

## Ventricular arrhythmia is predicted by sum absolute QRST integral but not by QRS width

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### Abstract

**Background:** There is a controversy regarding the association between QRS width and ventricular arrhythmias (VAs). We hypothesized that predictive value of the QRS width could be improved if QRS width were considered in the context of the sum magnitude of the absolute QRST integral in 3 orthogonal leads sum absolute QRST integral (SAI QRST). We explored correlations between QRS width, SAI QRST, and VA in primary prevention implantable cardioverter-defibrillator (ICD) patients with structural heart disease.

**Methods:** Baseline orthogonal electrocardiograms were recorded at rest in 355 patients with implanted primary prevention ICDs (mean age,  $59.5 \pm 12.4$  years; 279 male [79%]). Patients were observed prospectively at least 6 months; appropriate ICD therapies because of sustained VA served as end points. The sum magnitude of the absolute QRST integral in 3 orthogonal leads (SAI QRST) was calculated.

**Results:** During a mean follow-up of 18 months, 48 patients had sustained VA and received appropriate ICD therapies. There was no difference in baseline QRS width between patients with and those without arrhythmia ( $114.9 \pm 32.8$  vs  $108.9 \pm 24.7$  milliseconds;  $P = .230$ ). SAI QRST was significantly lower in patients with VA at follow-up than in patients without VA ( $102.6 \pm 27.6$  vs  $112.0 \pm 31.9$  mV·ms;  $P = 0.034$ ). Patients with SAI QRST ( $\leq 145$  mV·ms) had a 3-fold higher risk of ventricular tachycardia (VT)/ventricular fibrillation (VF) (hazard ratio [HR], 3.25; 95% confidence interval [CI], 1.59–6.75;  $P = .001$ ). In the univariate analysis, QRS width did not predict VT/VF. In the bivariate Cox regression model, every 1 millisecond of incremental QRS widening with a simultaneous 1 mV·ms SAI QRST decrease raised the risk of VT/VF by 2% (HR, 1.02; 95% CI, 1.01–1.03;  $P = .005$ ).

**Conclusion:** QRS widening is associated with ventricular tachyarrhythmia only if accompanied by low SAI QRST.

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### Keywords:

Ventricular tachyarrhythmia; QRS; Risk stratification; Implantable cardioverter-defibrillator

### Background

Controversy remains regarding the association between QRS width and sudden cardiac death (SCD). In the early analysis of the Multicenter Automatic Defibrillator Implantation Trial II Multicenter Automatic Defibrillator Implantation Trial (MADIT) II study, a wide QRS of greater than 150 milliseconds was associated with a more

substantial benefit from implantable cardioverter-defibrillator (ICD)<sup>1</sup> than was a narrow QRS of less than 120 milliseconds. Subsequent studies did not confirm the relation between QRS width and ventricular arrhythmia (VA) occurrence in primary and secondary prevention ICD patients with structural heart disease.<sup>2,3</sup> However, QRS width predicted SCD in medically treated MADIT II heart failure patients.<sup>3</sup>

We proposed a novel marker of susceptibility to VA, namely sum absolute QRST integral (SAI QRST), measured as the sum magnitude of the absolute QRST integral on 3 orthogonal electrocardiogram (ECG) leads. To study the predictive value of SAI QRST and to further elucidate

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associations between SAI QRST, QRS width, and VA, we undertook analysis of prospective observational cohort study Prospective Observational Study of the ICD in Sudden Cardiac Death Prevention (PROSE-ICD) patients with structural heart disease and routine indications for primary prevention single-chamber or dual-chamber ICD.

## Methods

All patients gave written informed consent before entering the study. The study protocol was approved by the Johns Hopkins University Institutional Review Board (Baltimore, MD).

