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ORIGINAL RESEARCH

Microvolt QRS Alternans in Hypertrophic Cardiomyopathy: A Novel Risk Marker of Late Ventricular Arrhythmias

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BACKGROUND: Unlike T-wave alternans (TWA), the relation between QRS alternans (QRSA) and ventricular arrhythmia (VA) risk has not been evaluated in hypertrophic cardiomyopathy (HCM). We assessed microvolt QRSA/TWA in relation to HCM risk factors and late VA outcomes in HCM.

METHODS AND RESULTS: Prospectively enrolled patients with HCM (n=130) with prophylactic implantable cardioverter-defibrillators underwent digital 12-lead ECG recordings during ventricular pacing (100–120 beats/min). QRSA/TWA was quantified using the spectral method. Patients were categorized as QRSA+ and/or TWA+ if sustained alternans was present in ≥2 precordial leads. The VA end point was appropriate implantable cardioverter-defibrillator therapy over 5 years of follow-up. QRSA+ and TWA+ occurred together in 28% of patients and alone in 7% and 7% of patients, respectively. QRSA magnitude increased with pacing rate (1.9±0.6 versus 6.2±2.0 μV; *P*=0.006). Left ventricular thickness was greater in QRSA+ than in QRSA– patients (22±7 versus 20±6 mm; *P*=0.035). Over 5 years follow-up, 17% of patients had VA. The annual VA rate was greater in QRSA+ versus QRSA– patients (5.8% versus 2.0%; *P*=0.006), with the QRSA+/TWA– subgroup having the greatest rate (13.3% versus 2.6%; *P*<0.001). In those with <2 risk factors, QRSA– patients had a low annual VA rate compared QRSA+ patients (0.58% versus 7.1%; *P*=0.001). Separate Cox models revealed QRSA+ (hazard ratio [HR], 2.9 [95% CI, 1.2–7.0]; *P*=0.019) and QRSA+/TWA– (HR, 7.9 [95% CI, 2.9–21.7]; *P*<0.001) as the most significant VA predictors. TWA and HCM risk factors did not predict VA.

CONCLUSIONS: In HCM, microvolt QRSA is a novel, rate-dependent phenomenon that can exist without TWA and is associated with greater left ventricular thickness. QRSA increases VA risk 3-fold in all patients, whereas the absence of QRSA confers low VA risk in patients with <2 risk factors.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02560844.

Key Words: alternans ■ ECG ■ hypertrophic cardiomyopathy ■ risk assessment ■ ventricular arrhythmia

Hypertrophic cardiomyopathy (HCM) is one of the most common causes of sudden cardiac death (SCD) in the young, primarily attributed to ventricular arrhythmias (VAs).[1] The abnormal myocardial substrate predisposing to VA in HCM includes myocyte hypertrophy/disarray, interstitial/replacement fibrosis, and abnormal cell-to-cell coupling from gap junction remodeling.[1] Transient myocardial ischemia during high heart rates and dynamic left ventricular (LV) outflow tract obstruction can further increase the vulnerability to VA.[1] Given the diversity and dynamic nature of this VA substrate, accurate SCD risk stratification to inform prophylactic implantable cardioverter-defibrillator (ICD) therapy in patients with

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CLINICAL PERSPECTIVE

What Is New?

- Microvolt QRS alternans elicited with ventricular pacing is a novel, rate-dependent phenomenon in patients with hypertrophic cardiomyopathy, which is associated with greater left ventricular wall thickness, suggesting conduction alternans through abnormal myoarchitecture as a putative mechanism.
- In 130 patients with hypertrophic cardiomyopathy with American College of Cardiology/American Heart Association guideline-directed prophylactic implantable cardioverter-defibrillators, microvolt QRS alternans independently predicts future ventricular arrhythmias, whereas American College of Cardiology/American Heart Association and European Society of Cardiology risk factors as well as microvolt T-wave alternans do not.
- The presence of microvolt QRS alternans increases the future risk of ventricular arrhythmias 3-fold over 5 years, whereas the risk is low (annual event rate <1%) in the subgroup without QRS alternans and <2 American College of Cardiology/American Heart Association risk factors; microvolt QRS alternans can exist in the absence of T-wave alternans, and this subgroup has a high future risk of ventricular arrhythmias in the following 5 years.

What Are the Clinical Implications?

- Microvolt QRS alternans identifies patients at both high and low risks for arrhythmias in a moderate-sized hypertrophic cardiomyopathy cohort and may improve ventricular arrhythmia risk stratification.
- These findings require validation in a larger cohort of unselected patients at low risk for hypertrophic cardiomyopathy and may guide prophylactic implantable cardioverter-defibrillator therapy.

Nonstandard Abbreviations and Acronyms

ACC/AHA	American College of Cardiology/American Heart Association
bpm	beats per minute
ESC	European Society of Cardiology
HCM	hypertrophic cardiomyopathy
LGE	late gadolinium enhancement
QRSA	QRS alternans
SCD	sudden cardiac death
TWA	T-wave alternans
VA	ventricular arrhythmia
V_{alt}	alternans magnitude

HCM remains challenging, yet is essential to their care.

In the enhanced American College of Cardiology/American Heart Association (ACC/AHA) risk stratification schema for HCM, the presence of myocardial scar by cardiac magnetic resonance (CMR), LV dysfunction, and LV apical aneurysm increased sensitivity (>85%) but reduced specificity (<80%) in predicting SCD.[2] The presence of an abnormal myoarchitecture pattern by diffusion tensor CMR has also been shown to correlate with VA burden in HCM.[3] Although LV structural imaging appears to improve risk assessment, robust ECG metrics to evaluate the electrophysiological manifestations of abnormal myoarchitecture have yet to be identified, which may further refine prognostication.

In this regard, electrical alternans describes the beat-to-beat variation in cardiac action potential and its QRS-T wave manifestation on the surface ECG. Visible (ie, macrovolt) QRS alternans (QRSA) and/or T-wave alternans (TWA) can develop in the presence of structural barriers in the myocardium, leading to increased action potential duration heterogeneity and the genesis of VA.[4] Microvolt TWA is a risk marker for VA in patients with cardiomyopathy, coronary ischemia, and inherited arrhythmia syndromes,[5] but it has not consistently predicted VA in small HCM cohorts.[6–9] In contrast to TWA, the pathogenesis and prognostic utility of microvolt QRSA has not been evaluated in HCM. We previously demonstrated that microvolt QRSA in patients with ischemic and dilated cardiomyopathy was independently associated with a 4-fold increased risk of late VA.[10] The aim of present study was to characterize the relationship between microvolt QRSA and TWA in patients with HCM and to evaluate the association of electrical alternans with HCM risk factors and future VA events.

METHODS

The authors declare that all supporting data are available within the article and its online supplementary files.

Patient Population

Patients >18 years of age and diagnosed with HCM who were treated with a prophylactic transvenous ICD according to contemporary ACC/AHA practice guidelines[11] were prospectively enrolled between 2009 and 2016 at the University Health Network. All patients had at least 1 of the following ACC/AHA risk markers and enhanced risk markers for SCD[2,11] at the time of implant: family history of SCD in ≥1 first-degree relative presumably caused by HCM, LV wall thickness ≥30 mm, unexplained syncope within previous 5 years, nonsustained ventricular tachycardia ≥3 beats

at a rate of ≥120 beats/min (bpm) on Holter, abnormal blood pressure response to exercise, LV ejection fraction (LVEF) <50%, LV apical aneurysm, or 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 at the University Health Network, and all patients provided written informed consent.

Pacing Protocol and Alternans Analysis

Microvolt QRSA and TWA were evaluated during ICD-based ventricular pacing at consecutive rates of 100, 110, and 120 bpm for 3 minutes each. Throughout pacing, digital 12-lead ECGs were continuously recorded at a sampling rate of 1 kHz using a 12-lead Holter monitor (CardioMem CM 3000-12BT, Getemed Inc.) while the patients remained supine. The ECG recordings were downloaded for analyses of QRSA and TWA.

For each pacing rate, alternans was measured in the precordial ECG leads (V1–V6) using the spectral method[12] with custom software previously developed and validated by our group (Data S1).[10,13] Alternans was not evaluated in the limb leads because they are not independent of each other (ie, all derived from leads I and II) and are more susceptible to motion artifacts and spurious results.[14] For each lead, QRSA and TWA were quantified over a 128-beat segment that was incrementally shifted by 16 beats from the beginning to the end of the 3-minute recording. Bad (ectopic or noisy) beats were replaced with the segment's average even or odd beat as appropriate,[15] whereas segments with >10% bad beats were excluded from analysis. For each remaining segment, power spectra were computed for each sample point in the QRS and JT interval and summed to create an aggregate power spectrum for the QRS and T wave, respectively. The spectra were used to calculate the alternans mean noise, alternans magnitude (V_{alt}), and signal:noise ratio as previously described.[12]

A 128-beat segment was classified as alternans positive if ≥2 precordial leads had an alternans signal:noise ratio of ≥3. Segments that did not meet these criteria were classified as alternans negative. Positive segments with a significant frequency peak (ie, alternans signal:noise ratio ≥3) at 0.25 cycle/beat were considered respiratory confounders and excluded because of the potential generation of artifactual alternans by a harmonic frequency. Negative segments that had >3 leads with an alternans mean noise >1 SD over the mean alternans mean noise of all patients were excluded because of the potential masking of true alternans by noise. The alternans magnitude for a positive segment was defined as the maximum V_{alt} among the precordial leads with an alternans signal:noise ratio of ≥3, whereas those of the negative segments were set to zero.

