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Usefulness of the Sum Absolute QRST Integral to Predict Outcomes in Patients Receiving Cardiac Resynchronization Therapy

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Abstract

Cardiac resynchronization therapy (CRT) reduces mortality and morbidity in selected heart failure (HF) patients, but up to one-third of patients are non-responders. Sum absolute QRST integral (SAI QRST) recently showed association with mechanical response on CRT. However, it is unknown whether SAI QRST is associated with all-cause mortality and HF hospitalizations in CRT patients. The study population included 496 patients undergoing CRT (mean age 69±10 years, 84% male, 65% left bundle branch block (LBBB), left ventricular ejection fraction 23±6%, 63% ischemic cardiomyopathy). Pre-implant digital 12-lead ECG was transformed into orthogonal XYZ ECG. SAI QRST was measured as an arithmetic sum of areas under the QRST curve on XYZ leads, and was dichotomized based on the median value (302mV*ms). All-cause mortality served as the primary endpoint. A composite of 2-year all-cause mortality, heart transplant, and HF hospitalization was a secondary endpoint. Cox regression models were adjusted for known predictors of CRT response. Patients with pre-implant low mean SAI QRST had an increased risk of both the primary (HR 1.8; 95%CI 1.01–3.2) and secondary (HR 1.6, 95% CI 1.1–2.2) endpoints following multivariable adjustment. SAI QRST was associated with secondary outcome in subgroups of patients with LBBB (HR 2.1 [95%CI 1.5-3.0]) and with non-LBBB (HR 1.7, [95%CI 1.0-2.6]). In patients undergoing CRT, pre-implant SAI QRST<302mV*ms was associated with an increased risk of all-cause mortality and HF hospitalization. After validation in another prospective cohort, SAI QRST may help to refine selection of CRT recipients.

Keywords

Cardiac resynchronization therapy; electrocardiology; heart failure; mortality

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Cardiac resynchronization therapy (CRT) is an established treatment for patients with systolic heart failure (HF) and electrical dyssynchrony¹. Despite established benefits, approximately one-third of patients demonstrates a lack of response following CRT, framing the continued need to refine selection for this beneficial but nonetheless costly therapy.

In keeping with the expected benefit of reversing electrical dyssynchrony and delayed activation of the lateral LV wall, there has been increasing interest in identifying electrical markers of dyssynchrony as predictors of outcome in patients undergoing CRT. For example, contemporary data have suggested that the benefits of CRT accrue primarily to patients with significantly (>150ms) prolonged QRS duration^{2–4} and those with a left bundle branch block (LBBB) morphology.^{3,5} In addition to these standard measures of electrical conduction (QRS duration and morphology), sum absolute QRST integral (SAI QRST)^{6–10} was recently shown to be associated with LV reverse remodelling in patients undergoing CRT¹¹. Analysis of SMART-AV clinical trial data showed that high pre-CRT SAI QRST has been associated with a higher likelihood of mechanical response (measured as a reduction in left ventricular end-systolic volume (LVESV) 6 months post-CRT), whereas low baseline SAI QRST values has predicted mechanical non-response¹¹. However, it remained unknown whether pre-CRT SAI QRST can predict clinical outcomes (mortality and HF hospitalizations). We, therefore, conducted retrospective cohort study and hypothesized that a low SAI QRST would be associated with an increased risk of adverse clinical outcomes. In addition, given the established use of standard ECG markers in predicting response to CRT, we also examined the prognostic value of SAI QRST in pre-specified subgroups defined by QRS duration and BBB morphology.

Methods

We conducted a retrospective cohort study and included consecutive patients receiving CRT implants (CRT-D or CRT-P) from 1999 through 2012 at a large volume tertiary care centre in Sweden. Inclusion criteria were HF with dilated or ischemic cardiomyopathy, optimal pharmacologic HF treatment and QRS duration ≥ 120 ms, meeting standard guideline-criteria for CRT implantation.^{12–14} All baseline data were gathered from an individual assessment of medical records by the same investigators (JJ and CR). Ischemic cardiomyopathy was diagnosed if there was a history of myocardial infarction or coronary revascularization or if the patient had verified coronary artery disease and the clinical evaluation had indicated ischemic cardiomyopathy. Patients with “non-standard” CRT indication or with failed CRT implant were excluded, as were patients without available digital baseline (pre-implant) ECG. The study complies with the Declaration of Helsinki, and was approved by the local ethics committee.

