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Dynamic Changes in High Sensitivity Cardiac Troponin I are Associated with Dynamic Changes in Sum Absolute QRST Integral on Surface Electrocardiogram in Acute Decompensated Heart Failure

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Abstract

Background—A three-dimensional ECG metric, the sum absolute QRST integral (SAI QRST), predicts ventricular arrhythmias in heart failure (HF) patients with implantable cardioverter defibrillator, and mechanical response to cardiac resynchronization therapy. We hypothesized that there is an association between patient-specific changes in SAI QRST and myocardial injury as measured by high-sensitivity troponin I (hsTnI).

Methods—SAI QRST on resting 12-lead ECG, and hsTnI were measured simultaneously, every 3 hours, during 12-hour observation period in a prospective cohort of emergency department patients (n=398; mean age 57.8±13.2y; 54% female, 64% black), diagnosed with acute coronary syndrome (ACS, n=28), acutely decompensated HF (ADHF, n=35), cardiac non-ACS (n=19), or non-cardiac condition (n=316). Random-effects linear regression analysis assessed the association of SAI QRST and myocardial injury, with adjustment for demographics (age, sex, race), prevalent cardiovascular disease (myocardial infarction, history of revascularization, stroke, HF), risk factors (diabetes, smoking, hypercholesterolemia, hypertension, cocaine use), and left bundle branch block.

Results—Within the entire cohort, SAI QRST decreased by 3(95%CI -5 to -1) mV*ms every 3 hours. A 10-fold increase in hsTnI was associated with a 7.7(0.6-14.9) mV*ms increase in SAI QRST. In the subgroup of acutely decompensated HF patients (n=35) a 10-fold increase in hsTnI was associated with a 61.0(5.9-116.1) mV*ms increase in SAI QRST.

Conclusion— Patient-specific time-varying changes in the surface ECG scalar measure of global electrical heterogeneity, as measured by SAI QRST, and in myocardial injury as measured by hsTnI, are independently and directly associated with each other, likely reflecting a common underlying mechanism.

Key words: Acute heart failure, high sensitivity troponin, electrocardiogram, remodeling.

Heart failure (HF) is a debilitating condition that is associated with high morbidity, mortality, and healthcare resource utilization[1]. HF is associated with a substantial risk of ventricular arrhythmias and sudden cardiac death (SCD)[2]. Accurate risk stratification is essential for appropriate clinical management of HF patients. An electrocardiographic (ECG) measure of global electrical heterogeneity and electrical remodeling, the sum absolute QRST integral (SAI QRST), which can be easily derived from a routine clinical 12-lead ECG, has been

shown associated with several clinically important outcomes in HF including: mechanical response to cardiac resynchronization therapy (CRT)[3], HF hospitalizations[4], ventricular tachyarrhythmias[5, 6], and SCD[4].

Across the spectrum of HF conditions, acute decompensated heart failure (ADHF) is characterized by the highest mortality[7, 8]. Biomarker of myocardial injury Troponin has been shown associated with increased mortality[9] in ADHF. High sensitivity cardiac troponin (hsTn) recently emerged as a sensitive biomarker of a dynamic myocardial injury. In hospitalized ADHF patients baseline, peak, and peak change hsTnT were associated with worse cardiovascular mortality[10] post-discharge.

SCD is associated with underlying subclinical myocardial injury[11]. Risk of SCD is dynamic, which could reflect remodeling and dynamic subclinical myocardial injury. In MADIT-II study SAI QRST correlated with the time passed since myocardial infarction (MI), and predicted both arrhythmic (SCD, sustained ventricular tachyarrhythmia s) and HF outcomes[4]. However, whether dynamic changes in the electrophysiological substrate, as quantified by the surface ECG, are a reflection of underlying dynamic myocardial injury remains unclear. In this study, we examined the association between ECG marker SAI QRST and myocardial injury as measured by a high sensitivity troponin I (hsTnI) assay. We hypothesized that the dynamic changes in the level of hsTnI are associated with the dynamic changes in the level of SAI QRST on the surface ECG.

Methods

We conducted an ancillary study of a prospective observational cohort[12] of emergency department (ED) patients evaluated for acute coronary syndrome (ACS). The study was approved by the Institutional Review Board, and all participants provided written informed consent. The original cohort[12] enrolled consecutive patients with suspected ACS of age 25 or older, who presented to the Johns Hopkins Hospital (JHH) ED with non-diagnostic initial ECG, chief complaints of chest pain or shortness of breath, and had cardiac troponin I (cTnI) ordered by treating clinicians. Patients with overt ST-elevation myocardial infarction (STEMI) or non–ST-elevation myocardial infarction (NSTEMI) at the time of initial presentation in the ED were excluded. Serial ECG and hsTnI measurements were performed every 3 hours during a period of observation in the ED. The Abbott Laboratories' (Abbott Park, IL) research-use ARCHITECT *STAT* assay was used for hsTnI measurements, as previously described[12, 13].