Alternans Classification

Our QRSA/TWA classification scheme has been previously described[10] and is detailed in Data S1 and illustrated in Figure 1. A pacing rate was classified as alternans positive if there were ≥3 consecutive alternans positive segments and was assigned an alternans magnitude equal to the maximum magnitude among the nonexcluded segments for that rate. Rates with <3 viable segments were excluded from analysis. A patient was classified as QRSA positive (QRSA+) and/or TWA positive (TWA+) if any of their individual pacing rates were QRSA+ and/or TWA+, respectively, and assigned an alternans magnitude equal to the maximum magnitude among their nonexcluded pacing rates. Based on the presence or absence of QRSA and TWA across all pacing rates, patients were further categorized as being QRSA–/TWA–, QRSA+/TWA–, QRSA–/TWA+, or QRSA+/TWA+. For comparison with prior clinical studies assessing the relationship between TWA and VA,[10,16,17] patients were also classified as being TWA nonnegative as previously described (ie, TWA V_{alt} >1.9 μV at ≤110 bpm or an indeterminate test).

Clinical Demographics and SCD Risk Variables

To reflect the most current patient risk profile, clinical demographics were collected at the time of the alternans study rather than at ICD implant. SCD risk variables were similarly recorded at the time of the alternans study, aside from blood pressure response to exercise and nonsustained ventricular tachycardia on Holter, which were typically only assessed before ICD implant. Electrocardiographic parameters were assessed from the 12-lead Holter ECG during 5 minutes of intrinsic rhythm collected before the alternans study. 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 alternans 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, the LGE percentage was assessed from a clinical LGE CMR study performed within 1 year before the alternans study as previously described.[18] The European Society of Cardiology (ESC) quantitative risk score was calculated as described by O'Mahony et al[19] to predict SCD event rates over 5 years starting from the time of the alternans study. The 5-year risk scores were categorized into the following 3 predefined subsets for ICD recommendation: low (<4%;

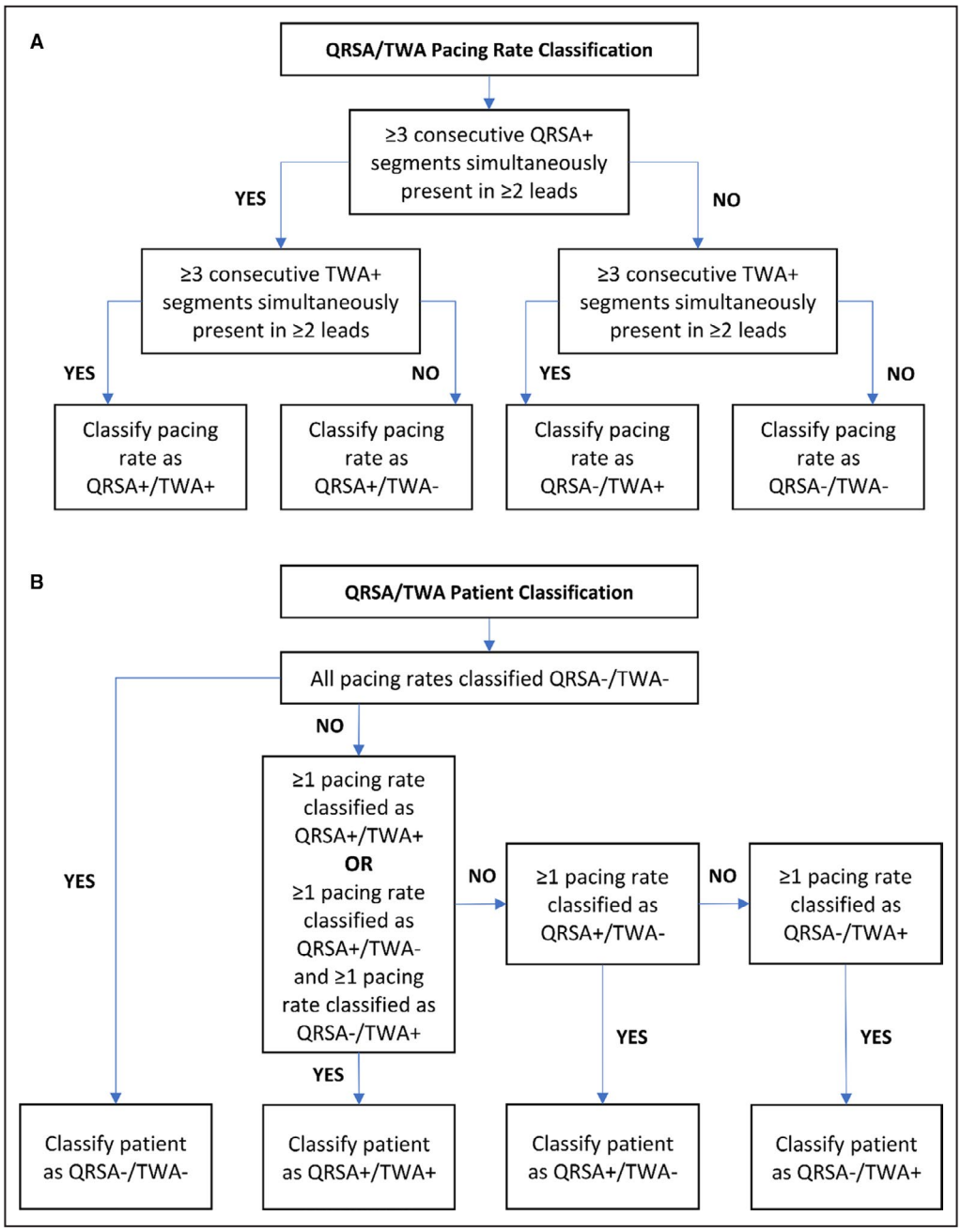

Figure 1. QRSA/TWA classification flowchart.
Flowcharts illustrating QRSA/TWA classification schemes used to classify (**A**) each pacing rate and (**B**) patients as QRSA–/TWA–, QRSA+/TWA–, QRSA–/TWA+, or QRSA+/TWA+. QRSA indicates QRS alternans; and TWA, T-wave alternans.

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 when possible 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. 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 alternans assessment in the ICD clinic every 6 months for 5 years to evaluate the primary clinical outcome of VA, defined as appropriate ICD therapy, either shock or antitachycardia pacing. Patients with <12 months follow-up who

did not reach the primary outcome were excluded from analysis.

Statistical Analysis

Continuous variables are presented as mean±SD or median and interquartile range (IQR; 25th–75th percentiles) where appropriate. The Student *t* test or Mann–Whitney *U* test was used for unpaired comparison 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. To control for excluded pacing studies and within-subject effects, linear mixed and logistic regression models with repeated measures were used to compare differences among the 3 pacing rates for continuous and categorical alternans metrics, respectively.

VA-free survival was determined for the alternans groups using Kaplan–Meier analysis and compared with the log-rank test. Univariable and multivariable Cox regression analyses were used to further assess the predictive value of QRSA, TWA, and other candidate covariates. Regression results are presented as the hazard ratio (HR) and 95% CI. The multivariable models included covariates with a univariable significance level of $P<0.1$. 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. 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.

RESULTS

Patient Population

A total of 130 patients were enrolled and all participated in the alternans pacing study, but 3 were excluded because of excessive ectopic or fused beats at all rates that made alternans assessment unreliable. The final study cohort of 127 patients was predominantly men (69%) with a mean age of 53±14 years. Their baseline clinical characteristics are presented in Table 1.

HCM ACC/AHA risk factors and ESC risk score components for SCD are presented in Table 2. Because LGE CMR data were only available in 78 (61%) patients, LGE CMR >15% of LV mass was excluded as a risk factor in subsequent analysis. After excluding LGE CMR >15% of LV, the mean number of risk factors was 1.7±0.8, with 59% of patients having >1 risk factor. The mean ESC risk score was 4.4±2.5%, with 50%, 32%, and 17% of patients being classified as low, intermediate, and high risk, respectively.

Microvolt QRSA and TWA

Mean alternans noise was relatively small (median alternans mean noise <5 μV) for all precordial leads as shown in Table S1. Among the 127 patients, there were 12 (9%), 8 (6%), and 11 (9%) pacing rates excluded at 100, 110, and 120 bpm, respectively. Of these 31 excluded pacing rates, 15 were because of excessive ectopy, 4 were because of excessive alternans noise, and 12 were because of the patient's inability to tolerate the pacing rate for 3 minutes. QRSA was detected in 35% of patients with a median alternans magnitude of 14.2 μV (IQR, 9.0–25.7 μV) among a median of 28% (IQR, 13%–50%) positive segments per pacing rate. TWA was detected in 35% of patients with a median alternans magnitude of 8.7 μV (IQR, 5.9–15.4 μV) among a median of 33% (IQR, 19–53%) positive segments per pacing rate. The relationship between pacing rate and alternans is presented in Table 3. The proportion of QRSA+ pacing studies, percentage of QRSA+ segments, and QRSA magnitude all increased with rate. The percentage of TWA+ segments and TWA magnitude increased with rate, and there was a trend toward an increase in the proportion of TWA+ pacing studies.

Interaction of QRSA and TWA

The proportion of patients classified as QRSA–/TWA–, QRSA+/TWA–, QRSA–/TWA+, and QRSA+/TWA+ was 58%, 7%, 7%, and 28%, respectively. Among the QRSA+/TWA+ patients, only 1 exhibited QRSA+/TWA– and QRSA–/TWA+ at different rates without being QRSA+/TWA+ at any rate. When comparing pacing at 100 to 120 bpm, the proportion of QRSA–/TWA– patients decreased (80% versus 67%; $P=0.005$) and the proportion of QRSA+/TWA+ patients increased (8% versus 23%; $P=0.004$), whereas there was no change in the proportions of QRSA+/TWA– (2% versus 5%; $P=0.125$) or QRSA–/TWA+ (10% versus 5%; $P=0.227$) patients.