### Study population

PROSE-ICD (NCT00733590) is an ongoing prospective observational multicenter cohort study of patients with either ischemic or nonischemic cardiomyopathy, who have routine indications for ICD as primary prevention of SCD. Patients were eligible for the study if the left ventricular ejection fraction (EF) was 35% or less, myocardial infarction was at least 4 weeks old, or nonischemic cardiomyopathy was present for at least 9 months. Patients were excluded if the ICD was indicated for secondary prevention of SCD, if the 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. Consecutive patients with indications for single-chamber or dual-chamber ICD, but not Cardiac Resynchronization Therapy Defibrillator (CRT-D), and followed up for at least 6 months were included in this report.

### Surface ECG recording

Digital orthogonal ECG was recorded before ICD implantation during 5 minutes at rest, using the modified Frank 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 and low-pass filter 350 Hz. QRS width on the clinical 12-lead ECG was measured automatically by the built-in algorithm (Marquette ECG 12SL & MUSE system, GE Healthcare Clinical Systems, Wauwatosa, WI, USA).

### QRST integral measurement

All ECGs were analyzed by customized software in a robust automated fashion. QRS onset and end of T wave were identified by the user (LGT). The first 15 beats were used by the algorithm to construct templates. The user viewed templates of all 3 orthogonal leads, selected the best quality lead (default lead X), and manually defined the onset of the QRS and end of T wave fiducial points. Then, the algorithm measured absolute QRST integral of each beat and calculated the average value for the time epoch. 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), averaged during a 5-minute epoch. The sum

magnitude of 3 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 points 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.

### Statistical analysis

Study participants were categorized according to their baseline SAI QRST value, with SAI QRST of 69 mV·ms or less labeled low, SAI QRST of 70 to 145 mV·ms labeled intermediate, and SAI QRST of greater than 145 mV·ms labeled high. Linear regression analysis was used to study the correlation between SAI QRST and QRS width. Adjusted by QRS width, Kaplan-Meier survival curves were constructed for subjects with low, intermediate, or high SAI QRST. The log-rank (Mantel-Cox) and Tarone-Ware statistics were computed to test the equality of survival distributions. Univariate, bivariate, and multivariate Cox proportional hazards regression analyses were performed. An interaction between SAI QRST and QRS duration was tested in the Cox model. STATA 10 software (StataCorp LP, College Station, TX) was used for calculations.

## Results

### Patient population

Baseline clinical characteristics of patients are presented in Table 1. Study participants (n = 355) were predominantly males with ischemic cardiomyopathy, heart failure NYHA classes II to III, and narrow QRS about 110 milliseconds at baseline. There were no statistically significant differences between baseline clinical and ECG characteristics of patients with low, intermediate, and high SAI QRST, with the exception of QRS duration. QRS was incrementally wider in

Table 1  
Clinical and baseline ECG characteristics of patients

Characteristic	n = 355
Age $\pm$ SD, y	59.5 $\pm$ 12.4
Male sex, n (%)	279 (78.6)
Whites, n (%)	238 (67.0)
Ischemic cardiomyopathy, n (%)	220 (62.0)
Baseline left ventricular EF $\pm$ SD, %	22.96 $\pm$ 9.19
QRS, ms	109.79 $\pm$ 26.04
Left ventricular diastolic diameter $\pm$ SD, cm	5.87 $\pm$ 0.93
Body mass index $\pm$ SD	28.67 $\pm$ 6.00
Beta blockers, n (%)	336 (94.6)
NYHA class I, n (%)	78 (22.0)
NYHA class II, n (%)	110 (31.0)
NYHA class III, n (%)	167 (47.0)
Inducible VT, n (%)	92 (25.9)
Heart rate $\pm$ SD, beats per minute	72.6 $\pm$ 14.3