A diagnosis of acute coronary syndrome was the primary outcome of the parent cohort study[12]. Final clinical diagnoses were adjudicated by an independent end-points adjudication committee comprised of five board-certified ED physicians and two board-certified cardiologists. As previously described[12], each study participant was finally diagnosed with one of the following conditions: (1) ACS, which included acute MI or unstable angina; (2) cardiac non-ACS diagnosis, which included myocarditis, pericarditis, valvular disorders, and cardiac arrhythmias; (3) ADHF; (4) non-cardiac volume overload; (5) pulmonary embolism; (6) other non-cardiac condition.

In this ancillary study we included participants with (1) available serial digital resting ECG, and (2) a final diagnosis of ACS, cardiac non-ACS, ADHF, and non-cardiac conditions. Digital ECGs were available for custom ECG analysis only for the parent cohort study participants who were enrolled at the JHH ED from January 16, 2012 to June 26, 2012[13]. Participants with a final diagnosis of non-cardiac volume overload and pulmonary embolism were excluded. In addition, we excluded participants with ventricular pacing on 12-lead ECG.

Serial digital resting 12-lead ECGs in sinus rhythm were extracted from the hospital's ECG MUSE database (GE Healthcare, Wauwatosa, WI, USA), and transformed into three-dimensional orthogonal XYZ ECGs by using an inverse Dower transformation matrix[14]. ECG analyses were performed by investigators (AF and LGT) blinded to participants' clinical characteristics and final diagnosis. The median beat was used for analysis. The absolute value of the area under the entire QRST waveform was measured on each orthogonal lead (X, Y, and Z). Absolute QRST integral values on X, Y, and Z leads were then summed to obtain SAI QRST as previously described[4-6, 15].

Statistical analysis was performed using STATA 14 (StataCorp LP, College Station, TX). Categorical variables were compared by Pearson's chi-square test. HsTnI values were log-10-transformed to normalize their distribution, prior to inclusion in regression models. ANOVA with Bonferroni correction for multiple comparisons was used to compare continuous variables across 4 clinical groups.

In order to determine whether the patient-specific time-varying changes in the SAI QRST are associated with the patient-specific time-varying hsTnI changes during 12-hour observation in the ED, we conducted generalized least squares random-effects linear regression analysis. Patient-specific time-varying hsTnI served as a predictor. Patient-specific time-varying SAI

QRST served as an outcome. We performed Hausman test to choose between the random-effect estimator (assuming that the unobserved time-invariant random component is unrelated to the predictors) and fixed-effect estimator (allowing the unobserved random component to be related to the predictors). In model #1 we adjusted for confounding demographic variables: age, sex, and race. Model #2 included all variables in the Model #1, as well as prevalent cardiovascular disease (prior myocardial infarction (MI), prior revascularization procedure (CABG or PCI), prior stroke, and HF). Model #3 included all the Model 2 variables, and known risk factors of cardiovascular disease (hypercholesterolemia, smoking, diabetes, hypertension, and cocaine use). With increasing complexity of the models, it was difficult to guarantee that unmeasured variables were not correlated with predictors in the model. In order to correct for endogeneity and simultaneity problems, in the Model #4 we conjectured that left bundle branch block (LBBB) was endogenous (i.e. correlated with predictors and outcome (SAI QRST), but uncorrelated with unobserved random variable) and used prevalent cardiovascular disease and its risk factors included in Model 3 as instrumental variables.

Results

This ancillary study included 398 participants (mean age 57.8±13.2y; 215(54%) female, and 256 (64.3%) black). Clinical characteristics of study participants are shown in Table 1. As expected, ADHF patients had the highest rate of HF history and LBBB on ECG. ACS patients had the highest probability of having prior coronary artery revascularization. Patients diagnosed with a non-cardiac condition were younger, and had the lowest probability of being admitted.

During the 12-hour observation period in ED, SAI QRST was measured on average 3.2 times, every 3 hours, and demonstrated fluctuations (both increases and decreases) in 317(80%) of study participants. Overall mean SAI QRST was 122.8±55.8 mV*ms. There was no statistically significant difference in baseline SAI QRST across study groups (Table 1), although there was a trend towards higher SAI QRST in ADHF. The average individual SAI QRST across study participants ranged widely, from 40.5 to 433.7 mV*ms. Figure 1 shows representative example of 12-lead ECG in ADHF patient with slowly but steadily decreasing values of both hsTnI and SAI QRST. Figure 2 displays patient-specific changes in SAI QRST and hsTnI over time for the whole study population. Both population averaged and patient-specific random effect regression models showed that within the entire cohort, SAI QRST decreased by a mean of 3 mV*ms every 3 hours (95% CI: from -5 to -1 mV*ms) during the 12-hour study period.