Because large-magnitude action potential alternans are associated with both QRSA and larger magnitude TWA,[20] we evaluated QRSA and TWA magnitudes when they occurred in isolation (ie, QRSA+/TWA– and QRSA–/TWA+) and simultaneously (ie, QRSA+/TWA+). Compared with the QRSA+/TWA+ patients, the median QRSA magnitudes were similar in the QRSA+/TWA– patients (QRSA magnitude, 12.9 μV [IQR, 9.3–20.6 μV] versus 12.0 μV [IQR, 5.1–18.1 μV]; $P=0.311$), whereas the median TWA magnitudes were significantly less in the QRSA–/TWA+ patients (TWA magnitude, 9.5 μV [IQR, 6.5–15.0 μV] versus 5.2 μV [IQR, 3.1–9.9 μV]; $P=0.002$).

Figure 2 and Figures S1, S2 illustrate QRSA and TWA during low and high pacing rates for 3 different patients who were classified as QRSA+/TWA–, QRSA–/TWA+,

Table 1. Clinical Demographics in Patients Who Were VA– and VA+

	All patients (N=127)	VA– (n=106)	VA+ (n=21)	*P* value
Age, y	53±14	54±13	50±17	0.195
Male sex	87 (69)	70 (67)	17 (77)	0.407
LVEF, %	60±10	61±9	56±13	0.046
Comorbidities				
Coronary artery disease	3 (2)	3 (3)	0 (0)	1.000
Prior revascularization	2 (2)	2 (2)	0 (0)	1.000
Hypertension	40 (32)	35 (33)	4 (19)	0.205
Diabetes	13 (10)	11 (10)	2 (10)	1.000
Renal dysfunction†	1 (1)	1 (1)	0 (0)	1.000
History of AF	39 (31)	31 (29)	8 (38)	0.422
Prior cointerventions				
Surgical myectomy	18 (14)	13 (12)	5 (24)	0.178
Alcohol septal ablation	2 (2)	1 (1)	1 (5)	0.304
Medications				
β-blocker	102 (80)	88 (83)	14 (67)	0.129
Class I antiarrhythmic	9 (7)	9 (9)	0 (0)	0.354
Class III antiarrhythmic	18 (14)	15 (14)	3 (14)	1.000
Calcium channel blockers	23 (18)	18 (17)	5 (24)	0.535
ACEI/ARB	32 (25)	26 (25)	6 (29)	0.697
Diuretic	23 (18)	19 (18)	4 (19)	1.000
ECG parameters				
Resting heart rate, bpm	59±10	58±10	61±9	0.175
PR interval, ms‡	184±42	183±40	192±50	0.373
QRSd, ms	114±28	113±28	119±31	0.402
QRSd ≥120 ms	42 (33)	33 (31)	9 (43)	0.297
QTc interval, ms	450±33	449±33	456±30	0.383

Data are provided as mean±SD or number (percentage). ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; AF, atrial fibrillation; bpm, beats per minute; LVEF, left ventricular ejection fraction; QRSd, QRS duration; and VA, ventricular arrhythmia.

†Estimated glomerular filtration rate <61 mL/min per 1.73 m^2.

‡PR interval could not be assessed in 11 patients with atrial arrhythmias (N=116).

and QRSA+/TWA+, respectively. QRSA magnitudes increase with a higher pacing rate in the QRSA+/TWA– and QRSA+/TWA+ patients, and TWA magnitudes increase with a higher pacing rate in the QRSA–/TWA+ and QRSA+/TWA+ patients. The magnitude of TWA in the patient who is QRSA+/TWA+ is greater than that of the patient who is QRSA–/TWA+, whereas the magnitude of the QRSA in the QRSA+/TWA– and QRSA+/TWA+ patients remain similar.

Relationship of QRSA and TWA to Ventricular Tachyarrhythmias

Following the alternans assessment, patients were followed prospectively for a median of 60 months (IQR, 60–60 months), and 21 (17%) experienced the primary clinical outcome of VA after a median of 28 months (IQR, 19–42 months). Among the 127 patients, 2 (2%) had heart transplants, 2 (2%) had their ICD explanted, 1 (1%) was lost to follow-up, and 1 (1%) had a nonarrhythmic death before completing the 5-year follow-up. In addition, there were 10 patients who were unable to attend their final follow-up appointment at 5 years because of scheduling delays arising from the COVID-19 pandemic. Among the 21 patients who experienced a VA event during prospective follow-up after their alternans study, 15 patients had monomorphic ventricular tachycardia (mean heart rate, 201±29 bpm), and 6 had polymorphic ventricular tachycardia or ventricular fibrillation (mean heart rate, 286±71 bpm). The VA events were successfully treated via ICD shock and antitachycardia pacing in 8 and 13 patients, respectively. Baseline clinical characteristics and SCD risk factors are compared between patients who were VA positive (VA+) and VA negative (VA–) in Tables 1 and 2, respectively. Patients who were VA+ had lower LVEF (56±13% versus 61±9%; *P*=0.046) and a trend toward a greater

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

	All patients (N=127)	VA– (n=106)	VA+ (n=21)	*P* value
ACC/AHA risk factors				
History of syncope*	34 (27)	26 (25)	8 (38)	0.200
History of NSVT†	79 (62)	65 (61)	14 (67)	0.644
Family history of SCD‡	33 (26)	29 (27)	4 (19)	0.428
LV wall thickness ≥30 mm	25 (20)	22 (21)	3 (14)	0.764
Abnormal BP response to exercise§,‖	25 (23)	21 (23)	4 (21)	1.000
LVEF <50%	14 (11)	11 (11)	3 (14)	0.702
LV apical aneurysm	9 (7)	8 (8)	1 (5)	1.000
Number of risk factors	1.7±0.8	1.7±0.8	1.8±0.8	0.816
>1 risk factor	75 (59)	61 (58)	14 (67)	0.437
ESC risk score components¶				
Age, y	53±14	54±13	51±17	0.399
Max LV thickness, mm	21±6	21±6	20±6	0.807
Left atrial diameter, mm	44±7	44±7	45±7	0.548
Max LVOT gradient, rest or valsalva, mm Hg	6 (2–14)	7 (2–17)	6 (3–9)	0.576
ESC risk score, %	4.4±2.5	4.2±2.3	5.2±3.1	0.085
ESC risk score category				0.434
Low, <4% for 5 y	64 (50)	56 (53)	9 (38)	
Intermediate, 4% to 6% for 5 y	41 (32)	32 (31)	9 (42)	
High, ≥6% for 5 y	22 (17)	18 (17)	4 (19)	

Data are provided as mean±SD, median (interquartile range), or number (percentage). ACC/AHA indicates 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; LVOT, left ventricular outflow tract; 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 beats per minute 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 17 patients (n=110).

¶History of syncope, NSVT, and family SCD detailed previously.

ESC risk score (5.2±3.1 versus 4.2±2.3; *P*=0.085). No other differences were observed.

Table 4 compares QRSA and TWA characteristics between patients who were VA+ and VA–. Although there was no difference in TWA characteristics between the VA groups, the proportions of patients with QRSA (62% versus 30%; *P*=0.006) and the QRSA magnitudes (4.1 μV [IQR, 0.0–14.7 μV] versus 0.0 μV [IQR, 0.0–7.5 μV]; *P*=0.011) were greater in the patients who were VA+. When considering the individual QRSA/TWA categories, there was a greater proportion of patients with isolated QRSA (QRSA+/TWA–, 29% versus 3%; *P*=0.001) in the VA+ group. However, there was no difference in the proportion of patients with no alternans (QRSA–/TWA–), isolated TWA (QRSA–/TWA+), or simultaneous QRSA and TWA (QRSA+/TWA+). No difference was observed in QRSA or TWA noise between patients who were VA+ and VA– (Table S1).

Survival Analysis

Kaplan–Meier event-free survival curves for QRSA, TWA, and between the 4 QRSA/TWA patient categories are presented in Figure 3. After 5 years of follow-up, QRSA– patients had greater freedom from VA compared with QRSA+ patients (annual event rate, 2.0% versus 5.8%; *P*=0.006), whereas VA outcome was similar between TWA– versus TWA+ patients (3.5% versus 3.2%; *P*=0.774) and TWA <1.9 μV versus TWA ≥1.9 μV patients (3.8% versus 2.4%; *P*=0.327). Among the QRSA/TWA categories, patients who were QRSA–/TWA– (*P*<0.001), QRSA–/TWA+ (*P*=0.004), and QRSA+/TWA+ (*P*=0.001) each had greater freedom from VA than QRSA+/TWA– patients (annual event rates of 2.3%, 0.0%, 3.9%, and 13.3%, respectively). There was no difference in survival outcomes between any of the other categories.

To evaluate if QRSA was similarly predictive of VA in a traditionally lower risk group, Kaplan–Meier analysis was also performed in the subgroup with <2 ACC/AHA SCD risk factors (n=52).[11] As shown in Figure 3D, among those with <2 risk factors, QRSA– patients had greater freedom from VA compared with QRSA+ patients (annual event rate, 0.58% versus 7.1%; *P*=0.001). On the other hand, VA outcomes were similar between TWA– versus TWA+ patients (annual event rate, 2.5% versus 3.2%; *P*=0.750) and TWA <1.9 μV versus TWA ≥1.9 μV patients (annual event rate, 2.3% versus 3.7%; *P*=0.487).