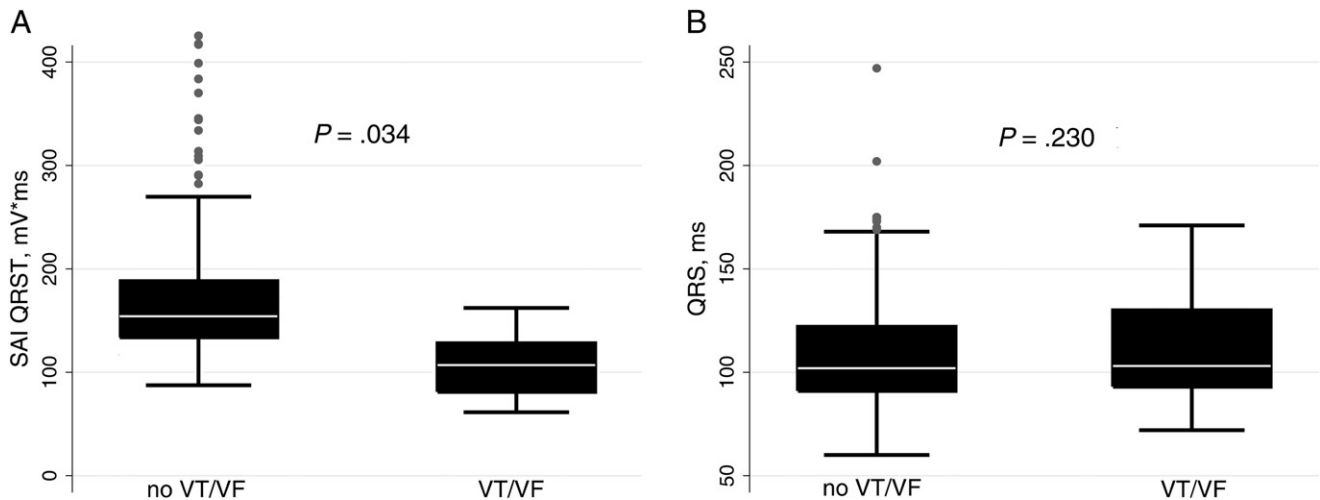


Fig. 1. Boxplot of baseline SAI QRST and QRS width in patients with and without VT/VF at follow-up. Median (white horizontal line crossing the box) and interquartile range (IQR) (box) of SAI QRST (A) and QRS width (B). Whiskers specify the adjacent values, defined as the most extreme values within 1.5 IQR of the nearer quartile.

patients with low, intermediate, and high SAI QRST ( $99.8 \pm 18.0$  vs  $111.2 \pm 24.3$  vs  $138.9 \pm 30.9$  milliseconds; analysis of variance  $P < .0001$ ). During a mean follow-up of  $18.0 \pm 16.5$  months, 48 of 355 patients (13.5% or 9.0% per person-year of follow-up) experienced sustained ventricular tachycardia (VTs) and received appropriate ICD therapies. Monomorphic VT with an average cycle length (CL) of  $294 \pm 40$  milliseconds was present in 31 patients (63%). Polymorphic VT (CL,  $228 \pm 18$  milliseconds) or ventricular fibrillation (VF) (CL,  $194 \pm 24$  milliseconds) was documented in 17 patients (27%).

#### SAI QRST and QRS width

SAI QRST was significantly lower in patients with VA at follow-up than in patients without VA ( $102.6 \pm 27.6$  vs  $112.0 \pm 31.9$  mV·ms;  $P = .034$ ) (Fig. 1A). There was no difference in baseline QRS width between patients with and those without arrhythmia ( $114.9 \pm 32.8$  vs  $108.9 \pm 24.7$  ms;  $P = .230$ ) (Fig. 1B).

SAI QRST was regressed on QRS width, heart rate, and QT duration. These 3 predictors accounted for approximately one third of the variance in SAI QRST ( $R^2 = 0.29$ ;  $P < .0001$ ). QRS width was the most influential predictor of the SAI QRST variance ( $\beta = 1.12$ ;  $P < .0001$ ), followed by heart rate ( $\beta = -0.56$ ;  $P = .025$ ). For every 1 millisecond increase of QRS width, SAI QRST increased by 3 mV·ms. In bivariate linear regression analysis, QRS width accounted for 27% of the variance in SAI QRST value ( $R^2 = 0.27$ ;  $P < .0001$ ), heart rate alone accounted for 3% of the variance in SAI QRST value ( $R^2 = 0.03$ ;  $P = .002$ ), and QT duration alone accounted for 5% of the variance in SAI QRST value ( $R^2 = 0.05$ ;  $P < .0001$ ). Plot of linear regression of SAI QRST on QRS width is presented in Fig. 2.