A 12-lead ECG was collected before CRT device implantation in all individuals and stored digitally in the hospital ECG database. Digital ECG data was exported from the local MUSE database (GE health care, UK) in xml. file format. All ECG files were de-identified and sent to an independent core-lab for analysis. ECG analysis was performed by investigators (EG, MK and LGT) blinded to the study outcomes and the patients' clinical characteristics. Customized Matlab (MathWorks, Inc, Natick, MA) software was used, and the digitized 12-lead ECG signal was transformed into three-dimensional orthogonal XYZ ECG by using an

inverse Dower transformation matrix (Figure 1).¹⁵ The median beat was used for analysis. The absolute value of the area under the entire QRST waveform was calculated for each orthogonal lead (X, Y, and Z). Absolute QRST integral values on X, Y, and Z leads were then added together to obtain averaged SAI QRST^{7–10}

The primary outcome was an all-cause mortality. A composite end-point of all-cause death, heart transplant, or HF hospitalization, whichever came first, served as a secondary endpoint. Endpoints were extracted from a review of the medical record with cross-validation utilizing the Swedish Pacemaker Registry and the Swedish Death and Hospital Discharge Registries.

Continuous variables were reported as mean $\pm$ standard deviation (SD) unless otherwise specified. The SAI QRST variable was dichotomized using the median value. The Pearson chi-square test or Fisher's exact test were used to compare categorical variables, as appropriate. Unadjusted Kaplan-Meier survival analysis was used. The log-rank statistic was computed to test the equality of survival distributions in participants with SAI QRST above and below the median value. Multivariable Cox regression analysis was performed to determine the association of SAI QRST with outcomes, after adjustment for clinically relevant confounders, which associated with outcome in univariable analysis at P -value <0.2 . Association of SAI QRST with outcomes was tested in the subgroups of participants with LBBB vs. non-LBBB; and patients with QRS duration ≥ 150 ms vs. and <150 ms. A P -value of <0.05 was considered statistically significant. SPSS 22.0 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp) was used for data analysis.

Results

Of 705 eligible CRT implanted patients, 496 had a digital ECG stored prior to the procedure, and these patients were included in the study. About two thirds of study population received CRT-P, and only one third – CRT-D devices. The median SAI QRST value was 302mV*ms. The baseline characteristics of the study population, stratified by median SAI QRST shown in Table 1. Patients with SAI QRST below the median were more likely to have ischemic cardiomyopathy, an atypical intraventricular conduction block on ECG, diabetes and a narrower QRS duration pre-implant.

During the 2 year follow-up period there were 113 deaths (68 in the low SAI QRST group and 40 in the high SAI QRST group), 5 heart transplants (4 and 1 respectively), and 226 patients experienced the combined endpoint of death, heart transplant or HF hospitalization (140 and 86 respectively).

In unadjusted Kaplan Meier analysis, SAI QRST was associated with the primary and secondary outcomes (Figure 2). In univariable Cox regression analysis (Table 2), SAI QRST below 302 mV*ms was associated with about twice higher mortality. After adjustment for age, sex, type of cardiomyopathy, NYHA class, QRS duration and morphology, presence of atrial fibrillation, comorbidities (creatinine, diabetes), HF medical management (diuretics, ACEi/ARBs), and type of CRT (with or without defibrillator), the association attenuated only slightly.

Similarly, a SAI QRST below 302 mV*ms was associated with 70% higher risk of the composite HF outcome (Table 3). The association between SAI QRST and secondary outcome persisted after multivariable adjustment (Table 3) including age, type of cardiomyopathy, QRS duration and conduction abnormality (LBBB vs. non-LBBB), HF severity (LVEF and NYHA class), comorbidities (diabetes, atrial fibrillation, creatinine level), HF medical management (use of angiotensin-converting enzyme inhibitor (ACEi), angiotensin II receptor blocker (ARB), and diuretics), and type of CRT (CRT-P vs CRT-D).

Given the established role of BBB morphology and QRS duration in identifying patients with electrical dyssynchrony likely to respond to CRT, we performed pre-specified subgroup analysis examining the association of SAI QRST and clinical outcome in patients stratified by the presence or absence of a LBBB and by QRS duration of more or less than 150ms.