The ACC/AHA risk factors, ESC risk score variables, and alternans metrics were evaluated with Cox regression analyses (Table 5). Univariable predictors of VA (*P*<0.1) included LVEF (per 5%: HR, 0.83 [95% CI, 0.70–1.00]; *P*=0.044), ESC risk score (HR, 1.13 [95% CI, 0.65–1.30]; *P*=0.091), QRSA+ (HR, 3.19 [95% CI, 1.32–7.69]; *P*=0.010), and QRSA+/TWA– (HR, 8.09 [95% CI, 3.12–21.00]; *P*<0.001). QRSA+ and QRSA+/TWA– were evaluated in 2 separate multivariable models adjusted for LVEF and ESC risk score. In the first model, QRSA+ (HR, 2.89 [95% CI, 1.19–7.04]; *P*=0.019) and LVEF (per 5%: HR, 0.82 [95% CI, 0.68–0.99]; *P*=0.037) were found to be the only independent predictors of VA (C-statistic, 0.71). In the second model, QRSA+/TWA– (HR, 7.91 [95% CI, 2.89–21.67]; *P*<0.001) and LVEF (per 5%: HR, 0.78 [95% CI, 0.64–0.95]; *P*=0.013) were the only independent predictors of VA (C-statistic, 0.72). Multicollinearity was not observed (variance

Table 3. QRSA/TWA Rate Relationship (N=127)

	100 bpm (n=115)	110 bpm (n=119)	120 bpm (n=116)	*P* value
QRSA				
Positive studies, n (%)	12 (10)	27 (23)	32 (28)	<0.001*
Positive segments, %	6±2	13±3	17±3	<0.004†
Alternans magnitude, μV	1.9±0.6	4.3±1.0	6.2±2.0	0.006†
TWA				
Positive studies, n (%)	20 (17)	26 (22)	32 (28)	0.077*
Positive segments, %	10±2	14±3	20±3	0.020†
Alternans magnitude, μV	1.3±0.3	2.8±0.7	3.0±0.7	0.014†

Continuous data are presented as mean±SE. bpm indicates beats per minute; QRSA, QRS alternans; and TWA, T-wave alternans.
*Statistical significance assessed using repeated-measures logistic regression.
†Statistical significance assessed using linear mixed model with repeated measures.

inflation factor <3) between any of the variables included in the multivariable models.

Characteristics of Patients With and Without QRSA

Baseline clinical characteristic and SCD risk variables of QRSA– and QRSA+ patients are presented in Tables S2 and S3, respectively. A greater proportion of QRSA+ patients than QRSA– patients were men (80% versus 62%; *P*=0.039). Maximal LV wall thickness was greater in QRSA+ versus QRSA– patients (22±7 versus 20±6 mm; *P*=0.035), and there was a trend toward a greater proportion of QRSA+ patients having an LV wall thickness ≥30 mm (29% versus 15%; *P*=0.053). Similar results were observed in TWA+ versus TWA– patients with respect to maximal LV wall thickness (22±7 versus 20±6 mm; *P*=0.020) and LV wall thickness ≥30 mm (29% versus 15%; *P*=0.053). No other differences were observed in baseline clinical characteristics or SCD risk variables between QRSA+ and QRSA– patients.

DISCUSSION

In this prospective study of patients with HCM with prophylactic ICDs, electrical alternans and its prognostic utility were comprehensively evaluated during ventricular pacing at 100 to 120 bpm. The main study findings are as follows: (1) microvolt QRSA and TWA were rate dependent and prevalent in one-third of patients, (2) QRSA existed without TWA in 7% of patients, and (3) QRSA and TWA were associated with greater LV wall thickness. Furthermore, the presence of QRSA was associated with an independent 3-fold increased risk of VA events during 5-year follow-up in all patients, whereas in the subgroup without TWA, the VA risk was 8-fold higher. Among patients deemed lower risk with <2 SCD risk factors,[11] the absence of QRSA identified a low-risk group with a VA annual event rate of only 0.58%. In contrast, TWA, the ESC risk score,[19,20] and the AHA/ACC risk factors[2,11] were not prognostic in multivariable modeling with QRSA.

Prevalence and Pathogenesis of Electrical Alternans in HCM

In small HCM cohorts, microvolt TWA has been evaluated using the spectral method during exercise testing, and the reported prevalence is 25% to 50%, although not all patients had ICDs and so were lower risk.[6–9] One-third of our patients demonstrated TWA during ventricular pacing at comparable rates to exercise testing targets, but our definition of TWA mandated a less-stringent V_{alt} >0 μV instead of the traditional V_{alt} >1.9 μV.[12,14] In contrast to TWA, microvolt QRSA has not been previously described in HCM, and its prevalence in one-third of our patients, based on a V_{alt} >0 μV, is a novel finding.

In myopathic hearts, action potential alternans arises from intracellular calcium alternans, which is mediated by abnormal intracellular calcium cycling at fast heart rates.[21,22] In these studies, TWA develops at lower heart rates than QRSA, but at higher heart rates, the 2 coexist because the magnitude of action potential alternans increases sufficiently to include phase 0 depolarization.[23] For HCM, the pathogenesis of electrical alternans has not been well defined, but TWA magnitude appears to correlate with the extent of myocyte disarray and interstitial fibrosis on histology[7,24] as well as CMR LGE.[25] Our patients with TWA were also found to have greater LV wall thickness compared with those without TWA, which is consistent with Puntmann et al.[8] Although abnormal intracellular calcium cycling may cause TWA with or without QRSA in HCM, this does not explain why 7% of our patients had isolated QRSA. An alternative mechanism may invoke myocardial conduction alternans, whereby propagation into the abnormal myoarchitecture alternates between 2 distinct conducting pathways leading to beat-to-beat alterations in ventricular activation.[26] The presence of multiple conducting pathways in high-risk patients with

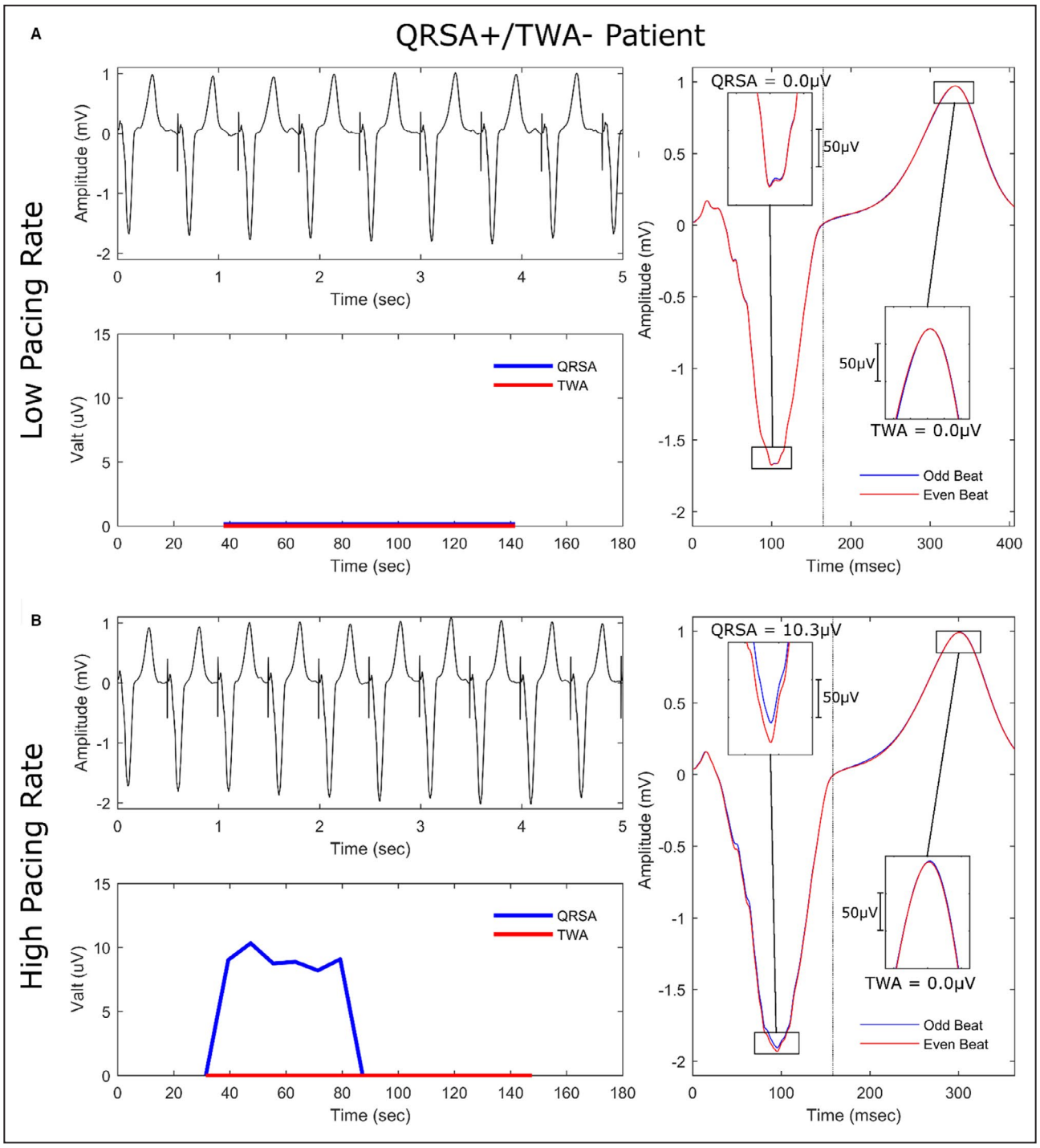

Figure 2. QRSA and TWA at low and high pacing rates in a patient with QRSA+/TWA–.
Illustration of microvolt QRSA and TWA in a patient with QRSA+/TWA– during (**A**) low and (**B**) high pacing rates. Upper left panel illustrates a representative 5-second ECG from lead V5 during the 3-minute ventricular pacing study. Lower left panel illustrates QRSA (blue) and TWA (red) magnitudes for each 128-beat segment in the 3-minute pacing study. Right panel illustrates superimposed mean odd (blue) and even (red) beats from a representative 128-beat segment to highlight the low-magnitude scale of alternans on the ECG. QRSA magnitudes increase from the low to high rate, whereas TWA is not present at either rate. QRSA indicates QRS alternans; and TWA, T-wave alternans.

