A new electrocardiogram marker to identify patients at low risk for ventricular tachyarrhythmias: sum magnitude of the absolute QRST integral☆,☆☆

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Abstract

Objective: We proposed and tested a novel electrocardiogram marker of risk of ventricular arrhythmias (VAs).

Methods: Digital orthogonal electrocardiograms were recorded at rest before implantable cardioverter-defibrillator (ICD) implantation in 508 participants of a primary prevention ICDs prospective cohort study (mean ± SD age, 60 ± 12 years; 377 male [74%]). The sum magnitude of the absolute QRST integral in 3 orthogonal leads (SAI QRST) was calculated. A derivation cohort of 128 patients was used to define a cutoff; a validation cohort (n = 380) was used to test a predictive value.

Results: During a mean follow-up of 18 months, 58 patients received appropriate ICD therapies. The SAI QRST was lower in patients with VA (105.2 ± 60.1 vs 138.4 ± 85.7 mV ∗ ms, P = .002). In the Cox proportional hazards analysis, patients with SAI QRST not exceeding 145 mV ∗ ms had about 4-fold higher risk of VA (hazard ratio, 3.6; 95% confidence interval, 1.96-6.71; P < .0001) and a 6-fold higher risk of monomorphic ventricular tachycardia (hazard ratio, 6.58; 95% confidence interval, 1.46-29.69; P = .014), whereas prediction of polymorphic ventricular tachycardia or ventricular fibrillation did not reach statistical significance.

Conclusion: High SAI QRST is associated with low risk of sustained VA in patients with structural heart disease.

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Sudden cardiac death (SCD) strikes about 350 000 victims in the United States every year.[1] Implantable cardioverter-defibrillators (ICDs) are the treatment of choice[2-4] for patients at risk for SCD. The need to extend risk stratification beyond use of ejection fraction (EF) is well recognized.[5,6] A U-shaped curve for ICD benefit was shown in the analysis of the Multicenter Automatic Defibrillator Implantation Trial II,[5] prompting a search for markers that identify low-risk patients who do not benefit from ICD implantation.

During the century of electrocardiography, multiple attempts were made to decipher complex information carried by cardiac electrical signal to obtain important clinical diagnostic and prognostic information. Several approaches have been proposed to develop composite electrocardiogram (ECG) metrics that account for both amplitude and duration of ECG waveforms, with the goal to diagnose hypertrophy,[7,8] to determine localization and size of the scar,[9-11] and to assess heterogeneity of action potential.[12] Although modern imaging modalities question utility of diagnostic ECG, prognostic ECG markers remain of interest. Arrhythmogenic substrate in patients susceptible to ventricular arrhythmia (VA) with structural heart disease is characterized by specific electrophysiologic properties of a scar, cardiac hypertrophy, and dilatation, resulting in the conditions of source-sink mismatch[13,14] and dispersion of refractoriness.[15-17]

In this work, we proposed a novel ECG metric: sum magnitude of the absolute QRST integral (SAI QRST). We hypothesized that the SAI QRST predicts VA in primary prevention ICD patients with structural heart disease.

Methods

The study protocol was approved by the Johns Hopkins University institutional review board, and all patients gave written informed consent before entering the study.

Study population

Prospective Observational Study of the ICD in Sudden Cardiac Death Prevention (PROSE-ICD) (NCT00733590) is a prospective, observational, multicenter cohort study of primary prevention ICD patients with either ischemic or nonischemic cardiomyopathy. Patients were eligible for the study if the left ventricular (LV) EF was less than or equal to 35%, myocardial infarction was at least 4 weeks old, or nonischemic LV dysfunction was present for at least 9 months. Patients were excluded if the ICD was indicated for secondary prevention of SCD, if patient had a permanent pacemaker or a class I indication for pacing, if the patient had New York Heart Association (NYHA) class IV, or if the patient was pregnant. Electrophysiologic testing to assess inducibility of ventricular tachycardia (VT) was performed in 373 patients (73%) at the time of ICD implantation. Left ventricular diastolic diameter (LVDD) was assessed by 2-dimensional echocardiography in 225 patients (44.3%). Single-chamber ICD was implanted in 263 patients (52%), dual-chamber ICD in 92 patients (18%), and cardiac resynchronization therapy defibrillator (CRT-D) in 153 patients (30%). The PROSE-ICD study is an ongoing active project that continues to enroll new patients. This report presents data analysis of study participants with at least 6 months of follow-up, recruited at the Johns Hopkins Hospital site.

Surface ECG recording

Digital orthogonal ECG was recorded before ICD implantation during 5 minutes at rest, using the modified Frank[18] orthogonal XYZ leads by PC ECG machine (Norav Medical Ltd, Thornhill, Ontario, Canada), with a 1000-Hz sampling frequency, high-pass filter 0.05 Hz, low-pass filter 350 Hz, and notch filter 60 Hz.