Patient-specific analysis showed that SAI QRST increased at all time points in 45 (11%) of participants, decreased at all time points in 29 (7%) of participants, and did not change at all time points in 7 (2%) of participants. The majority of study participants (80%) experienced fluctuations of SAI QRST. The range of individual changes during 12-hour ED observation time, relative to the overall mean SAI QRST was substantial (from reduction by 93.3 mV*ms to the growth by 303.3 mV*ms). Clinical characteristics of patients with different SAI QRST dynamics during 12-hour ED observation period were remarkably similar (Table 2), with few exceptions. Patients with steadily falling SAI QRST were likely current cocaine users. Patients with fluctuating SAI QRST were more likely to have had prior coronary artery revascularization.

Similar to SAI QRST, hsTnI was measured every 3 hours (on average 2.4 times) during 12-hour observation period in ED. Overall median hsTnI was 7.2 (IQR 3.7-20.8) ng/L, which was below the 99th% URL of this assay (34.2 ng/L for males, 15.6 ng/L for females and 26.2 ng/L overall). The average individual hsTnI across study participants ranged from zero to 6,782 ng/L. Dynamic changes in hsTnI had a similar pattern, as compared to the dynamic changes in SAI QRST (Figure 2). Most study participants (n=244; 63%) had fluctuations in hsTnI during the 12-hour observation period, whereas hsTnI was constantly rising in 134(34%) participants. Only 12(3%) participants had steadily falling hsTnI. The range of individual changes relative to the overall mean hsTnI was large (from reduction by 783 ng/L to the growth by 1,423 ng/L).

The Hausman test indicated that the random-effects estimators were the most consistent and efficient for all models. Thus, random-effects estimators are reported for all models in this study (Table 3). Results showed a significant association between dynamic changes in SAI QRST and hsTnI. Dynamic changes in SAI QRST and hsTnI were concordant. Overall, a 10-fold increase in hsTnI in a specific study participant was associated with about 8 mV*ms increase in SAI QRST in the same participant. Accordingly, a 10-fold decrease in hsTnI in another patient was associated with 8 mV*ms decrease in SAI QRST in that patient.

Subgroups analyses (Figure 3 and Table 3) showed that direct association between dynamic changes in hsTnI and SAI QRST was especially prominent in the ADHF group: 10-fold increase in hsTnI in an ADHF patient was associated with 61.0(95%CI 5.9-116.1) mV*ms increase in SAI QRST in that patient. Overall, adjustment by demographic characteristics, prevalent cardiovascular disease, and its risk factors did not attenuate the association. However, some heterogeneity in response was seen in ACS and cardiac-non-ACS subgroups.

Discussion

The main finding of this study is an observation of a significant independent direct patient-specific time-varying association between the surface ECG scalar measure of global electrical heterogeneity and remodeling SAI QRST and hsTnI. Association between SAI QRST and hsTnI was especially prominent in ADHF, which suggest that common underlying mechanisms (e.g. increasing wall stress, oxidative stress, neurohormonal activation, altered calcium handling, and inflammation) could simultaneously affect both ventricular conduction, remodeling and global electrical heterogeneity (resulting in SAI QRST change), and cardiomyocytes injury (resulting in hsTnI change). Monitoring of ECG is a standard of care in hospitalized ADHF patients. After validation in another independent cohort, dynamic monitoring of SAI QRST on ECG could help to monitor the degree of cardiomyocyte injury and effect of HF treatments in ADHF, which could improve outcomes in this high risk population. Further prospective interventional studies are needed to test this hypothesis.

SAI QRST has been shown to be associated with ventricular arrhythmia,[5, 6] SCD[4], appropriate ICD shocks[4-6], HF outcomes[4], and mechanical response on cardiac resynchronization therapy.[3] Our novel finding of the dynamic patient-specific association of SAI QRST with hsTnI in ADHF help to understand the mechanisms underlining acute changes in SAI QRST. The nearly simultaneous dynamic changes in SAI QRST and hsTnI suggests that they are both governed by a similar underlining mechanism.

High sensitivity troponin has been shown associated with SCD in the general population, after adjustment for prevalent and incident HF and MI, and known risk factors.[11] In this cohort Korley et al[12] showed that participants with elevated initial hsTnI but non-elevated cardiac troponin measured by a current generation assay had a higher risk of all-cause mortality and subsequent cardiac hospitalizations. Mechanisms behind hsTnI elevation in HF have been characterized in details[16]. Observed in this study nearly simultaneous concordant changes in SAI QRST and hsTnI in ADHF suggest that acute dynamic changes in the transmural wall stress, left ventricular chamber size and pressure, oxidative stress, neurohormonal activation, calcium handling, and inflammation likely cause acute remodeling (manifested by serial changes in SAI QRST and hsTnI), acute changes in the electrophysiological substrate (manifested by SAI QRST dynamics), as well as cardiomyocyte injury, as manifested by hsTnI.