#### Survival analysis

Patients with low and intermediate SAI QRST ( $\leq 145$  mV·ms) had a 3-fold higher risk of VT/VF (hazard ratio

[HR], 3.25; 95% confidence interval [CI], 1.59–6.75;  $P = .001$ ). In the univariate survival analysis, QRS width did not predict VA. Because the QRS width was different among SAI QRST groups, we adjusted our multivariate model of VT/VF prediction by QRS width. Kaplan-Meier survival analysis showed that the SAI QRST adjusted by QRS width above or below 124 ms was significantly predictive for freedom from VT/VF during follow-up (log-rank test,  $P = .0001$ ) (Fig. 3). To adjust our model for a different sample size at different times of follow-up, we also performed a weighted-by-sample-size Tarone-Ware test of equality of survival functions. The Tarone-Ware test confirmed a significant difference between the survival functions ( $P = .0007$ ). Cox regression analysis found no significant interaction between SAI QRST and QRS width, implying a similar predictive value of SAI QRST across any QRS width.

Several variables were tested in the univariate Cox models as potential predictors of VA, including EF, NYHA class, left

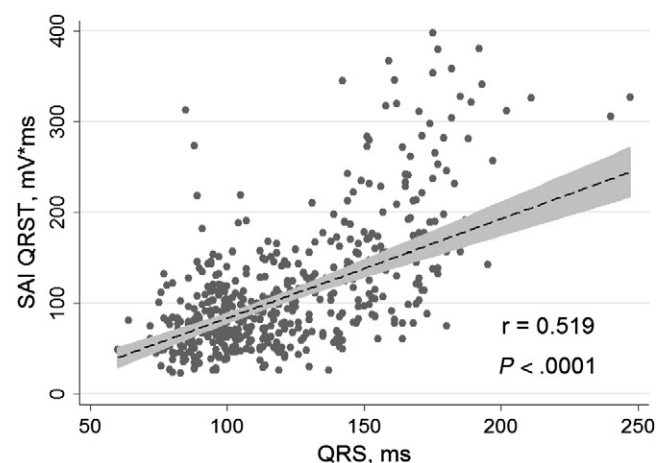


Fig. 2. Correlation between QRS width and SAI QRST. Linear regression fitted line of SAI QRST on QRS width (dashed line) with 95% CI (gray zone).

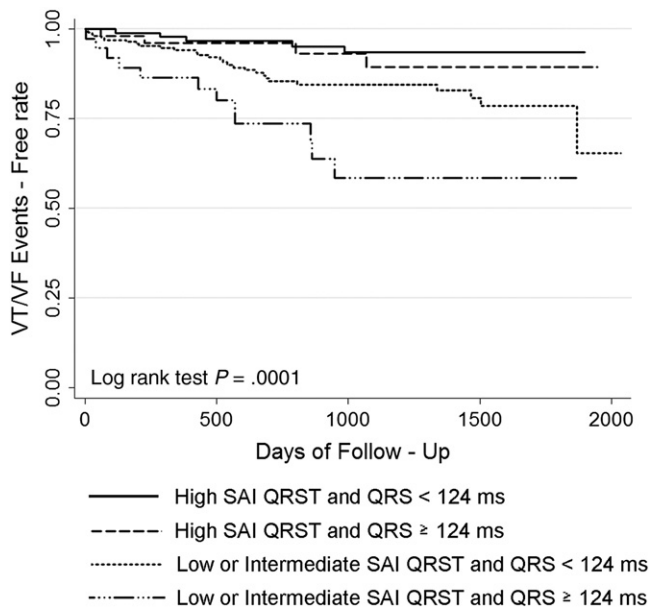


Fig. 3. Kaplan-Meier curves for freedom from VA events in patients with low, intermediate, and high SAI QRST, adjusted by QRS width.