QRST integral measurement

All ECGs were analyzed by customized software in a robust automated fashion. Noise and ventricular premature and ventricular-paced beats were excluded from analysis, but ECG recordings during atrial fibrillation were analyzed. Images of areas under the QRST curve were reviewed to ensure appropriate ECG wave detection. Absolute QRST integral was measured as the arithmetic sum of areas under the QRST curve (absolute area under the QRST curve above baseline was added to the area below baseline; Fig. 1), averaged during a 5-minute epoch. The sum magnitude of 3
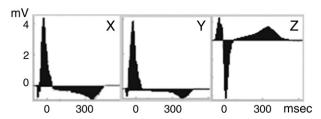

Fig. 1. Example of SAI QRST measurement. The sum of the areas under QRST curve on 3 orthogonal ECG leads is calculated.

orthogonal leads absolute QRST integral (SAI QRST) was calculated.

End points

Appropriate ICD therapies (either shock or antitachycardia pacing) for VA served as the primary end point for analysis. Programming of the ICD was based on the attending electrophysiologist's clinical evaluation. The ICD device was interrogated during follow-up visits every 6 months. All ICD interrogation data were reviewed by an independent end points adjudication committee blinded to the results of SAI QRST analysis. Implantable cardioverter-defibrillator therapies for monomorphic VT (MMVT), polymorphic VT (PVT), or ventricular fibrillation (VF) were classified as appropriate. *Monomorphic VT* was defined as a sustained VT with stable cycle length (CL) and electrogram morphology. *Polymorphic VT* was defined as a sustained VT with unstable CL and electrogram morphology and average CL of at least 200 milliseconds. *Ventricular fibrillation* was defined as sustained ventricular tachyarrhythmia with unstable CL and electrogram morphology and average CL less than 200 milliseconds. Sustained appropriately treated VT/VF events were categorized as MMVT group and PVT/VF group.

Statistical analysis

The first 128 consecutive participants of the PROSE-ICD study were included in the derivation cohort. The validation cohort included the remaining 380 PROSE-ICD study participants who were followed prospectively for at least 6 months.

Derivation data set analysis

Cutoff points of SAI QRST were determined in the preliminary analysis of 128 study patients, 15 of whom had sustained VT/VF events during 13 ± 10 months of follow-up. In this derivation set, the lowest SAI QRST quartile was less than or equal to 69 mV ∗ ms; and the highest quartile was greater than 145 mV ∗ ms. Preliminary survival analysis of the derivation set showed that the lowest quartile of the SAI QRST predicted VT/VF (log-rank test, $P < .0001$) with 100% sensitivity, 78% specificity, 37% positive predictive value, and 100% negative predictive value.

Validation data set analysis

Validation cohort participants were categorized according to their baseline SAI QRST value, with SAI QRST less than or equal to 69 mV ∗ ms labeled *low*, SAI QRST of 70 to

Table 1
Clinical and baseline ECG characteristics of derivation and validation cohort

Characteristic	Derivation cohort (n = 128)	Validation cohort (n = 380)	P
Age ± SD (y)	59.8 ± 10.8	60.3 ± 12.5	.679
Male sex, n (%)	97 (75.8)	280 (73.7)	.639
White race, n (%)	89 (69.5)	267 (70.3)	.876
Ischemic CM, n (%)	65 (50.8)	218 (57.4)	.194
Baseline LVEF ± SD (%)	21.98 ± 7.69	21.99 ± 9.08	.990
QRS (ms)	124.48 ± 34.36	120.65 ± 31.65	.272
Complete BBB, n (%)	28 (21.9)	96 (25.3)	.440
CRT-D device, n (%)	40 (31.2)	113 (29.4)	.189
LVDD ± SD (cm)	6.05 ± 1.02	5.90 ± 0.84	.304
Body mass index ± SD (kg/m^2)	29.34 ± 5.99	28.91 ± 6.13	.497
β-Blockers, n (%)	126 (98.4)	356 (93.7)	.018
PTCA and/or CABG history, n (%)	86 (67.2)	204 (53.7)	.045
Statins, n (%)	120 (93.8)	321 (84.5)	.018
NYHA class II, n (%)	40 (31.3)	110 (29.0)	.283
NYHA class III, n (%)	58 (45.3)	199 (52.5)	.283
Inducible VT, n (%)	30 (23.4)	93 (24.5)	.821
Heart rate ± SD, beats/min	72.67 ± 14.21	73.30 ± 14.68	.805

CM indicates cardiomyopathy; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft.

145 mV ∗ ms labeled *intermediate*, and SAI QRST greater than 145 mV ∗ ms labeled *high*. Linear regression analysis was used to study what physiologic parameters correlate with the SAI QRST. One-way analysis of variance was used to compare among 3 groups of SAI QRST, with Bonferroni correction for multiple comparisons. Unadjusted and adjusted Kaplan-Meier survival curves were constructed for subjects with low, intermediate, or high SAI QRST. The log-rank (Mantel-Cox) statistic was computed to test the equality of survival distributions. Univariate and multivariate Cox proportional hazards regression analyses were performed. An interaction between SAI QRST and bundle-branch block (BBB) status, as well as between SAI QRST and LVDD, was tested in the Cox model. The receiver operating characteristic (ROC) curves with area under the curve (AUC), sensitivity, specificity, and predictive values of SAI QRST for freedom from VT/VF were calculated. STATA 10 software (StataCorp LP, College Station, TX) was used for calculations.