When stratified by BBB morphology, a low SAI QRST remained significantly associated with worse clinical outcomes for patients with and without a LBBB (Figure 3 A and B). SAI QRST remained significantly predictive of the clinical outcomes even after adjustment for standard predictors of CRT response (age, sex, etiology of cardiomyopathy) in patients with LBBB (HR 2.1, 95% CI: 1.5-3.0, $p<0.001$) and with non-LBBB (HR 1.7, 95% CI: 1.0-2.6, $p=0.04$).

When looking at different subgroups of QRS duration - as expected - high SAI QRST values were much more common in patients with QRS ≥ 150 ms (Table 4). However, within the subgroup with QRS ≥ 150 ms (class I indication for CRT), almost half of all patients still had low SAI QRST values, likely indicative of modest dyssynchrony, regardless of BBB morphology (Table 4). There was no significant interaction between dichotomized SAI QRST and dichotomized at 150ms QRS duration ($P_{\text{interaction}}=0.09$). In the subgroup of patients with QRS ≥ 150 ms, in unadjusted Cox regression analysis, low SAI QRS was associated with a two-fold increased hazard of the composite HF endpoint (HR 2.0, [95% C.I. 1.5–2.8]). After adjustment for the same covariates as in Table 2, an association strengthened (HR 2.5 [95%CI 1.5–4.2]; $P<0.001$). In the subgroup of patients with QRS <150 ms the association was non-significant (unadjusted HR 1.1 [95% C. I. 0.6–2.1]).

Discussion

The main finding of this study is that in patients undergoing CRT, a simple ECG measure SAI QRST is predictive of clinical outcomes: all-cause mortality and HF hospitalizations. Patients with SAI QRST <302 mV*ms were at 60–70% increased risk of the death and composite HF endpoint (all-cause mortality, heart transplant or HF hospitalization), compared to patients with SAI QRST ≥ 302 mV*ms. Of note, the relationships between SAI QRST and clinical outcomes persisted even after comprehensive adjustment for demographic characteristics (age, sex), known predictors of CRT response (QRS duration and morphology, type of cardiomyopathy), HF severity (NYHA class and LVEF), comorbidities (diabetes, stroke, atrial fibrillation, level of creatinine), HF medical management (diuretics, ACEI/ARBs), and type of CRT.

In non-invasive electrocardiographic imaging study SAI QRST correlated with electrical dyssynchrony index, measured as a standard deviation of ventricular activation times on the epicardium⁶. Therefore, we assume that SAI QRST reflects electrical dyssynchrony. The results of our present study are consistent with the previous results of the SMART-AV trial, which showed that SAI QRST predicted echocardiographic non-response¹¹.

Large SAI QRST signifies the presence of a large late-activated area of the left ventricle (LV)⁶, which increases chances of successful LV lead placement without any guidance (as in this study). If the late-activated area of LV is large, pacing from any location within this large late-activated area (except the adjacent scar) is beneficial. In contrast, patients with relatively small SAI QRST (<302 mV*ms in this study) have relatively small late-activated LV area. Attaining CRT response in patients with small SAI QRST would require guided approach of LV lead placement, and decreases chances of accidental success.

Presently, consensus guidelines have utilized both LBBB and QRS duration > 150 msec as electrical markers of dyssynchrony which favour response to CRT.^{16,17} However, our study showed that in the subgroup of patients with QRS duration >150 msec a low SAI QRST continued to demonstrate a significant association with worse clinical outcome. Our results are concordant with a smaller study of 81 patients, where three-dimensional QRS-area was larger in echocardiographic responders than in non-responders and was a stronger predictor than both strict LBBB-criteria and QRS duration alone.¹⁸

Given the delayed activation of the lateral/posterolateral LV in patients with a LBBB, it is unsurprising that patients with LBBB generally derive greater benefit following CRT⁵. Those with a wide QRS >120ms and non-specific intraventricular conduction delay (IVCD) are a heterogeneous group, where results generally are less favourable.^{19,20} In addition, myocardial scar may influence LV activation pattern and response to CRT. In that context, SAI QRST may represent a particularly appealing and integrative barometer of dyssynchrony. In this study, SAI QRST was prognostic in both the LBBB and non-LBBB subgroups making it potentially useful to 'real-world' population of CRT candidates. Future prospective studies are warranted to evaluate predictive value of SAI QRST for mechanical response and clinical outcomes.