HCM is supported by studies where programmed ventricular stimulation provoked fractionation in local ventricular electrograms.[27] In a computational model of patchy fibrosis activated at high rates, conduction heterogeneity was evident that caused large fluctuations in diastolic interval, alternating conduction block, and

Table 4. Alternans and Arrhythmic Outcomes

	All patients (N=127)	VA– (n=106)	VA+ (n=21)	*P* value
QRSA metrics				
QRSA+ study	45 (35)	32 (30)	13 (62)	0.006
QRSA+ segments, %	0 (0–14)	0 (0–14)	7 (0–13)	0.078
QRSA magnitude, μV	0.0 (0.0–10.2)	0.0 (0.0–7.5)	4.1 (0.0–14.7)	0.011
TWA metrics				
TWA+ study	45 (35)	38 (36)	7 (32)	0.826
TWA ≥1.9 μV study	35 (28)	31 (29)	4 (19)	0.339
TWA+ segments, %	0 (0–21)	0 (0–21)	0 (0–13)	0.873
TWA magnitude, μV	0.0 (0.0–6.1)	0.0 (0.0–6.1)	0.0 (0.0–9.9)	0.891
QRSA/TWA classification				<0.001†
QRSA–/TWA–	73 (58)	65 (61)	8 (38)	0.049
QRSA+/TWA–	9 (7)	3 (3)	6 (29)	0.001‡
QRSA–/TWA+	9 (7)	9 (9)	0 (0)	0.354
QRSA+/TWA+	36 (28)	29 (27)	7 (33)	0.579

Data are provided as median (interquartile range) or number (percentage). QRSA indicates QRS alternans; TWA, T-wave alternans; and VA, ventricular tachyarrhythmia.

†χ^2 test.

‡Individual category statistical significance at Bonferroni corrected $P<0.0125$.

action potential alternans.[28] The severity of fibrosis in HCM has been shown to correlate with the magnitude of ventricular hypertrophy,[3,29] and this may explain why our patients with QRSA had greater LV wall thickness than those without QRSA.

A hallmark of TWA is rate dependency, whereby magnitude and prevalence increase with higher heart rates, and this was also evident in our patients. The presence of QRSA rate dependency is a novel finding in HCM and was not apparent in patients with ischemic or nonischemic cardiomyopathy using comparable ventricular pacing rates of 100 to 120 bpm by our group.[10] This distinction may be the result of greater regional conduction heterogeneity in the abnormal myoarchitecture of HCM, whereas other cardiomyopathy subtypes exhibit more global conduction delays as evidenced by a higher prevalence of QRS prolongation and bundle branch block.[30] Furthermore, the HCM substrate may be prone to ischemia at faster rates as a result of increased wall stiffness and intramural, small vessel disease,[29] which may accentuate preexisting conduction heterogeneity by reducing cell-to-cell coupling. These features may explain why QRSA magnitude was larger and independent of TWA in HCM compared with ischemic and nonischemic cardiomyopathy.[10]

Arrhythmogenicity of Electrical Alternans in HCM

In myopathic hearts, action potential alternans can increase repolarization gradients sufficiently to induce unidirectional conduction block and reentrant VA.[4] Ambulatory ECG monitoring has demonstrated surges in TWA magnitude before VA events in patients with ischemic and nonischemic cardiomyopathy.[31] Despite this, TWA has not been shown to predict VA in large prospective, cardiomyopathy cohorts.[16,17] In HCM, the prevalence and magnitude of TWA are greater in high versus low-risk patients.[6,7,25] However, there are conflicting reports regarding the prognostic utility of TWA for future VA events.[8,9] In our larger, high-risk HCM cohort, TWA did not predict VA over a 5-year follow-up period using either the traditional TWA definition of V_{alt} >1.9 μV or V_{alt} >0. In contrast, QRSA was strongly predictive of VA, especially in the absence of TWA. This is a finding not previously described in HCM but recently reported by our group in patients with ischemic and nonischemic cardiomyopathy.[10] A plausible explanation for the arrhythmogenic potential of QRSA is that it is a marker of localized conduction heterogeneity in multiple cardiomyopathy subtypes. Typically, large activating wavefronts that change direction will cause secondary repolarization changes.[32] In the case of isolated QRSA, there may be a critical mass of myocardium with multiple conducting pathways that is large enough to manifest QRSA but still small enough to conceal secondary repolarization alternans.[33] Alternating conducting pathways may be anatomic or functional. The latter may arise from rate-dependent conduction block (ie, conduction velocity restitution) and/or repolarization heterogeneity (ie, conduction block from tissue refractoriness).[28] Localized conduction and repolarization

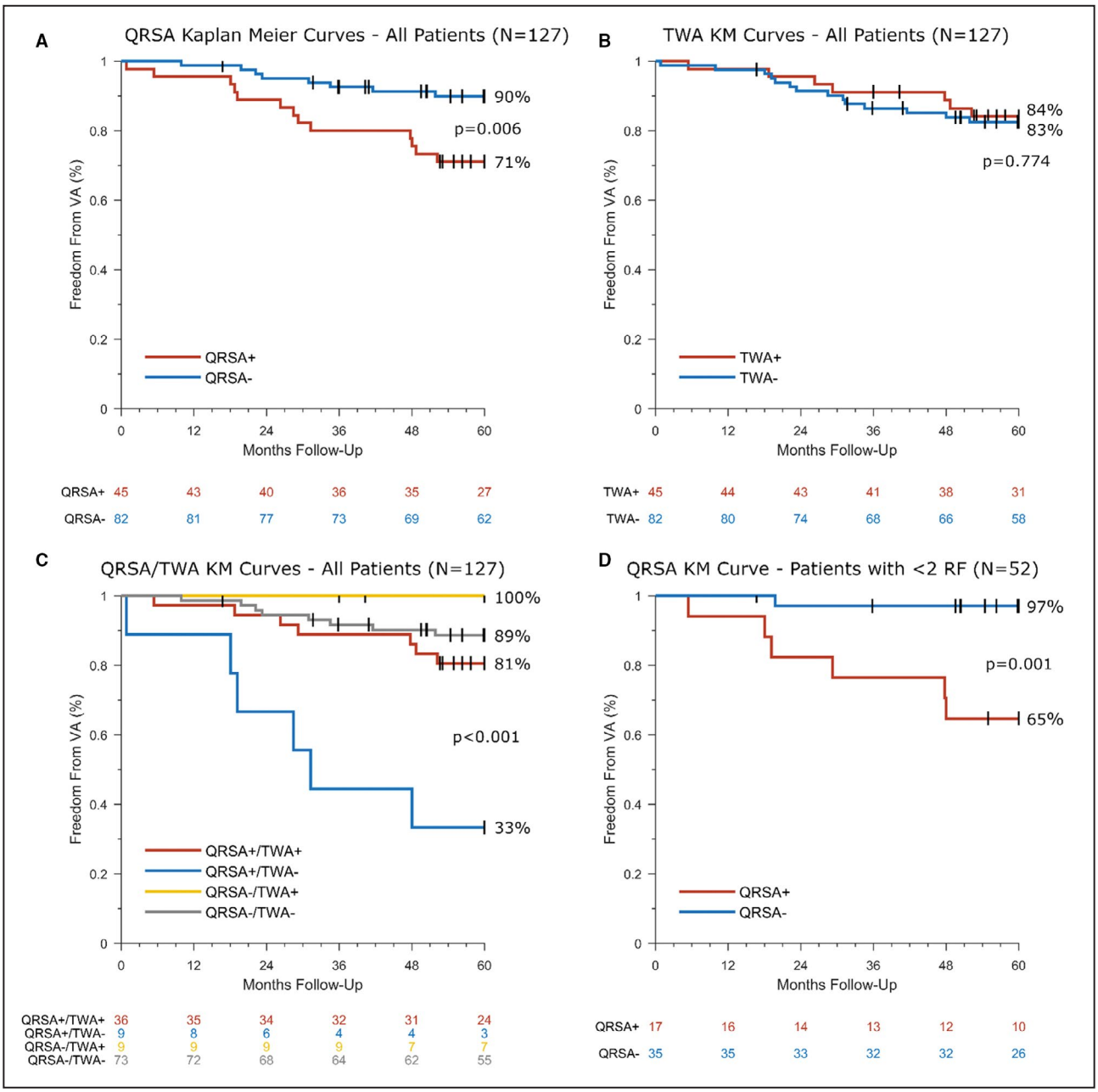

Figure 3. KM survival curves for VA events.
KM survival curves for VA events in all patients (N=127) stratified by (**A**) QRSA, (**B**) TWA, and (**C**) the combined QRSA/TWA classification. **D**, KM survival curves for VA events in the subgroup with <2 SCD risk factors (n=52) stratified by QRSA. KM indicates Kaplan–Meier; QRSA, QRS alternans; SCD, sudden cardiac death; TWA, T-wave alternans; and VA, ventricular arrhythmia.

heterogeneity can provide the milieu for reentrant VA in postinfarct animal models,[34] and this may also be relevant in HCM.