Results

Patient population

Clinical characteristics of the derivation and validation cohort patients are outlined in Table 1. There were no statistically significant differences between baseline characteristics of the 2 cohorts. Neither did the rate of VT/VF events differ significantly (15 patients [11.7%] in derivation cohort vs 43 patients [11.3%] in validation cohort experienced VT/VF; P = .901). A few differences in patient management were observed: derivation cohort patients were more frequently on β-blockers and statins, with a slightly higher rate of revascularization procedures.

Ventricular tachyarrhythmias during follow-up

During a mean (SD) follow-up of 18.0 (16.5) months, 43 (11.3%; or 7.5% per person-year of follow-up) of the 380 validation cohort patients experienced sustained VA and received appropriate ICD therapies. Monomorphic VT with an average (SD) CL of 293 (38) milliseconds was present in 31 patients (72%). Polymorphic VT/VF with an average (SD) CL of 214 (18) milliseconds was documented in 12 patients (3.2%; or 2.1% per person-year of follow-up). There were significantly fewer patients on β-blockers among those patients receiving subsequent appropriate ICD therapies (Table 2).

Predictive value of SAI QRST in validation cohort

Representative examples of baseline SAI QRST ECG in a patient with and one without subsequent sustained ventricular tachyarrhythmia and appropriate ICD therapy at follow-up are shown in Fig. 2. The SAI QRST was significantly lower in patients with sustained VA during follow-up (Wilcoxon rank sum test P = .004 and Student t test P = .002; Fig. 3). Kaplan-Meier survival analysis showed that the SAI QRST was significantly predictive for freedom from VT/VF during follow-up (Fig. 4A).

In the univariate Cox proportional hazards analysis, patients with high SAI QRST had a 41% decrease in risk of VA compared with patients with intermediate SAI QRST; and accordingly, patients with intermediate SAI QRST had a 41% decrease in risk of VA compared with patients with low SAI QRST (hazard ratio [HR] for variable "low-intermediate-high SAI QRST," 0.59; 95% confidence interval [CI], 0.39-0.89; P = .012). The SAI QRST predicts MMVT (HR, 0.45; 95% CI, 0.20-0.99; P = .049), rather than PVT/VF (HR, 0.65; 95% CI, 0.40-1.06; P = .085). Importantly, the risk of VA in patients with low or intermediate SAI QRST was 4-fold higher than in patients with high SAI QRST (HR,

Table 2
Comparison of clinical and baseline ECG characteristics of patients with and those without subsequent appropriate ICD therapy for VT/VF

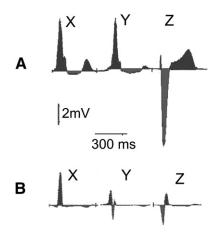| Characteristic	No VT/VF events (n = 337)	VT/VF events at follow-up (n = 43)	P
Age ± SD (y)	60.2 ± 12.7	60.7 ± 11.3	.776
Male sex, n (%)	245 (72.7)	35 (81.4)	.223
White race, n (%)	233 (69.1)	34 (79.1)	.180
Ischemic CM, n (%)	189 (56.1)	29 (67.4)	.156
Baseline LVEF ± SD (%)	22.20 ± 9.20	20.38 ± 7.98	.178
QRS (ms)	121.57 ± 31.92	114.05 ± 29.07	.122
BBB, n (%)	83 (24.6)	13 (30.2)	.426
CRT-D device, n (%)	106 (31.6)	7 (16.3)	.122
LVDD ± SD (cm)	5.86 ± 0.96	6.41 ± 0.71	.026
Body mass index ± SD (kg/m^2)	28.79 ± 6.14	29.88 ± 5.99	.270
β-Blockers, n (%)	332 (95.5)	35 (81.4)	<.0001
PTCA and/or CABG history in ischemic CM patients, n (%)	133 (77.3)	16 (57.1)	.023
NYHA class II, n (%)	95 (28.3)	15 (34.9)	.414
NYHA class III, n (%)	181 (53.9)	18 (41.9)	.414
Heart rate ± SD (beats/min)	72.66 ± 14.51	69.54 ± 15.86	.226

Fig. 2. Representative baseline SAI QRST ECG in a patient without (A) and one with (B) subsequent sustained ventricular tachyarrhythmia and appropriate ICD therapy at follow-up.

4.05; 95% CI, 2.00-8.20; *P* < .0001). Risk of MMVT was more than 6-fold higher (HR, 6.58; 95% CI, 1.46-29.69; *P* = .014; Fig. 4B). However, prediction of freedom from PVT/VF with high SAI QRST did not reach statistical significance (HR, 0.16; 95% CI, 0.021-1.25; *P* = .080; Fig. 4C).

Low, intermediate, and high SAI QRST

Characteristics of the patients with low, intermediate, and high SAI QRST are presented in Table 3. There were more nonischemic cardiomyopathy patients with low LVEF and, at the same time, more patients with BBB and implanted CRT-D device among the high SAI QRST group. Patients with low SAI QRST had higher body mass index and were more frequently diagnosed with ischemic cardiomyopathy.

