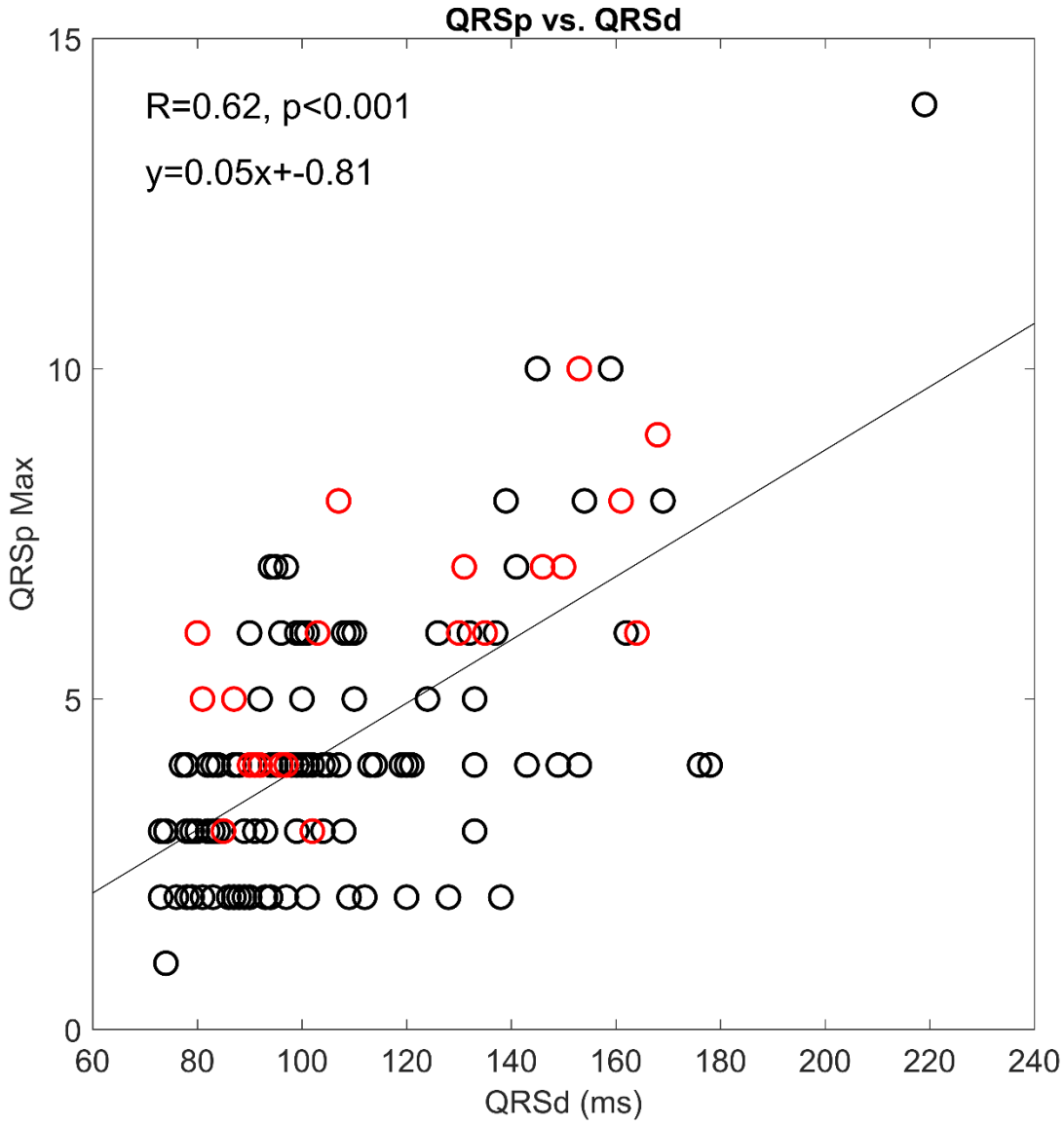

Figure S1: Correlation of QRSp and QRSd

Scatter plot illustrating a significant ($p<0.001$) but modest ($R=0.62$) linear correlation between the QRSp Max and QRSd for all 134 hypertrophic cardiomyopathy patients. The 21 patients who experienced arrhythmic events in follow-up are highlighted with red circles. QRSd – QRS duration.