Serial assessment of biomarkers has been shown to inform prognosis[17] in ADHF. It is known that hsTn is useful to determine prognosis in HF[16]. Due to dynamic nature of ADHF serial measurements of biomarkers to guide ADHF management is especially promising. Recent meta-analyses[18, 19] showed that the use of dynamic monitoring of biomarkers to guide HF therapy significantly reduced mortality and HF hospitalizations. Pivotal trial "GUIDE-IT" is currently ongoing to give definitive answer about benefit of biomarker-guided HF management[20]. Importantly, SAI QRST cannot be used to diagnose ACS, ADHF, or any other cardiac condition.

Dynamic monitoring of hsTnI is performed via serial measurements. Unlike assessment of HF biomarkers in the blood, continuous ECG monitoring is a standard of care for ADHF management in intensive cardiac care units. Addition of computational algorithm to calculate SAI QRST could be easily performed, which would provide a low-cost opportunity to non-invasively monitor remodeling and effect of therapeutic interventions in ADHF. Future studies are needed to determine if SAI QRST-guided management of ADHF could demonstrate improved outcomes[21].

Left ventricular (LV) remodeling process is frequently asymptomatic, has no specific symptoms, and detected by imaging studies at advanced stage. Constantly elevated hsTnI (measured serially) over a long period of time was shown associated with deleterious LV remodeling and provided independent risk information for poor cardiovascular outcomes[22]. Low cost of surface ECG and dynamic SAI QRST assessment will help to implement an idea to identify unique treatment opportunities for patients with serial changes in SAI QRST, as a step towards precision care medicine and individualization of care.

In addition, it is possible that joint use of both SAI QRST and hsTnI can provide complementary prognostic value. Recent study showed that elevated hsTn identified elderly individuals at high risk for new-onset HF, particularly HF with reduced ejection fraction[23], amongst study participants with LV hypertrophy. Similarly, measurement of hsTnI in a high-risk subgroup of individuals with pre-existed remodeling, as detected by SAI QRST, might identify small subgroup of very-high risk persons, in whom immediate intervention would be warranted. Future randomized clinical trials are needed to test this hypothesis.

It is important to emphasize that appropriate statistical analytical approach should be applied to assess dynamic changes in biomarkers. In this study (unlike in many other previously

conducted studies of serial measurements) we used patient-specific analytical approach, which is necessary for appropriate patient-specific modeling and interpretation of results. We employed random-effect estimator, which assumed that an unobserved random component might affect association between predictor and outcome. We performed comprehensive adjustment for demographic characteristics, presence of prevalent cardiovascular disease, and known risk factors of cardiovascular disease. Moreover, in the model 4 we corrected for possible endogeneity and simultaneity problems by instrumenting endogenous variable LBBB by prevalent cardiovascular disease and its risk factors variables. Applied analytical strategy enabled patient-specific interpretation of serial changes in SAI QRST and hsTnI.

The fact that ECG reflects myocardial injury has been well known for about a century. ST segment elevation is a fundamental sign of ST-segment elevation myocardial infarction (STEMI), whereas specific dynamics of the ST segment depression and T-wave inversion characterize non-ST-segment elevation myocardial infarction (NSTEMI)[24]. The Selvester score[25] correlates the QRS complex morphology with the infarct size and coronary artery lesion. In ACS patients an association between HsTnI and the proprietary ECG marker CEB™ has been recently shown[13].

However, elevation of hsTnI in ADHF has different underlying mechanisms. We observed fluctuations in hsTnI and associated fluctuations in SAI QRST over 12-hour ED observation period in the vast majority of study participants. This “waxing and waning” fluctuation of hsTnI and SAI QRST is a characteristic feature of HF. Surface ECG is a non-invasive, easily available for everyday use tool, which recently became available on mobile devices. Previous analysis of this ED cohort showed that study participants with initial hsTnI elevation above 99th% have a higher risk of all-cause death and cardiac hospitalizations[12]. Observed in this study significant dynamic association of hsTnI with SAI QRST opens an opportunity to detect progression of the myocardial injury in HF patients early, and thus to prevent adverse outcomes.

Use of the hsTnI (rather than hsTnT) assay is an important strength of the study. hsTnI assay is more sensitive than hsTnT assay and detects values in 96% of normal subjects.[26] Several limitations of our study have to be considered. First, there were missing data in serial measurements of both hsTnI and SAI QRST, and it is possible that missing data was not at random. Second, the size of the subgroups in this study was small. Especially, cardiac non-ACS

subgroup was small, and the group itself was heterogeneous and, therefore, statistical power was not sufficient to explain weakening of the strength of association after adjustment. However, importantly, those limitations do not dismiss the main study finding of the strong association between hsTnI and SAI QRST in the whole study population, which was especially prominent in the ADHF subgroup.