Several parameters were statistically significantly correlated with the SAI QRST: age ($r = 0.115$, $P = .010$), LVDD ($r = 0.138$, $P = .009$; Fig. 5A), EF ($r = -0.162$, $P = .0001$; Fig. 5B), body mass index ($r = -0.102$, $P = .024$; Fig. 5C), duration of the QT interval ($r = 0.274$, $P < .0001$; Fig. 5D), heart rate ($r = -0.101$, $P = .022$; Fig. 5E), beat-to-beat QT
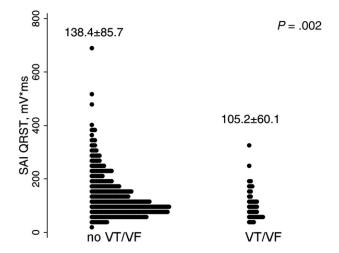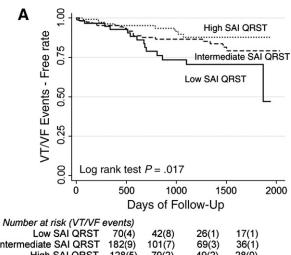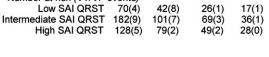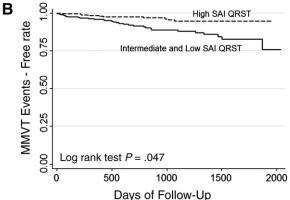

Fig. 3. The distribution of SAI QRST in validation cohort patients without and with sustained VA at follow-up.
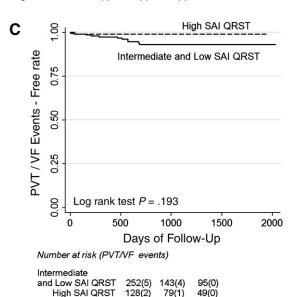

Fig. 4. Kaplan-Meier curves for freedom from VT/VF events in validation cohort patients with low, intermediate, and high SAI QRST. A, Kaplan-Meier, all VT/VF event-free survival. B, Kaplan-Meier, MMVT event-free survival. C, Kaplan-Meier, PVT/VF event-free survival.

Table 3
Comparison of patients with low, intermediate, and high SAI QRST

Characteristic	Low SAI QRST ≤69 mV ∗ ms (n = 71)	Intermediate SAI QRST 70-145 mV ∗ ms (n = 181)	High SAI QRST >145 mV ∗ ms (n = 128)	ANOVA P
Age ± SD (y)	57.6 ± 12.9	60.0 ± 12.5	62.0 ± 12.0	.057
Male, n (%)	53 (74.7)	140 (77.4)	86 (67.2)	.133
White race, n (%)	52 (73.2)	126 (69.6)	89 (69.5)	.832
Ischemic CM, n (%)	92 (67.7)	90 (56.3)	35 (41.7)	.008
Baseline LVEF ± SD (%)	23.5 ± 8.9	22.4 ± 8.5	20.6 ± 8.8	.043
NYHA class II, n (%)	36 (26.5)	46 (28.8)	28 (33.7)	.555
LVDD ± SD (cm)	5.90 ± 0.89	5.82 ± 0.87	6.06 ± 1.13	.423
QRS (ms)	97.5 ± 14.9	111.0 ± 25.0	147.3 ± 30.8	<.0001
BBB, n (%)	2 (2.8)	28 (15.5)	66 (51.6)	<.0001
CRT-D device, n (%)	7 (9.9)	34 (18.8)	72 (56.3)	<.0001
Heart rate ± SD (beats/min)	73.4 ± 15.0	73.2 ± 14.7	70.6 ± 14.3	.251
QT ± SD (ms)	462 ± 61	471 ± 62	498 ± 62	.0001
Body mass index ± SD (kg/m^2)	30.9 ± 7.4	28.7 ± 5.8	28.0 ± 5.5	.006
β-Blockers, n (%)	62 (95.4)	151 (93.8)	100 (92.6)	.763
Revascularization history in ischemic CM patients, n (%)	61 (67.0)	62 (77.5)	26 (90.0)	.214

ANOVA indicates analysis of variance.

variability index[19] ($r = -0.176$, $P < .0001$), and QRS width ($r = 0.634$, $P < .0001$; Fig. 5F). The SAI QRST was significantly higher in patients with either left or right complete BBB ($212.5 ± 100.8$ vs $109.4 ± 56.62$, $P < .00001$), and it was diminished in patients with ischemic cardiomyopathy ($121.86 ± 67.48$ vs $150.45 ± 96.52$, $P = .0002$).

Multivariate survival analysis in validation cohort

Among other clinical and ECG parameters, use of β-blockers, implanted CRT-D device, and LVDD greater than 6 cm were significant in the univariate Cox regression for prediction of VA. Neither QT nor QRS duration predicted VT/VF events. Ejection fraction with cutoffs of 20%, 25%, and 30% was not associated with the risk of VA.

No significant interaction was found between SAI QRST and presence of BBB, or between SAI QRST and LVDD. In the multivariate Cox regression analysis for VT/VF events, high SAI QRST remained a significant predictor of freedom from VT/VF after adjustment[20] for the use of β-blockers, implanted CRT-D, LVDD, and LVEF. The most complete multivariate Cox regression model for VT/VF prediction is shown in Table 4. Use of β-blockers and LVDD greater than 6 cm remained significant predictors in the multivariate model, too.