Several limitations of our study must be considered. While we adjusted our analyses for possible confounders of CRT response, it is possible that residual confounding influenced our results. Data on the percentage of pacing after implant was not available, and, therefore, we were not able to adjust for this important confounder of CRT outcomes. However, we adjusted our analyses for the presence of atrial fibrillation as a main contributor to the successful CRT delivery. Data of LV lead position were not available for analysis, and therefore, we were not able to evaluate possible interaction between the LV lead position and scar location in patients with ischemic cardiomyopathy. Due to retrospective nature of our study we were unable to assess the association between SAI QRST and mechanical response on CRT. However, such association was recently demonstrated in SMART-AV trial¹¹.

It is important to highlight the strengths of our study. This is a very large cohort of about 500 CRT patients. Importantly, about two thirds of study population received CRT-P, and only

one third – CRT-D, which permitted adjustment for the type of CRT device. Furthermore, detailed information was available on the use of HF medications, which allowed evaluation and adjustment for the specifics of best medical therapy.

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Figure 1. Measurement of sum absolute QRST integral. A. Twelve lead ECG median beat is taken into analysis. B. Dower transformation is performed and orthogonal XYZ ECG waveform is obtained. Absolute area under the QRST curve (from the onset of QRS to the offset of T wave) is measured separately on X, Y, and Z leads (grey colour areas) and summed all together ($X + Y + Z$). Panel A and C show a patient with QRS duration 160ms and low SAI QRST and panel B and D show a patient with similar QRS duration but high SAI QRST.

Figure 2.

Kaplan Meier curves for the freedom from (A) composite heart failure endpoint (all-cause death, HF hospitalization, or heart transplant), and (B) all-cause mortality in patients with SAI QRST above and below median value of 302mV*ms.

Figure 3.

Kaplan Meier curves for the freedom from the composite HF endpoint in patients with SAI QRST above and below median value of 302mV*ms in the subgroups: with LBBB (A) and non-LBBB (B), and with QRS ≥ 150 ms (C) and QRS<150ms (D).

Table 1

Baseline characteristics of study participants with SAI QRST above and below median value

Variable	All patients n=496	SAI QRST (mV*ms)		P-value
		<302 (n=249)	302 (n=247)	
Age at implant (years)	69±10	69±10	70±10	0.14
Women	16%	14%	17%	0.39
Ischemic cardiomyopathy	63%	72%	53%	<0.001
Left Ventricular Ejection Fraction (%)	23±6	24±6	23±7	0.16
QRS duration (ms)	169±28	158±24	180±27	<0.001
Electrocardiographic morphology				
Left bundle branch block	65%	61%	69%	0.06
Right bundle branch block	2%	1%	2%	0.34
Intraventricular conduction delay	13%	20%	5%	<0.001
Paced QRS	20%	17%	24%	0.07
NYHA class (mean±SD)	2.9±0.5	2.9±0.5	2.9±0.5	0.28
S-Creatinine (mg/dL)	1.32±0.51	1.35±0.55	1.29±0.47	0.27
Hypertension	38%	36%	41%	0.31
Diabetes mellitus	35%	42%	28%	0.001
History of atrial fibrillation	49%	51%	48%	0.47
Previous stroke / TIA	11%	10%	11%	0.48
Loop diuretic treatment	91%	91%	91%	1
Beta-blocker	84%	81%	86%	0.27
ACEi/ARB	93%	94%	92%	0.72
Upgrade from previous PM/ICD	20%	17%	24%	0.09
Cardiac resynchronization therapy defibrillator	35%	39%	31%	0.09

TIA=transient ischemic attack, ACEi=angiotensin converting enzyme inhibitor, ARB=angiotensin II receptor blocker, NYHA=New York Heart Association classification of heart failure, PM=pacemaker, ICD=implantable defibrillator, SAI QRST=sum absolute QRST integral.

Table 2

Association of the dichotomized SAI QRST with the all-cause mortality.