In conclusion, patient-specific time-varying changes in the surface ECG scalar measure of global electrical heterogeneity SAI QRST are independently and directly associated with patient-specific time-varying changes in hsTnI, likely reflecting common underlying mechanisms. Dynamic monitoring of SAI QRST on surface ECG in ADHF could be beneficial as a non-invasive tool of monitoring of cardiomyocyte injury, to guide HF management. This proof of concept study is an important first step towards future personalized medicine.

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Figure legends

Figure 1A-C. Representative examples of 12-lead ECGs (recorded within 3 hours apart) in acute decompensated heart failure (ADHF) patient with steadily decreasing SAI QRST and hsTnI pattern.

Figure 2. "Spaghetti" plots of individual patient-specific longitudinal relationships between log-10-transformed SAI QRST, log-10-trensformed hsTnI and time, in all study participants. **Figure 3**. Subgroups analysis. "Spaghetti" plots of individual patient-specific longitudinal relationships between log-10-transformed SAI QRST, log-10-trensformed hsTnI and time, for each subject with (A acute coronary syndrome (ACS); (B) cardiac non-ACS condition; (C) acute decompensated heart failure (ADHF); (D) non-cardiac condition.

Table 1. Clinical and demographic characteristics of the study participants

	ACS (n=28)	Cardiac non-ACS DS (n=19)	ADHF (n=35)	Non-cardiac DS (n=316)	ANOVA/χ^2 P-value
Age(SD), y	**62.4(10.7)**	**67.7(10.7)**	**61.1(13.3)**	**56.4(13.2)**	**0.0002**
Men, n(%)	17(60.7)	9(47.4)	16(45.7)	141(44.6)	0.441
African-Americans, n(%)	13(46.4)	10(52.6)	24(68.6)	209(66.1)	0.123
Hypertension, n(%)	19(67.9)	13(68.4)	28(80.0)	194(61.4)	0.161
Diabetes, n(%)	**16(57.1)**	**6(31.6)**	**17(48.6)**	**87(27.5)**	**0.001**
Heart failure Hx, n(%)	**9(32.1)**	**4(21.1)**	**26(74.3)**	**62(19.6)**	**<0.0001**
Current smokers, n(%)	9(32.1)	3(15.8)	9(25.7)	124(39.2)	0.156
Current cocaine users, n(%)	1(3.6)	0(0)	1(2.9)	22(7.0)	0.657
Hypercholesterolemia, n(%)	18(64.3)	11(57.9)	19(54.3)	134(42.4)	0.059
Family Hx CHD, n(%)	11(39.3)	6(31.6)	14(40.0)	112(35.4)	0.902
Prior stroke, n(%)	6(21.4)	1(5.3)	4(11.4)	46(14.6)	0.444
Prior myocardial infarction, n(%)	11(39.3)	3(15.8)	6(17.1)	65(20.6)	0.102
Prior revascularization, n(%)	**13(46.4)**	**5(26.3)**	**7(20.0)**	**68(21.5)**	**0.026**
LVH on ECG, n(%)	5(17.9)	1(5.3)	7(20.0)	37(11.71)	0.307
Right bundle brunch block, n(%)	2(7.1)	0(0)	2(5.7)	15(4.8)	0.713
Left Bundle branch block, n(%)	**0(0)**	**1(5.3)**	**3(8.6)**	**5(1.6)**	**0.039**
Admitted from ED, n(%)	**26(92.9)**	**14(73.7)**	**32(91.4)**	**156(49.4)**	**<0.0001**
Baseline SAI QRST, mV*ms(SD)	124.2(41.7)	134.7(48.2)	145.0(82.8)	126.2(52.4)	0.328

SAI QRST up/up&down/down, n(%)	2(7)/22(79)/4(14)	1(6)/14(82)/2(12)	5(15)/26(79)/1(6)	37(12)/255(82)/21(7)	0.690

Table 2. Clinical characteristics of the study participants with steadily increasing, decreasing, and fluctuating SAI QRST