The ROC curve measuring the accuracy of the SAI QRST for freedom from VT/VF showed an AUC of 0.628 (95% CI, 0.538-0.717; Fig. 6A). An SAI QRST less than or equal to 145 mV ∗ ms demonstrated 79% sensitivity, 65% specificity, 14% positive predictive value, and 93% negative predictive value for prediction of VA during 1.5 years of follow-up.
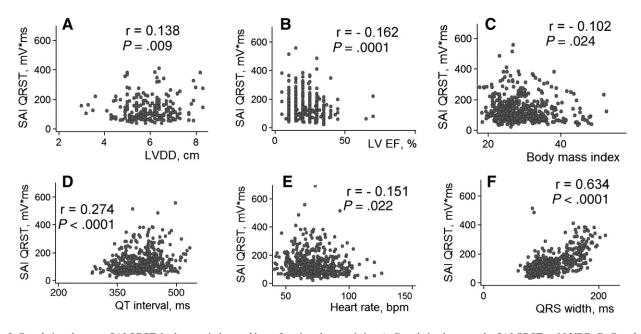

Fig. 5. Correlations between SAI QRST, body mass index, and heart function characteristics. A, Correlation between the SAI QRST and LVDD. B, Correlation between SAI QRST and LVEF. C, Correlation between SAI QRST and body mass index. D, Correlation between SAI QRST and QT interval. E, Correlation between SAI QRST and heart rate. F, Correlation between SAI QRST and QRS width.

Table 4
Univariate and multivariate HRs of tested predictors of VT/VF

Predictor	Unadjusted HR (95% CI) and *P* value	Adjusted HR (95% CI) and *P* value
Low-intermediate-high		
SAI QRST	0.59 (0.39-0.89), *P* = .012	0.54 (0.33-0.88), *P* = .013
CRT-D device	0.42 (0.17-0.94), *P* = .035	0.68 (0.29-1.58), *P* = .369
LVDD >6 cm	3.57 (1.28-10.01), *P* = .015	3.74 (1.30-10.77), *P* = .014
LVEF ≤25%	1.12 (0.55-2.28), *P* = .749	1.47 (0.68-3.18), *P* = .332
Use of β-blockers	0.28 (0.13-0.62), *P* = .001	0.19 (0.08-0.45), *P* = .0001

SAI QRST and QRS width

No significant interaction was found between SAI QRST and the presence of BBB in the multivariate Cox regression model. This outcome means that the SAI QRST predicts VT/VF in patients with and those without BBB. However, SAI QRST was significantly larger in patients with either left or right complete BBB (212.51 ± 100.8 vs 109.35 ± 56.62, *P* < .00001). Therefore, we suggest that the best cutoff value of SAI QRST should be different for patients with wide vs narrow QRS. For the purpose of this analysis, we combined derivation and validation cohorts and categorized all 508 study patients as part of either the *narrow QRS* subgroup (QRS ≤120 milliseconds, n = 272 [53.5%]) or the *wide QRS* subgroup (QRS >120 milliseconds, n = 236 [46.5%]). To define the best SAI QRST cutoff value, ROC curves were constructed separately in patients with narrow and patients with wide QRS (Fig. 6B, C). In patients with narrow QRS less than or equal to 120 milliseconds, the SAI QRST of 82 mV ∗ ms provided 60% sensitivity and 55% specificity. In patients with wide QRS greater than 120 milliseconds, the SAI QRST of 138 mV ∗ ms provided 64% sensitivity and 70% specificity. A test on the equality of ROC areas between patients with narrow and those with wide QRS did not show a statistically significant difference.
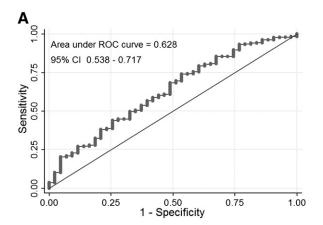
SAI QRST in CRT-D patients

Both derivation and validation cohorts patients were included in this analysis. The VT/VF events were less frequent in CRT-D recipients as compared with ICD patients (log-rank test *P* = .017; Fig. 7A). There was no statistically significant difference in the MMVT rate between ICD and CRT-D patients. However, PVT/VF was observed in 7 patients with single-chamber ICD (3.7%) and 4 patients with dual-chamber ICD (5.2%), but in only 1 CRT-D patient (0.9%; log-rank test *P* = .017). In univariate Cox regression analysis, risk of sustained VT/VF was lower in patients with implanted CRT-D device than in ICD patients (HR, 0.45; 95% CI, 0.24-0.88; *P* = .020).
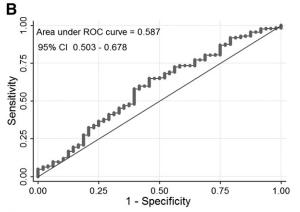
Baseline SAI QRST predicted sustained VA events in CRT-D patients (Fig. 7B). In multivariate Cox regression analysis (all-patients cohort) in the model that included SAI QRST, presence of BBB, use of β-blockers, LVDD, and type of device (CRT-D or ICD), SAI QRST less than 145 mV ∗ ms was associated with 4-fold higher risk of VA (HR, 4.13; 95% CI, 1.96-8.72; *P* < .0001); use of β-blockers reduced

the risk of VA (HR, 0.286; 95% CI, 0.131-0.623; *P* = .002); and presence of BBB was associated with 3-fold higher risk of VA (HR, 2.91; 95% CI, 1.38-6.13; *P* = .005).