ventricular diastolic diameter, use of medications ( $\beta$ -blockers, statins, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, aldosterone antagonists), age, sex, race, diabetes mellitus, type of cardiomyopathy, QRS width, QT duration, and heart rate. However, only use of  $\beta$ -blockers and SAI QRST in the univariate Cox regression were significant predictors of VA, and QRS width of 124 milliseconds or greater was borderline significant ( $P = .071$ ). In our final multivariate model, we included predictors that were significant in the univariate analysis (SAI QRST, QRS, use of  $\beta$ -blockers) and type of cardiomyopathy as a clinically important variable. In the multivariate Cox regression analysis, SAI QRST  $\leq 145$  mV·ms remained a significant predictor of freedom from VA after adjustment for QRS width, type of cardiomyopathy, and use of  $\beta$ -blockers (HR, 4.06; 95% CI, 1.91–8.65;  $P < 0.0001$ ). QRS width of 124 milliseconds or greater was a significant predictor of VA events in this multivariate Cox regression model, too (HR, 2.58; 95% CI, 1.37–4.86;  $P = .003$ ). In the bivariate Cox regression model, every 1 millisecond of incremental QRS widening with simultaneous 1 mV·ms SAI QRST decrease raised the risk of VA by 2% (HR, 1.02; 95% CI, 1.01–1.03;  $P = .005$ ).

SAI QRST of  $\leq 145$  mV·ms predicted VA with 82% sensitivity, 41% specificity, 14% positive predictive value, and 95% negative predictive value. Combined marker (SAI QRST  $\leq 145$  mV·ms and QRS  $\geq 124$  milliseconds) demonstrated 25% sensitivity, 90% specificity, 28% positive predictive value, and 88% negative predictive value for prediction of sustained VA with appropriate ICD therapies.

## Discussion

The major finding of our study is that QRS width is associated with ventricular tachyarrhythmia only if accompanied by low SAI QRST.

## Controversy around association of QRS duration with ventricular tachyarrhythmia

Several early studies of medically treated heart failure patients demonstrated that wide QRS is associated with increased all-cause mortality in heart failure patients,<sup>4</sup> including an association between the QRS width and SCD.<sup>5–7</sup> Consistently, several major ICD trials, including Multicenter Unsustained Tachycardia Trial (MUSTT), MADIT II, and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), showed the predictive value of QRS duration for all-cause mortality, SCD, and appropriate ICD shocks.<sup>6,8,9</sup> Retrospective analysis of both primary and secondary prevention ICD patients also revealed that QRS duration of 100 ms or greater predicted appropriate ICD therapies during long-term follow-up.<sup>10</sup> A recent prospective study of ICD patients showed that QRS duration of 100 milliseconds predicted appropriate ICD shocks.<sup>11</sup> However, a large prospective The Pacing Fast VT Reduces Shock Therapies trial (PainFREE Rx II) study did not confirm predictive value of QRS duration for occurrence of VTs.<sup>2</sup> Moreover, it showed that patients with left bundle branch block were less likely to experience sustained VT/VF than patients with narrow QRS of less than 120 milliseconds. Subsequent post hoc analysis of MADIT-II data<sup>3</sup> demonstrated that prolonged QRS of 140 milliseconds or greater did not predict appropriate ICD therapy for rapid VT/VF in the ICD-treated arm but did predict SCD in medically treated patients. This finding has become an important argument supporting the opinion that appropriate ICD therapy is not equivalent to SCD. Nonequivalence of SCD and ICD therapies cannot be tested in a randomized clinical trial for ethical reasons. Nonetheless, results of our study provide new data that suggest another possible explanation of the MADIT II findings.<sup>3</sup> In our study, prolonged QRS did not predict appropriate ICD therapy in univariate analysis, a finding consistent with the results of the PainFREE Rx II and MADIT II studies. However, bivariate Cox regression analysis showed that QRS width predicts VT/VF if it is accompanied by low SAI QRST. We revealed that every 1 millisecond of incremental QRS widening with a simultaneous 1 mV·ms SAI QRST decrease raised the risk of VT/VF by 2%. Patients with subsequent VT/VF were notably different in this regard, whereas in patients without arrhythmia, every 1 millisecond of incremental QRS widening was accompanied by a simultaneous 3 mV·ms SAI QRST increase.