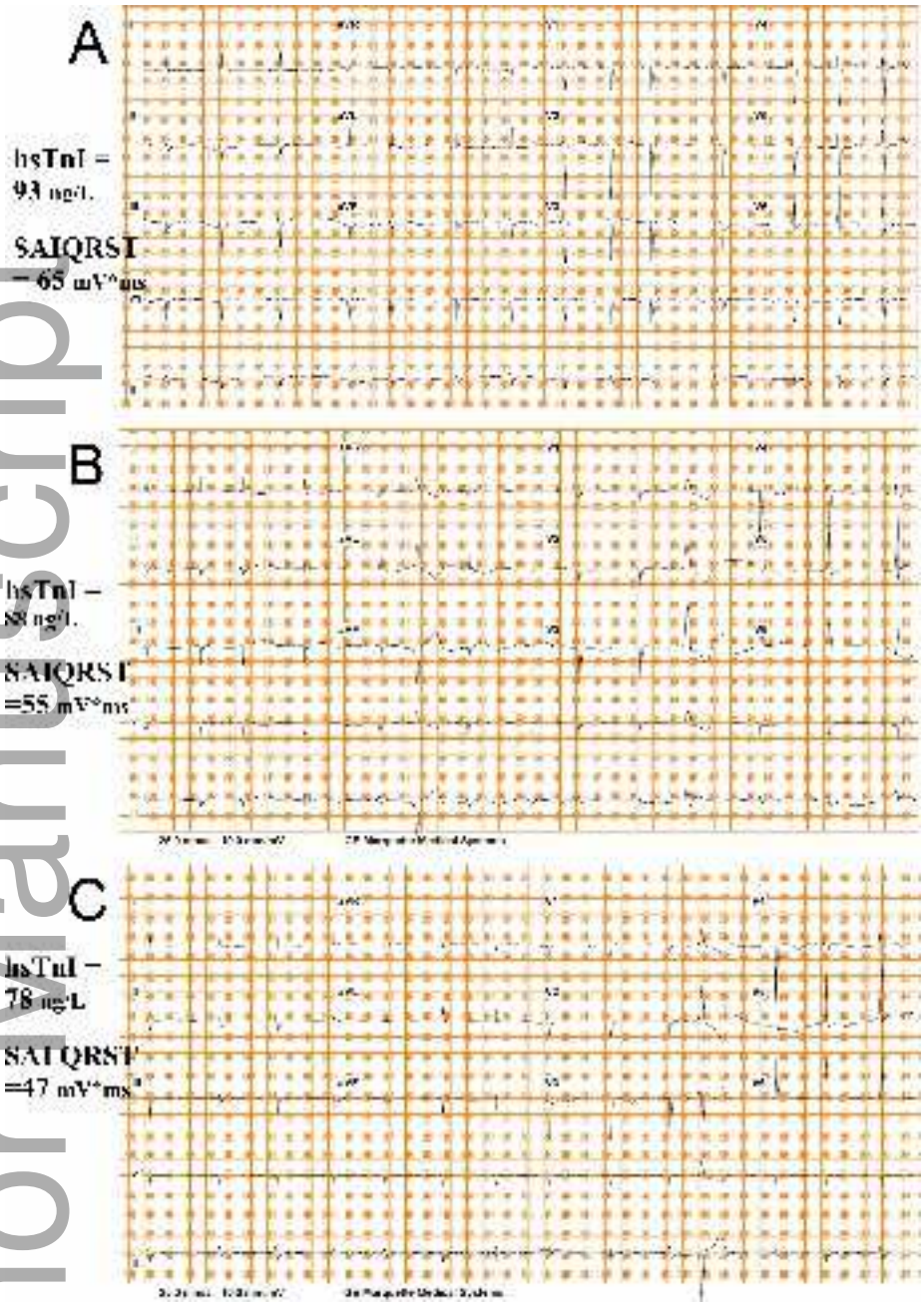
	Increasing SAI QRST (n=45)	Fluctuating SAI QRST (n=317)	Decreasing SAI QRST (n=29)	ANOVA or χ^2 P-value
Age(SD), y	55.6(11.7)	58.2(13.3)	57.6(14.2)	0.457
Men, n(%)	21(46.7)	145(45.7)	15(51.7)	0.962
African-Americans, n(%)	29(64.4)	203(64.0)	19(65.5)	0.987
Hypertension, n(%)	22(48.9)	209(65.9)	17(58.6)	0.073
Diabetes, n(%)	20(44.4)	93(29.3)	9(31.0)	0.123
Heart failure Hx, n(%)	11(24.4)	81(25.6)	5(17.2)	0.610
Current smokers, n(%)	17(37.8)	116(36.6)	10(34.5)	0.934
Current cocaine users, n(%)	**3(6.7)**	**17(5.4)**	**4(13.8)**	**0.050**
Hypercholesterolemia, n(%)	18(40.0)	148(46.7)	13(44.8)	0.679
Family Hx CHD, n(%)	11(24.4)	117(36.9)	13(44.8)	0.157
Prior stroke, n(%)	10(22.2)	45(14.2)	2(6.9)	0.172
Prior myocardial infarction, n(%)	7(15.6)	75(23.7)	3(10.3)	0.141
Prior revascularization, n(%)	**8(17.8)**	**81(25.6)**	**2(6.9)**	**0.049**
LVH on ECG, n(%)	3(6.7)	44(13.9)	2(6.9)	0.249
Right bundle brunch block, n(%)	2(4.44)	14(4.42)	2(6.90)	0.829
Left Bundle branch block, n(%)	3(6.7)	6(1.9)	0(0)	0.094
Admitted from ED, n(%)	**17(37.8)**	**187(59.0)**	**19(65.5)**	**0.017**
Baseline SAI QRST, mV*ms(SD)	**112.9(64.1)**	**128.8(53.1)**	**147.9(49.4)**	**0.038**