Discussion

In this study, we present a new marker of low risk of ventricular tachyarrhythmias and show that SAI QRST greater than 145 mV ∗ ms is associated with a low risk of arrhythmia in structural heart disease patients with implanted ICD for primary prevention of SCD.
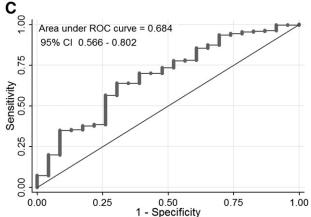

Fig. 6. Results of ROC analysis. Receiver operating characteristic curve on the prediction of freedom from sustained VT/VF events for all patients (A), for patients with narrow QRS not exceeding 120 milliseconds (B), and for patients with wide QRS greater than 120 milliseconds (C).
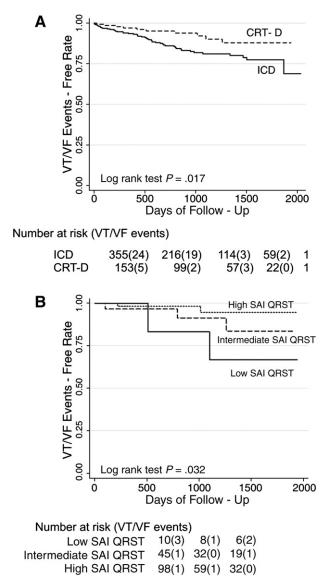
Fig. 7. A, Kaplan-Meier curves for freedom from VT/VF events in patients with the ICD and CRT-D device (n = 508). B, Kaplan-Meier curves for freedom from VT/VF events in CRT-D patients with the low, intermediate, and high SAI QRST.

Substantial evidence supports the idea that patients with structural heart disease have some degree of risk of VA during their lifetime. The strategy of identifying patients at low, rather than high, risk of VA maximizes the benefit of primary prevention ICD, excluding those at low risk of VT/VF for whom the risk-benefit ratio of the ICD, including congestive heart failure progression,[21] is not favorable. Biostatistical studies[22-24] have identified the requirements for a good screening test and underscored the value of ROC analysis. Hazard ratios of most commonly used predictors of SCD[25] range from 2 to 4, which are insufficient for discrimination. In this analysis, the SAI QRST ROC exhibited a large AUC and HR range of 4 to 6, as well as high sensitivity and negative predictive value, and therefore could be considered as one of the methods for screening of patients with structural heart disease to avoid ICD implantation in those at very low risk of VA.

What is SAI QRST?

The QRST integral was conceived by Wilson et al[12] as the time integral of the heart vector[26] and expresses the heterogeneity of the action potential (AP) morphology.[27] We calculated sum absolute QRST integral, which is a different metric not previously explored. Our choice of orthogonal ECG over 12-lead ECG was based on the advantages provided by orthogonal ECG, which permits assessment of the heart vector. Summation of absolute QRST integral of all 3 orthogonal ECG leads allows assessment of the magnitude of total cardiac electrical power and eliminates bias of single-lead axis position. The precise electrophysiologic meaning of SAI QRST remains to be elucidated. We speculate that (1) the low SAI QRST characterizes significant cancellation of electrical forces as an important preexisting condition that may facilitate sustained VA, (2) low SAI QRST reflects reduced mass of viable myocardium in patients with structural heart disease, and (3) SAI QRST characterizes specific geometry of the heart chambers.

Cancellation of electrical forces results in low SAI QRST

Cancellation of electrical forces in the heart may reduce ECG amplitudes. An estimated 75% of the electrical energy is canceled during ventricular depolarization,[28] and 92% to 99% is canceled during repolarization.[29] Previous experiments showed that AP morphology gradients in different sites of the heart may have opposing directions and cancel out.[30] We speculate that decrease in the sum absolute QRST integral due to cancellation coexists with the locally observed increase in action potential duration (APD) gradients and increased native QRST integral, or "ventricular gradient," as marker of a heterogeneity of repolarization or heterogeneity of AP morphology.[31,32]

SAI QRST and QRS width

Our results showed significant correlation between SAI QRST and QRS width. Consistent with previous studies,[33,34] we did not find a relation between ventricular conduction abnormalities and VT/VF occurrence in the cohort of all study patients. In addition, antiarrhythmic effect of CRT could affect VT/VF rate in patients with wide QRS and BBB at baseline, as about one third of our study patient population had a CRT-D device implanted. Indeed, we confirmed a statistically significantly lower rate of VT/VF events in CRT-D patients. Subgroup analysis showed that presence of BBB was a significant predictor of VT/VF events in ICD patients, but not in CRT-D patients. Although a correlation between the QRS duration and the SAI QRST is obvious, these metrics are not identical. Notably, SAI QRST predicted VT/VF events in patients with any QRS width. Surprisingly, the predictive accuracy of SAI QRST in patients with wide QRS greater than 120 milliseconds was at least as good as in patients with narrow QRS less than or equal to 120 milliseconds. This important finding may lead to reevaluation of the approach to BBB ECG assessment. A recent report raised the issue of reliability and reproducibility of manual QRS duration measurement.[35] The robust automated

measurement of SAI QRST could become a reasonable alternative in the future.