## SAI QRST—novel predictor of ventricular tachyarrhythmia

In this article, we describe a novel marker of low VA risk—SAI QRST. Our study showed high 95% negative predictive value of this novel marker along with 82% sensitivity in predicting VA risk. The idea of our new metric arose from analysis of early works by Wilson et al<sup>12</sup> who proposed to calculate the time integral of the heart vector.<sup>13</sup> Further studies showed that the QRST integral expresses the heterogeneity of the action potential morphology.<sup>14</sup> It is important to emphasize, however, that our metric SAI QRST differs from the native QRST integral proposed by Wilson. First, we calculated sum absolute QRST integral to adjust

our analysis to the modern requirements dictated by acquired filtered ECG signal. Doing so gave our metric the added benefit of less dependence on a precise definition of the isoelectric baseline position. Second, we used the advantages provided by orthogonal ECG leads, which permit assessment of the heart vector. Summation of absolute QRST integral of all 3 orthogonal ECG leads measures the magnitude of total cardiac electrical power and eliminates the bias of a single lead axis position. We speculate that the SAI QRST characterizes significant cancellation of forces as an important preexisting condition that may facilitate sustained VA. Previous experiments showed that action potential gradients in different sites of the heart may have opposing directions and cancel out.<sup>15–17</sup> Modeling studies showed that sum QRST integral was decreased if various values of action potential durations (APDs) were randomly assigned in the model to mimic APD heterogeneity in the heart.<sup>18</sup> Importantly, random APD assignment made the model more susceptible to VF initiation. We speculate that decrease in the sum QRST integral (SAI QRST) due to cancellation of electrical forces coexists with the locally observed increase in APD gradients, as marker of a heterogeneity of repolarization or heterogeneity of action potential morphology, as shown previously.<sup>19,20</sup> However, the precise electrophysiological meaning of SAI QRST remains to be elucidated.

#### *Associations between SAI QRST, QRS width, and ventricular tachyarrhythmia*

Patients included in this analysis predominantly had normal QRS width, as only patients with indications for ICD, but not CRT-D, were included in this analysis. The fact that very few patients had bundle branch block limited assessment of the predictive value of ventricular conduction abnormalities in this work. Previous studies showed that higher mortality, suggesting higher SCD rate, is associated with left bundle branch block and intraventricular conduction delay but not with right bundle branch block.<sup>6,21</sup> However, a direct association between electrocardiographic conduction abnormalities as measured by QRS width and the development of VA in patients with structural heart disease has not been reported before. We believe that our results support this important association and underscore the fact that QRS width is not the perfect measure of conduction abnormalities. Indeed, the complex assessment provided by SAI QRST revealed links between intraventricular conduction, heterogeneity of ventricular action potential, and VA in the case of low SAI QRST.

It is important to emphasize that we did not study SAI QRST in a normal healthy population, and the range of SAI QRST values in healthy subjects is unknown at present. Results of our study should be interpreted carefully in populations other than patients with structural heart disease and systolic dysfunction ( $EF \leq 35\%$ ).

#### **Conclusion**

SAI QRST is a novel 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. QRS widening is associated with ventricular tachyarrhythmia only if accompanied by low SAI QRST.

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