Baseline heart rate, bpm(SD)	81.1(17.5)	78.5(16.8)	79.3(15.3)	0.630
Baseline QRS duration, ms(SD)	89.0(26.5)	91.3(21.0)	84.9(23.8)	0.348
Baseline QTc, ms(SD)	430.3(74.0)	436.3(51.9)	418.6(96.4)	0.338

Table 3. Patient-specific time-varying difference (95%CI) in SAI QRST by high sensitivity Troponin I

Model	All Participants (n=398)		ACS (n=28)		Cardiac Non-ACS (n=19)		ADHF (n=35)		Non-Cardiac (n=316)	
	Per 10-fold hsTnI (95%CI) increase	P	Per 10-fold hsTnI (95%CI) increase	P	Per 10-fold hsTnI (95%CI) increase	P	Per 10-fold hsTnI (95%CI) increase	P	Per 10-fold hsTnI (95%CI) increase	P
1	+8.7(1.5-16.0)	0.018	+4.2(-8.3-16.6)	0.512	+21.3(-16.3-58.9)	0.267	+65.9(-2.5-134.4)	0.059	+9.0(0.1-17.9)	0.046
2	+7.5(-0.01-15)	0.050	+4.8(-9.3-18.9)	0.503	+29.6(-30.8-90.1)	0.337	+71.9(-2.4-146.1)	0.058	+8.7(-0.6-17.9)	0.066
3	+6.9(-0.7-14.5)	0.077	+8.1(-6.8-23.1)	0.288	+4.6(-54.8-63.9)	0.880	+98.8(10.4-187.2)	0.028	+7.8(-1.5-17.2)	0.103
4	+7.7(0.6-14.9)	0.034	+4.2(-8.1-16.5)	0.504	-1.3(-33.0-210.0)	0.955	+61.0(5.9-116.1)	0.030	+9.1(-0.1-18.4)	0.053

Model 1 is a random-effects linear (generalized least squares, GLS) panel-data model adjusted for demographic characteristics (age, sex, and race). Model 2 is a random-effects linear GLS panel-data model adjusted for demographic characteristics and prevalent cardiovascular disease [CVD] (myocardial infarction [MI], revascularization, stroke, heart failure [HF]). Model 3 is a random-effects linear GLS panel-data model adjusted for demographic characteristics (age, sex, and race), prevalent CVD (MI, revascularization, stroke, and HF), and known risk factors (hypertension, smoking, diabetes, hypercholesterolemia, and cocaine use). Model 4 is a random-effects linear GLS panel-data model adjusted for demographic characteristics (age, sex, and race), with endogenous variable LBBB, while prevalent CVD (MI, revascularization, stroke, and HF), and known risk factors (hypertension, smoking, diabetes, hypercholesterolemia, and cocaine use) are entered as instruments for LBBB.



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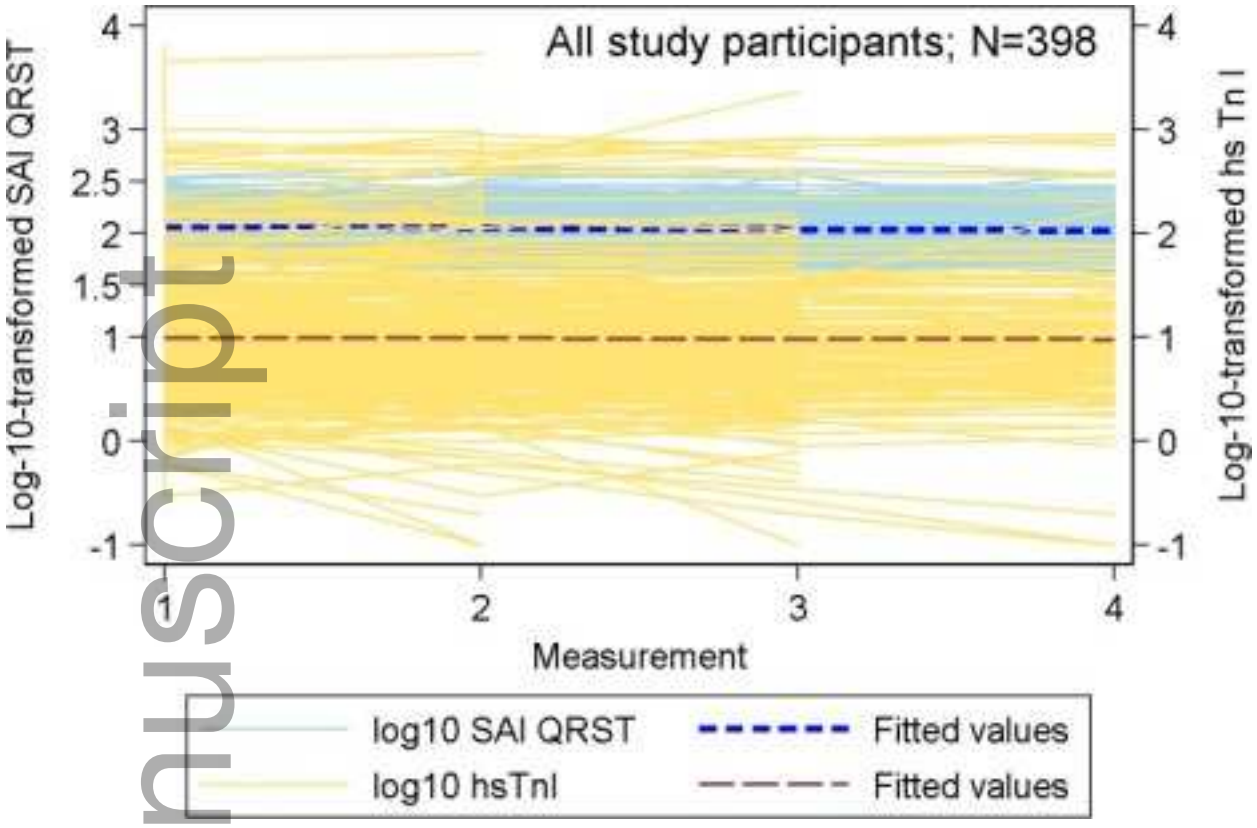