SAI QRST and LV size

Our results revealed significant correlation between SAI QRST and LVDD. Further studies are necessary to determine the relations between SAI QRST and LV geometry, hypertrophy, and dilatation. Of note, our study patients at baseline had remarkably impaired systolic function, LV dilatation, and frequently a large area of myocardial scar. Several previous studies, focused on healthier population of hypertensive patients, showed that Cornell voltage-duration product (RaVL + SV3 [+6 mm in women] ∗ QRS duration) is associated with the risk of SCD.[36-38] Interestingly, in contrast to our findings, a large instead of a small Cornell voltage-duration product was associated with the risk of SCD. Another study of patients with hypertrophic cardiomyopathy showed that higher (not lower) ECG amplitudes and a high 12-lead QRS amplitude sum predict SCD in hypertrophic cardiomyopathy patients.[39] Further studies are necessary to clarify this intriguing issue. We speculate that the SAI QRST characterizes electrical rather than geometrical characteristics of the heart, signifying cancellation of electrical forces in patients with large APD heterogeneity and high risk of life-threatening VA.

Methodology of SAI QRST

This is the first report showing the predictive value of SAI QRST. Ongoing analysis is determining whether 5 minutes of recorded ECG is necessary or whether a shorter recorded ECG can be enough. Ongoing analysis is also making 2 additional comparisons: the predictive value of SAI QRST calculated from orthogonal ECG vs inverse Dower transforms derived from standard 12-lead ECG and the predictive value of the QRS amplitude vs SAI QRST.

Importantly, virtually any ECG recorded during sinus rhythm or atrial fibrillation is amenable to this analysis, thereby extending the opportunity for noninvasive VT/VF risk stratification in patient populations that would not be eligible for it otherwise.

Further studies are needed to clarify the extent to which SAI QRST reflects underlying cardiac anatomy (LV hypertrophy and/or dilatation, scar size). In this study, SAI QRST remained the significant predictor in the model in the presence of the LVDD variable, thus confirming the complementary predictive value of the sum electrical forces descriptor.

Limitations

Appropriate ICD therapy as a surrogate for sudden death may overestimate the frequency of SCD.[34] This is a well-recognized and unavoidable limitation in the ICD era, as it would be unethical to withhold ICD therapy to study the actual death rate. The use of ICD events as the end point for validation of a risk stratifier is frequently viewed as a weak surrogate for actual mortality. However, as soon as the VT/VF risk stratification guides the decision about whether to

implant an ICD, then a risk marker that predicts the occurrence of successfully manageable by an ICD rhythms seems more appropriate than a marker that predicts events for which ICD placement would be of no benefit. At the same time, recent studies showed that patients after appropriate ICD shocks demonstrated higher mortality.[21]

Statistical power of survival analysis for primary end point (all sustained VA events) and MMVT in this study is good. However, low rate of PVT/VF resulted in low statistical power of survival analysis with PVT/VF end point. The SAI QRST in this study did not predict PVT/VF, but it was highly predictive for MMVT in the primary prevention population of structural heart disease patients. Larger study cohort and longer follow-up are needed for conclusion regarding predictive value of SAI QRST for PVT/VF. At the same time, this preliminary finding may indicate differences in underlying mechanisms of these 2 types of VT and underscores the difficulties in predicting PVT/VF.

Assessment of scar, LV size, and geometry was limited in this study. Further investigation is necessary to determine correlations between SAI QRST and scar size, LV mass, LV hypertrophy and dilatation, and LV volumes.

In summary, SAI QRST is an inexpensive and easily measured at-rest ECG marker for the assessment of VA risk in patients with structural heart disease. High SAI QRST is associated with low risk of sustained VA.

References

1. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009;119:480.
2. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. N Engl J Med 1997;337:1576.
3. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877.
4. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225.
5. Goldenberg I, Vyas AK, Hall WJ, et al. Risk stratification for primary implantation of a cardioverter-defibrillator in patients with ischemic left ventricular dysfunction. J Am Coll Cardiol 2008;51:288.
6. Buxton AE, Lee KL, Hafley GE, et al. Limitations of ejection fraction for prediction of sudden death risk in patients with coronary artery disease: lessons from the MUSTT study. J Am Coll Cardiol 2007;50:1150.
7. Okin PM, Roman MJ, Devereux RB, Borer JS, Kligfield P. Electrocardiographic diagnosis of left ventricular hypertrophy by the time-voltage integral of the QRS complex. J Am Coll Cardiol 1994;23:133.
8. Okin PM, Roman MJ, Devereux RB, Kligfield P. Electrocardiographic identification of increased left ventricular mass by simple voltage-duration products. J Am Coll Cardiol 1995;25:417.
9. Palmeri ST, Harrison DG, Cobb FR, et al. A QRS scoring system for assessing left ventricular function after myocardial infarction. N Engl J Med 1982;306:4.
10. Selvester RH, Wagner GS, Hindman NB. The Selvester QRS scoring system for estimating myocardial infarct size. The development and application of the system. Arch Intern Med 1985;145:1877.