Variable	Univariable Cox regression			Multivariable Cox regression		
	HR	95 CI	P-value	HR	95 CI	P-value
Age at implant (years)	1.04	1.02–1.07	<0.001	1.03	0.99–1.06	0.09
Ischemic cardiomyopathy	12.2	1.4–3.4	0.001	1.4	0.71–2.7	0.33
Women	0.61	0.34–1.1	0.11			
LVEF (%)	0.99	0.97–1.0	0.63			
QRS duration (ms)	0.99	0.99–1.0	0.17			
Left bundle branch block	0.75	0.51–1.1	0.13			
NYHA class	2.6	1.7–3.9	<0.001	2.4	1.4–4.1	0.01
S-Creatinine (mg/dL)	2.0	1.5–2.6	<0.001	1.3	0.92–1.8	0.15
Diabetes mellitus	11.4	0.95–2.0	0.09			
Atrial fibrillation	1.6	1.1–2.4	0.01	0.88	0.51–1.5	0.65
Previous stroke / TIA	2.3	0.76–2.2	0.35			
Loop diuretic treatment	2.2	0.90–5.4	0.09			
Beta-blocker	0.75	0.47–1.2	0.23			
ACEi/ARB	0.31	0.18–0.52	<0.001	0.37	0.18–0.75	0.006
Cardiac resynchronization therapy defibrillator	0.58	0.38–0.90	0.01	0.82	0.45–1.5	0.52
<i>SAI QRST < 302 mV*ms</i>	1.9	1.3–2.8	0.001	1.8	1.0–3.2	0.048

TIA= transient ischemic attack, ACEi= angiotensin converting enzyme inhibitor, ARB=angiotensin II receptor blocker, NYHA=New York Heart Association classification of heart failure, SAI QRST = sum absolute QRST integral.

Table 3

Association of the dichotomized SAI QRST with composite HF endpoint.

Variable	Univariable Cox regression			Multivariable Cox regression		
	HR	95 CI	P-value	HR	95 CI	P-value
Age at implant (years)	1.01	1.0–1.02	0.16	1.02	0.99–1.0	0.11
Ischemic cardiomyopathy	1.6	1.2–2.1	0.002	1.1	0.78–1.6	0.56
Women	1	0.74–1.5	0.78			
Left ventricular ejection fraction (%)	0.98	0.96–1.0	0.09	0.97	0.95–1.0	0.03
QRS duration (ms)	0.99	0.99–1.0	0.01	0.998	0.99–1.0	0.54
Left bundle branch block	0.79	0.61–1.0	0.08	0.928	0.62–1.4	0.715
NYHA class	2.4	1.7–3.3	<0.001	1.6	1.2–2.2	0.003
S-Creatinine (mg/dL)	1.5	1.2–1.9	0.001	1.3	1.00–1.7	0.047
Diabetes mellitus	1.3	1.0–1.7	0.03	1.3	0.97–1.8	0.08
Atrial fibrillation	1.3	1.0–1.7	0.02	1.1	0.82–1.5	0.46
Previous stroke / TIA	1.1	0.77–1.7	0.51			
Loop diuretic treatment	2.3	1.2–4.1	0.009	2.2	1.2–4.3	0.02
Beta-blocker	0.73	0.53–1.0	0.064			
ACEi/ARB	0.65	0.41–1.0	0.07	0.75	0.41–1.4	0.36
Cardiac resynchronization therapy defibrillator	0.88	0.67–1.21	0.36	1.02	0.99–1.0	0.11
<i>SAI QRST < 302 mV*ms</i>	<i>1.70</i>	<i>1.4–2.1</i>	<i>< 0.001</i>	<i>1.60</i>	<i>1.1–2.20</i>	<i>0.01</i>

TIA= transient ischemic attack, ACEi= angiotensin converting enzyme inhibitor, ARB=angiotensin II receptor blocker, NYHA=New York Heart Association classification of heart failure, SAI QRST = summed absolute QRST integral.

Table 4

Clinically important study subgroups

N=496	QRS width <150ms		QRS width ≥150ms	
	LBBB	Non-LBBB	LBBB	Non-LBBB
SAI QRST <302mV*ms	56 (80%)	34 (89%)	95 (38%)	64 (47%)
SAI QRST ≥302mV*ms	14 (20%)	4 (11%)	156 (62%)	73 (53%)

LBBB=left bundle branch block, SAI QRST=summed absolute QRST integral.