Clinical Implications

Accurate risk stratification and appropriate use of prophylactic ICD therapy remains the most challenging and relevant issue in the management of HCM because the population-wise risk of SCD is low (<1% per year), whereas the complication rate from ICDs is high in the long term (4%–10% per year).[2,11,20] In our high-risk HCM cohort with at least 1 AHA/ACC risk factor, QRSA with or without TWA was associated with a 3-fold increased risk of VA, resulting in an annual event rate of 5.8%. However, in the subgroup with <2 risk factors, the VA annual event rate among those without QRSA was only 0.58%. In contrast, the ESC risk score and AHA/ACC risk markers were not predictive in multivariable modeling that included QRSA. These findings suggest that the presence of QRSA may identify

Table 5. Cox Regression Analysis for Prediction of VA Events (N=127)

	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	0.88 (0.76–1.03)	0.111				
Male sex	0.65 (0.24–1.77)	0.401				
LVEF, per 5%	0.83 (0.70–1.00)	0.044	0.82 (0.68–0.99)	0.037	0.78 (0.64–0.95)	0.013
History of syncope	1.70 (0.70–4.09)	0.240				
History of NSVT	1.18 (0.48–2.92)	0.724				
Family history of SCD	0.67 (0.23–1.99)	0.470				
Septal thickness ≥30 mm	0.68 (0.20–2.30)	0.530				
Abnormal BP response to exercise§	0.93 (0.31–2.83)	0.899				
LVEF <50%	1.41 (0.41–4.79)	0.583				
Apical aneurysm	0.71 (0.09–5.29)	0.737				
>1 risk factor	1.21 (0.51–2.89)	0.665				
No. of risk factors	1.06 (0.62–1.81)	0.842				
Max LV thickness, per 5 mm	0.99 (0.71–1.40)	0.972				
Left atrial diameter, per 5 mm	1.09 (0.79–1.49)	0.610				
Max LVOT gradient, per 5 mm Hg	0.90 (0.75–1.09)	0.296				
ESC risk score	1.13 (0.98–1.30)	0.091	1.14 (0.99–1.32)	0.072	1.10 (0.97–1.26)	0.138
ESC risk score ≥6%	1.15 (0.39–3.41)	0.804				
QRSA+	3.19 (1.32–7.69)	0.010	2.89 (1.19–7.04)	0.019		
TWA+	0.88 (0.35–2.17)	0.774				
QRSA+/TWA–	8.09 (3.12–21.00)	<0.001			7.91 (2.89–21.67)	<0.001

BP indicates blood pressure; ESC, European Society of Cardiology; HCM, hypertrophic cardiomyopathy; HR, hazard ratio; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NSVT, nonsustained ventricular tachycardia; QRSA, QRS alternans; SCD, sudden cardiac death; TWA, T-wave alternans; and VA, ventricular tachyarrhythmia.

*Model 1: C-statistic, 0.71.

†Model 2: C-statistic, 0.72.

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

a very high-risk subgroup, whereas the absence of QRSA in patients with <2 AHA/ACC risk factors may select a low-risk population. The prognostic utility of QRSA with or without TWA requires further validation in a larger, unselected cohort of lower risk patients with HCM without ICDs to refine the use of prophylactic ICD therapy.

Limitations

Several limitations should be acknowledged. First, electrical alternans was evaluated during ventricular pacing and not during traditional exercise stress testing or atrial pacing, which both engage the cardiac conduction system. Ventricular pacing improved detection of microvolt-level alternans by reducing noise and motion artifact. Atrial pacing was attempted in earlier studies, but was limited because of single-chamber ICDs in 35% of patients and AV nodal Wenckebach in another 14% of patients. Notwithstanding this, a high concordance between TWA induced with ventricular versus atrial pacing has been reported.[35] In our study, among the 66 patients who had atrial and ventricular pacing performed, there was no difference in QRSA or TWA metrics between the 2 pacing modes at 100, 110, and 120 bpm, including their response to increasing rate (Table S4). We also observed no difference in the proportion of QRSA+ patients, TWA+ patients, or the QRSA/TWA patient-level classifications between atrial and ventricular pacing (Table S5). Second, β-blockers were not held before alternans assessment to avoid arrhythmias during β-blocker withdrawal. Although this may attenuate TWA,[36] the effect would be similar between patients who were VA+ and VA– because their β-blocker usage was no different. Third, CMR LGE was not included in the multivariable modeling to assess VA risk because 39% of patients had not undergone CMR assessment of LGE. Extensive LGE is a strong predictor of VA events,[18] and future studies are warranted to determine whether QRSA improves risk stratification in patients with or without extensive LGE. However, among our 78 patients with CMR LGE assessments, there was no difference in QRSA or TWA metrics between the patients with or without extensive LGE (≥15% of LV mass) as shown in Table S6. Finally, our HCM cohort was modest in size and considered high risk with indications for prophylactic ICD therapy

based on the AHA/ACC enhanced risk stratification strategy. The subgroup with isolated QRSA was also small, and the association with an 8-fold increased VA risk is preliminary but warrants further validation.

CONCLUSIONS

In patients with HCM with prophylactic ICDs, microvolt QRSA is a novel phenomenon with a prevalence of 35%. QRSA is dependent on heart rate and LV wall thickness and can exist without TWA in 7% of patients, suggesting conduction alternans through abnormal myoarchitecture as a putative mechanism. The presence of QRSA is associated with a 3-fold increased risk of VA events for 5 years, which may be 8-fold higher in the subgroup without TWA. Among lower risk patients with HCM with <2 risk factors, the absence of QRSA identifies a low-risk subgroup with a VA annual event rate of only 0.58%. Based on these findings, QRSA is a promising ECG risk marker that may inform prophylactic ICD therapy in HCM, but further validation is required in a larger cohort of lower risk patients.

ARTICLE INFORMATION

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Disclosures

Dr. Viswanathan previously served as a consultant for Pfizer in a capacity unrelated to this manuscript. The remaining authors have no disclosures to report.

Supplementary Material

Data S1
Tables S1–S6
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Data S1.

SUPPLEMENTAL METHODS

Details of Pre-processing and Spectral Method for Alternans Analysis

For each lead, microvolt QRS and T wave alternans were quantified over consecutive 128-beat segments which were incrementally shifted by 16 beats from the beginning to the end of the 3-minute recording. To obtain an initial template QRST complex, an expert observer manually demarcated the QRS onset, QRS end (i.e. J point) and T wave end on the superimposed 3-minute signal average ECGs of all six precordial leads. Baseline wander was removed from each lead by subtracting an interpolated cubic spline fit to an iso-electric point prior to each QRST complex. The individual beats were then aligned by determining the location of maximum dot product when iteratively comparing the signal averaged QRS complex from 50ms before to 50ms after the initial QRS detection of each beat. Bad beats, defined as QRST complexes with prematurity >5% of the pacing cycle length or a Pearson correlation coefficient <90% when compared to the average QRST complex, were replaced with the 128-beat segment's average even or odd QRST complex as appropriate. Segments with >10% bad beats were excluded from analysis. After excluding the bad beats, the alignment was further refined by using the signal average QRS complex of only the good beats.

The pre-processed ECG was assessed for alternans in each 128-beat segment using the spectral method. A 128 x *n* matrix was constructed corresponding to the amplitude of each aligned point in the 128-beat series, where *n* represents the number of sampled time points in the interval of interest (i.e. QRS or JT interval). A fast Fourier transform was applied to the amplitude series to generate power spectra for each time point, which were then summed to

generate an aggregate power spectrum. The unadjusted alternans magnitude was defined as the spectral power at a frequency of 0.5 cycles/beat ($power_{0.5}$), while the spectral power of the noise band was defined as the power of the preceding frequencies from 0.44 to 0.49 cycles/beat ($power_{0.44\text{-}0.49}$). The alternans mean noise (S_{NB}), signal to noise ratio (k value) and magnitude (V_{alt}) were calculated as follows:

$$S_{NB} = \sqrt{mean(power_{0.44-0.49})}$$

$$k\ value = \frac{(power_{0.5} - mean(power_{0.44-0.49}))}{standard\ deviation(power_{0.44-0.49})}$$

$$V_{alt} = \sqrt{power_{0.5} - mean(power_{0.44-0.49})}$$

Alternans Classification Scheme

The alternans classification scheme is illustrated in Figure 1. A pacing rate was classified as alternans positive if there were ≥3 consecutive alternans positive segments, otherwise the pacing rate was considered alternans negative. Individual alternans positive segments among pacing rates classified as negative were considered spurious and thus reclassified as negative and reassigned an alternans magnitude of zero. Pacing rates with <3 viable analysis segments were excluded from analysis. The alternans magnitude for a pacing rate was defined as the maximum alternans magnitude from the non-excluded segments. A patient was classified as QRSA positive (QRSA+) or TWA positive (TWA+) if any of their individual pacing rates were classified as QRSA+ or TWA+, respectively. The alternans magnitude for a patient was defined as the maximum alternans magnitude across all pacing rates. For comparison with prior clinical studies assessing the relationship between TWA and VA, patients were also classified as being TWA non-negative if: (1) TWA was present with a magnitude ≥1.9μV at pacing rates ≤110bpm, or (2)

the pacing rate at 110bpm was excluded from analysis and the pacing rate at 120bpm was either also excluded or exhibited TWA with a magnitude ≥1.9μV (i.e. an indeterminate TWA test).

Each pacing rate was further classified into one of four mutually exclusive categories based on the presence or absence of QRSA and TWA at that rate, namely QRSA-/TWA-, QRSA+/TWA-, QRSA-/TWA+, and QRSA+/TWA+. Each patient was then similarly classified based on the presence of these categories across the different pacing rates as follows: (1) Patients that were QRSA-/TWA- at all rates were classified as QRSA-/TWA-, (2) patients with any rate classified as QRSA+/TWA- and no TWA+ rates were classified as QRSA+/TWA-, (3) patients with any rate classified as QRSA-/TWA+ and no QRSA+ rates were classified as QRSA-/TWA+, and (4) patients that were QRSA+/TWA+ at any rate, or QRSA+/TWA- and QRSA-/TWA+ at different rates were classified as QRSA+/TWA+.

Table S1. QRSA and TWA noise in VA- and VA+ Patients.