11. Wagner GS, Freye CJ, Palmeri ST, et al. Evaluation of a QRS scoring system for estimating myocardial infarct size. I. Specificity and observer agreement. Circulation 1982;65:342.

12. Wilson FN, Macleod AG, Barker PS, Johnston FD. The determination and the significance of the areas of the ventricular deflections of the electrocardiogram. Am Heart J 1934:46.

13. Kleber AG, Rudy Y. Basic mechanisms of cardiac impulse propagation and associated arrhythmias. Physiol Rev 2004;84:431.

14. Romero L, Trenor B, Alonso JM, Tobon C, Saiz J, Ferrero Jr JM. The relative role of refractoriness and source-sink relationship in reentry generation during simulated acute ischemia. Ann Biomed Eng 2009;37:1560.

15. Han J, Moe GK. Nonuniform recovery of excitability in ventricular muscle. Circ Res 1964;14:44.

16. Allessie MA, Bonke FI, Schopman FJ. Circus movement in rabbit atrial muscle as a mechanism of tachycardia. II. The role of nonuniform recovery of excitability in the occurrence of unidirectional block, as studied with multiple microelectrodes. Circ Res 1976;39:168.

17. Laurita KR, Rosenbaum DS. Interdependence of modulated dispersion and tissue structure in the mechanism of unidirectional block. Circ Res 2000;87:922.

18. Frank E. An accurate, clinically practical system for spatial vectorcardiography. Circulation 1956;13:737.

19. Berger RD, Kasper EK, Baughman KL, Marban E, Calkins H, Tomaselli GF. Beat-to-beat QT interval variability: novel evidence for repolarization lability in ischemic and nonischemic dilated cardiomyopathy. Circulation 1997;96:1557.

20. Gregory WM. Adjusting survival curves for imbalances in prognostic factors. Br J Cancer 1988;58:202.

21. Poole JE, Johnson GW, Hellkamp AS, et al. Prognostic importance of defibrillator shocks in patients with heart failure. N Engl J Med 2008;359:1009.

22. Pepe MS, Janes H, Longton G, Leisenring W, Newcomb P. Limitations of the odds ratio in gauging the performance of a diagnostic, prognostic, or screening marker. Am J Epidemiol 2004;159:882.

23. Wald NJ, Hackshaw AK, Frost CD. When can a risk factor be used as a worthwhile screening test? BMJ 1999;319:1562.

24. Ware JH. The limitations of risk factors as prognostic tools. N Engl J Med 2006;355:2615.

25. Goldberger JJ. Evidence-based analysis of risk factors for sudden cardiac death. Heart Rhythm 2009;6:S2.

26. Burger HC. A theoretical elucidation of the notion ventricular gradient. Am Heart J 1957;53:240.

27. Geselowitz DB. The ventricular gradient revisited: relation to the area under the action potential. IEEE Trans Biomed Eng 1983;30:76.

28. Abildskov JA, Klein RM. Cancellation of electrocardiographic effects during ventricular excitation. Sogo Rinsho 1962;11:247.

29. Burgess MJ, Millar K, Abildskov JA. Cancellation of electrocardiographic effects during ventricular recovery. J Electrocardiol 1969;2:101.

30. Urie PM, Burgess MJ, Lux RL, Wyatt RF, Abildskov JA. The electrocardiographic recognition of cardiac states at high risk of ventricular arrhythmias. An experimental study in dogs. Circ Res 1978; 42:350.

31. Burton FL, Cobbe SM. Dispersion of ventricular repolarization and refractory period. Cardiovasc Res 2001;50:10.

32. Gardner MJ, Montague TJ, Armstrong CS, Horacek BM, Smith ER. Vulnerability to ventricular arrhythmia: assessment by mapping of body surface potential. Circulation 1986;73:684.

33. Buxton AE, Sweeney MO, Wathen MS, et al. QRS duration does not predict occurrence of ventricular tachyarrhythmias in patients with implanted cardioverter-defibrillators. J Am Coll Cardiol 2005; 46:310.

34. Dhar R, Alsheikh-Ali AA, Estes III NA, et al. Association of prolonged QRS duration with ventricular tachyarrhythmias and sudden cardiac death in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II). Heart Rhythm 2008;5:807.

35. DE GM, Thambo JB, Ploux S, et al. Reliability and reproducibility of QRS duration in the selection of candidates for cardiac resynchronization therapy. J Cardiovasc Electrophysiol 2010.

36. Wachtell K, Okin PM, Olsen MH, et al. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive therapy and reduction in sudden cardiac death: the LIFE study. Circulation 2007;116:700.

37. Morin DP, Oikarinen L, Viitasalo M, et al. QRS duration predicts sudden cardiac death in hypertensive patients undergoing intensive medical therapy: the LIFE study. Eur Heart J 2009;30:2908.

38. Okin PM. Serial evaluation of electrocardiographic left ventricular hypertrophy for prediction of risk in hypertensive patients. J Electrocardiol 2009;42:584.

39. Ostman-Smith I, Wisten A, Nylander E, et al. Electrocardiographic amplitudes: a new risk factor for sudden death in hypertrophic cardiomyopathy. Eur Heart J 2010;31:439.