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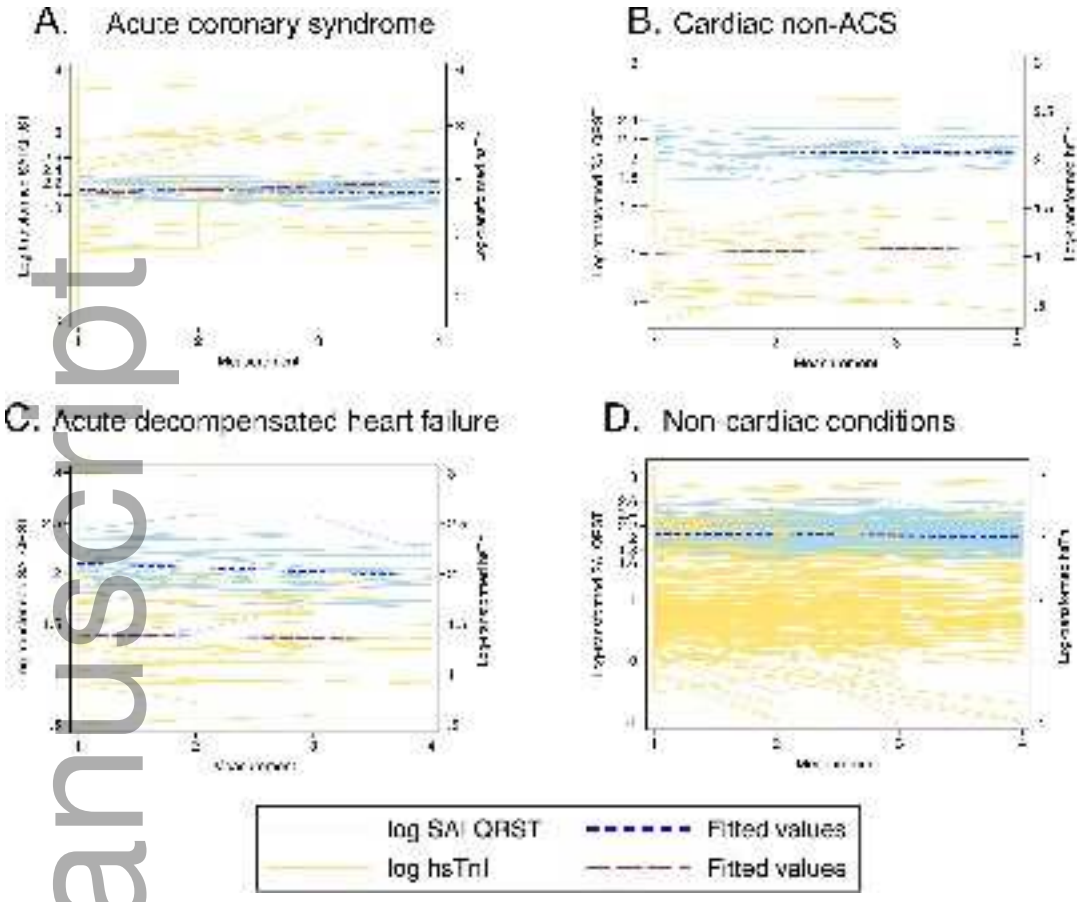

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