	All Patients (N=127)	VA- (N=106)	VA+ (N=21)	*P*
QRSA S_{NB}, µV				
V1	3.3 (2.2-6.0)	3.3 (2.1-6.0)	3.5 (2.3-5.7)	0.697
V2	4.7 (3.1-7.9)	4.7 (3.1-7.9)	5.0 (3.0-7.8)	0.834
V3	5.0 (3.1-7.7)	5.0 (3.1-7.7)	5.0 (3.0-7.8)	0.986
V4	4.9 (3.2-8.0)	4.9 (3.2-8.3)	4.9 (3.0-7.5)	0.619
V5	4.4 (2.7-7.0)	4.4 (2.7-7.1)	4.3 (2.8-6.9)	0.871
V6	3.4 (2.2-5.1)	3.4 (2.1-5.6)	3.4 (2.5-4.8)	0.738
TWA S_{NB}, µV				
V1	2.4 (1.5-3.8)	2.5 (1.4-3.7)	2.3 (1.5-3.9)	0.394
V2	3.0 (1.9-4.9)	3.0 (1.9-5.0)	3.2 (1.8-4.9)	0.943
V3	3.4 (2.0-5.3)	3.3 (2.0-5.5)	3.5 (2.4-4.5)	0.984
V4	3.5 (2.0-5.5)	3.4 (2.0-5.7)	3.7 (2.4-5.0)	0.746
V5	2.9 (1.9-4.5)	2.8 (1.8-4.7)	3.0 (2.1-4.1)	0.969
V6	2.4 (1.5-3.7)	2.4 (1.5-3.8)	2.4 (1.9-3.4)	0.906

QRSA – QRS alternans; S_{NB} – alternans mean noise; TWA – T wave alternans; VA – ventricular tachyarrhythmia

Table S2. Clinical Demographics in QRSA- and QRSA+ Patients.

	All Patients (N=127)	QRSA- (N=82)	QRSA+ (N=45)	*P*
Age, yrs	53±14	54±13	51±15	0.182
Male sex, n (%)	87 (69)	51 (62)	36 (80)	**0.039**
LVEF, %	60±10	60±11	60±10	0.936
Co-morbidities				
Coronary Artery Disease, n(%)	3 (2)	1 (1)	2 (4)	0.286
Prior revascularization, n (%)	2 (2)	1 (1)	1 (2)	1.000
Hypertension, n (%)	40 (32)	26 (32)	14 (31)	0.945
Diabetes, n (%)	13 (10)	8 (10)	5 (11)	0.770
Renal dysfunction†, n (%)	1 (1)	1 (1)	0 (0)	1.000
History of AF, n (%)	39 (31)	26 (32)	13 (29)	0.742
Prior Co-interventions				
Surgical Myectomy, n (%)	18 (14)	13 (16)	5 (11)	0.464
Alcohol Septal Ablation, n (%)	2 (2)	0 (0)	2 (4)	0.124
Medications				
Beta-blocker, n (%)	102 (80)	68 (83)	34 (76)	0.318
Class I anti-arrhythmic, n (%)	9 (7)	7 (9)	2 (4)	0.490
Class III anti-arrhythmic, n (%)	18 (14)	12 (15)	6 (13)	0.841
Calcium channel blockers, n (%)	23 (18)	16 (20)	7 (16)	0.580
ACE-I/ARB, n (%)	32 (25)	20 (24)	12 (27)	0.777
Diuretic, n (%)	23 (18)	17 (21)	6 (13)	0.300
ECG Parameters				
Resting heart rate, bpm	59±10	59±10	58±10	0.672
PR interval, ms*	184±42	187±42	180±42	0.405
QRSd, ms	114±28	114±29	115±26	0.789
QRSd ≥120ms, n (%)	42 (33)	27 (33)	15 (33)	0.963
QTc interval, ms	450±33	450±35	451±28	0.815

ACE-I/ARB – angiotensin converting enzyme inhibitor / angiotensin II receptor blocker; AF – atrial fibrillation; LVEF – left ventricular ejection fraction; QRSA – QRSA alternans; QRSd – QRS duration

*PR interval could not be assessed in 11 patients with atrial arrhythmias (N=116)

†eGFR<61mL/min/1.73m^2

Table S3. HCM ACC/AHA Risk Factors and ESC Risk Score for SCD in QRSA- and QRSA+ Patients.

	Patients (N=127)	QRSA- (N=82)	QRSA+ (N=45)	P
ACC/AHA Risk Factors, n (%)				
History of Syncope*	34 (27)	25 (31)	9 (20)	0.202
History of NSVT†	79 (62)	48 (59)	31 (69)	0.250
Family history of SCD‡	33 (26)	23 (28)	10 (22)	0.474
LV Wall Thickness ≥30mm	25 (20)	12 (15)	13 (29)	**0.053**
Abnormal BP response to exercise§‖	25 (23)	17 (24)	8 (20)	0.606
LVEF <50%	14 (11)	10 (12)	4 (9)	0.769
LV Apical Aneurysm	9 (7)	6 (7)	3 (7)	1.000
No. of Risk Factors	1.7±0.8	1.7±0.8	1.7±0.8	0.927
>1 Risk Factor, n(%)	75 (59)	47 (57)	28 (62)	0.591
ESC Risk Score Components¶				
Age	53±14	53±14	51±15	0.182
Max LV Thickness, mm	21±6	20±6	22±7	**0.035**
LA diameter, mm	44±7	43±7	44±5	0.390
Max LVOT gradient (Rest or Valsalva), mmHg	6 (2-14)	5 (2-14)	8 (4-12)	0.355
ESC Risk Score, %	4.4±2.5	4.2±2.4	4.7±2.6	0.318
ESC Risk Score Category, n (%)				0.477
Low (<4% over 5yrs)	64 (50)	44 (54)	20 (44)	
Intermediate (4-6% over 5yrs)	41 (32)	26 (32)	15 (33)	
High (≥6% over 5ys)	22 (17)	12 (15)	10 (22)	

ACC/AHA – American College of Cardiology/American Heart Association; BP – blood pressure; ESC – European Society of Cardiology; HCM – hypertrophic cardiomyopathy; LA – left atrial; LV – left ventricular; LVEF – left ventricular ejection fraction; LVOT – left ventricular outflow tract; NSVT – non-sustained ventricular tachycardia; QRSA – QRS alternans; SCD – sudden cardiac death

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

† ≥3 consecutive ventricular beats at a rat 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 17 patients (N=110)

¶ History of syncope, NSVT and family SCD detailed above

Table S4. QRSA/TWA Rate Characteristics with Atrial vs. Ventricular Pacing (N=66).

			100 bpm (N=64)	110 bpm (N=54)	120 bpm (N=46)	*P*
Atrial Pacing	**QRSA**	Positive studies, n (%)	9 (14)	17 (32)	21 (46)	<0.001‡
		Positive segments, %	8±3	25±5*	34±6	<0.001†
		Alternans magnitude, µV	1.6±0.6	4.6±1.2	7.4±1.5	<0.001†
	TWA	Positive studies, n (%)	15 (23)	17 (32)	18 (39)	0.075‡
		Positive segments, %	15±4	23±5	22±5	0.120†
		Alternans magnitude, µV	1.4±0.4	1.9±0.4	2.5±0.6	0.110†
			100 bpm (N=63)	**110 bpm (N=64)**	**120 bpm (N=58)**	***P***
Ventricular Pacing	**QRSA**	Positive studies, n (%)	8 (13)	16 (25)	20 (34)	0.003‡
		Positive segments, %	8±3	14±4*	21±5	0.042†
		Alternans magnitude, µV	2.4±0.9	4.3±1.2	5.3±1.7	0.097†
	TWA	Positive studies, n (%)	16 (25)	18 (28)	20 (35)	0.415‡
		Positive segments, %	15±4	16±4	23±5	0.135†
		Alternans magnitude, µV	2.0±0.6	2.9±0.8	2.7±0.6	0.421†

Continuous data is presented as mean ± SE. QRSA – QRS alternans; TWA – T wave alternans

* Significant difference ($p<0.05$) in paired comparison between atrial and ventricular pacing using McNermar or Wilcoxon test where appropriate

† Statistical significance assessed using linear mixed model with repeated measures

‡ Statistical significance assessed using repeated measures logistic regression

Table S5. Patient-level QRSA/TWA Classification with Atrial vs. Ventricular Pacing (N=66).

	Atrial Pacing	Ventricular Pacing	*P**
QRSA+ patients, n (%)	29 (44)	26 (39)	0.690
TWA+ patients, n (%)	26 (39)	28 (42)	0.815
QRSA/TWA patients			
QRSA-/TWA-, n (%)	32 (49)	34 (52)	0.795
QRSA+/TWA-, n (%)	9 (14)	4 (6)	
QRSA-/TWA+, n (%)	5 (8)	6 (9)	
QRSA+/TWA+, n (%)	20 (30)	22 (33)	

*Statistical significance assessed using McNemar test for paired proportions

QRSA – QRS alternans; TWA – T wave alternans; VA – ventricular tachyarrhythmia

Table S6. Alternans in Patients with and without Extensive LGE (N=78).

	All Patients (N=78)	No Extensive LGE* (N=34)	Extensive LGE* (N=44)	*P*
QRSA Metrics				
QRSA+ study, n (%)	30 (39)	12 (35)	18 (41)	0.613
QRSA+ segments, %	0 (0-25)	0 (0-16)	0 (0-35)	0.320
QRSA magnitude, µV	0.0 (0.0-12.4)	0.0 (0.0-8.9)	0.0 (0.0-17.8)	0.322
TWA Metrics				
TWA+ study, n (%)	34 (44)	14 (41)	20 (46)	0.706
TWA+ segments, %	0 (0-22)	0 (0-21)	0 (0-30)	0.526
TWA magnitude, µV	0.0 (0.0-7.5)	0.0 (0.0-4.9)	0.0 (0.0-10.2)	0.301
QRSA/TWA Classification				0.942
QRSA-/TWA-, n (%)	42 (54)	19 (56)	23 (52)	
QRSA+/TWA-, n (%)	2 (3)	1 (3)	1 (2)	
QRSA-/TWA+, n (%)	6 (8)	3 (9)	3 (7)	
QRSA+/TWA+, n (%)	28 (36)	11 (32)	17 (39)	

*LGE ≥15% of LV mass or visually estimated to be extensive;
LGE – late gadolinium enhancement; LV – left ventricular QRSA – QRS alternans; TWA – T wave alternans

Figure S1. QRSA and TWA at low and high pacing rates in a QRSA-/TWA+ patient.

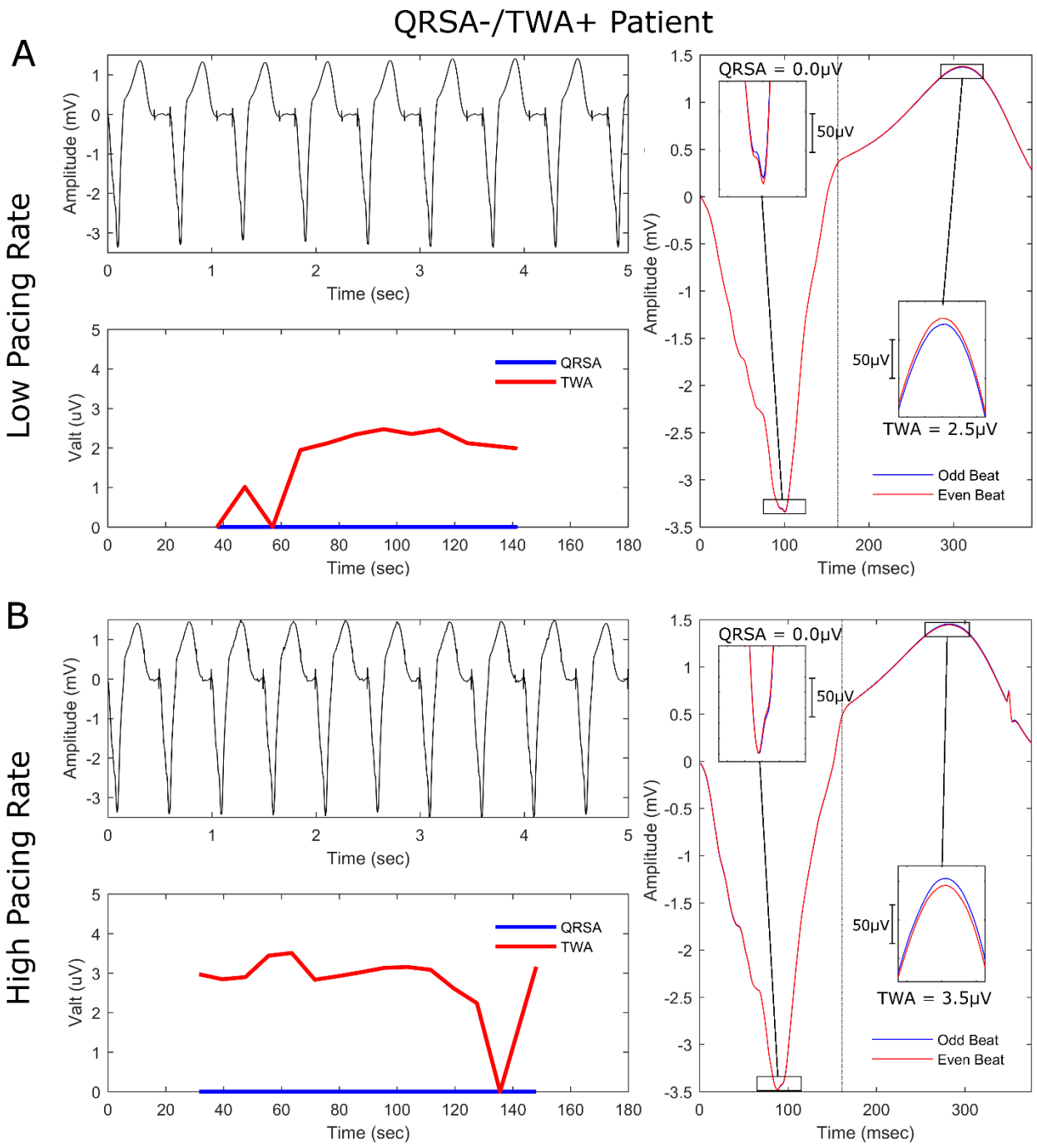

Illustration of microvolt QRSA and TWA in a QRSA-/TWA+ patient during (A) low and (B) high pacing rates. Upper left panel illustrates a representative 5-sec ECG from lead V5 during the 3-min ventricular pacing study. Lower left panel illustrates QRSA (blue) and TWA (red)

magnitudes for each 128-beat segment in the 3-min pacing study. Right panel illustrates superimposed mean odd (blue) and even (red) beats from a representative 128-beat segment to highlight the low-magnitude scale of alternans on the ECG. TWA magnitudes increase from the low to high rate, whereas QRSA is not present at either rate. QRSA – QRS alternans; TWA – T wave alternans

Figure S2. QRSA and TWA at low and high pacing rates in a QRSA+/TWA+ patient.

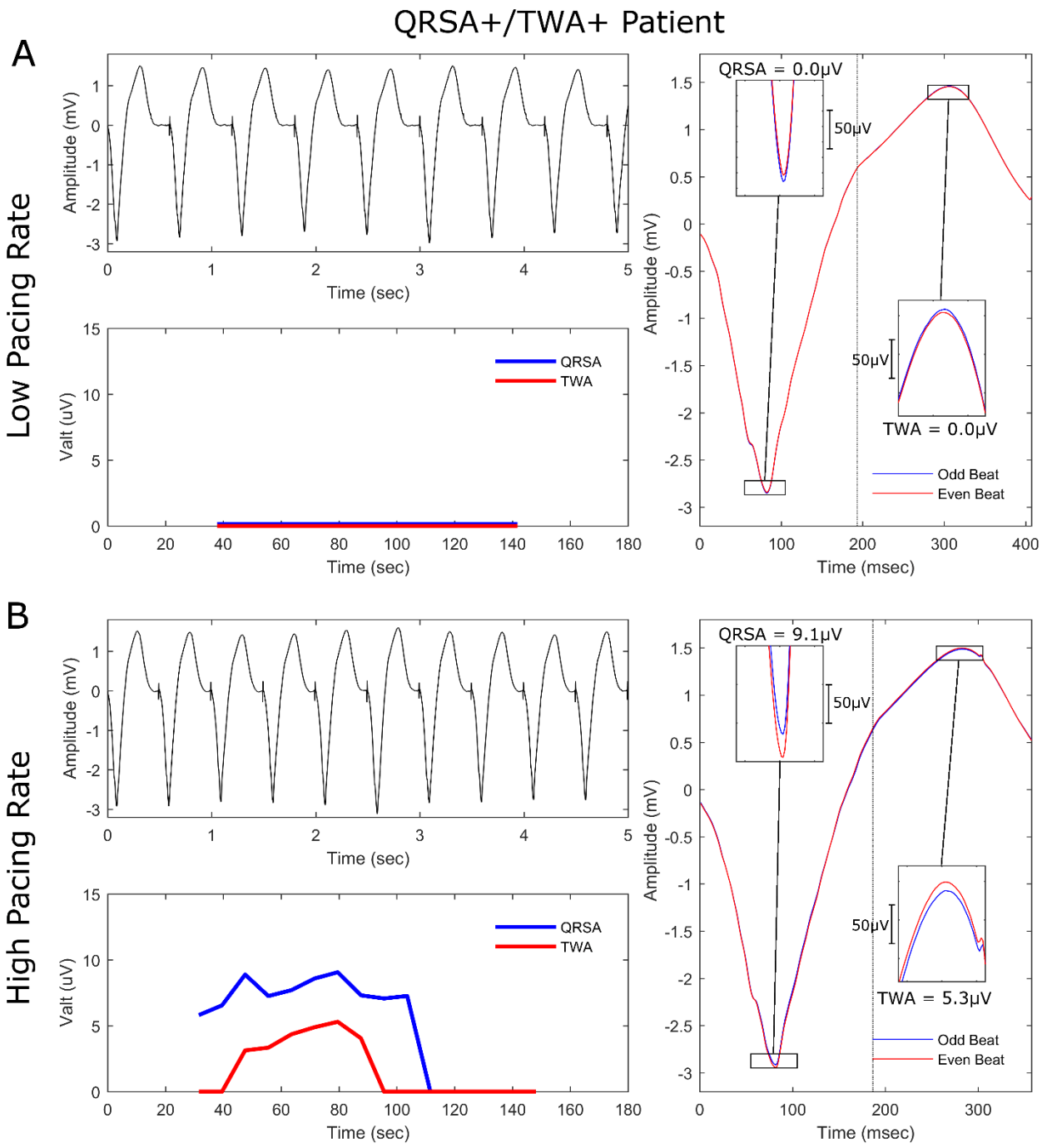

Illustration of microvolt QRSA and TWA in a QRSA+/TWA+ patient during (A) low and (B) high pacing rates. Upper left panel illustrates a representative 5-sec ECG from lead V3 during the 3 min ventricular pacing study. Lower left panel illustrates QRSA (blue) and TWA (red)

magnitudes for each 128-beat segment in the 3-min pacing study. Right panel illustrates superimposed mean odd (blue) and even (red) beats from a representative 128-beat segment to highlight the low-magnitude scale of alternans on the ECG. Both QRSA and TWA magnitudes increase from the low to high rate. QRSA – QRS alternans; TWA – T wave alternans