Supplement to Global Electrical Heterogeneity Associated with Drug-Induced Torsades de Pointes

Supplemental Methods: ECG Processing and Annotation

Provided ECG recordings were first processed with both low- (125.00 Hz) and high-pass (0.49 Hz) wavelet filters using the Symlets 4 and Daubechies 4 wavelets, respectively, to remove noise and baseline wander. As the area of a QRST complex is insensitive to small high frequency deflections in the signal, low pass filtering has minimal effect on the measured areas/GEH values, but does improve annotation accuracy. We constructed median beat vectorcardiograms (VCGs) from the ECGs by transformation into the Frank X, Y, and Z leads using the Kors transformation matrix [18]. The X, Y, and Z leads were then baseline corrected so that the flattest part of the TP segment was the zero reference point for both area calculations and the origin of the VCG as this part of the ECG is isoelectric [14].

One of the authors, who was blinded to case or control status, manually assigned the fiducial points ($\mathrm{QRS_{onset}}$, $\mathrm{QRS_{end}}$, and $\mathrm{T_{end}}$) and measured the QT interval with digital calipers on the vector magnitude (VM) lead which was defined as $\mathrm{VM} = \sqrt{\mathrm{X}^2 + \mathrm{Y}^2 + \mathrm{Z}^2}$.

Supplemental Methods: GEH Calculations

The **SVG** is defined as the vector sum of the area QRS- and area T-vectors, which are obtained by integrating the QRS complex and T wave [11]. This is equivalent to calculating the area under the entire QRST complex:

$$\begin{aligned}\mathbf{SVG} &= \mathbf{QRS} + \mathbf{T} \\ &= \int_{\mathrm{QRS_{beg}}}^{\mathrm{QRS_{end}}} \mathbf{V}(t)\,\mathrm{d}t + \int_{\mathrm{QRS_{end}}}^{\mathrm{T_{end}}} \mathbf{V}(t)\,\mathrm{d}t \\ &= \left[\int_{\mathrm{QRS_{beg}}}^{\mathrm{T_{end}}} V_x(t)\,\mathrm{d}t, \int_{\mathrm{QRS_{beg}}}^{\mathrm{T_{end}}} V_y(t)\,\mathrm{d}t, \int_{\mathrm{QRS_{beg}}}^{\mathrm{T_{end}}} V_z(t)\,\mathrm{d}t\right],\end{aligned} \tag{2}$$

where $\mathbf{V}(t) = [V_x(t), V_y(t), V_z(t)]$ is the value of the vectorcardiogram at time t. These and subsequent integrals were all approximated using the trapezoidal rule. Since **V** is the equivalent cardiac dipole moment, the **SVG** is equal to the average dipole moment over the cardiac cycle

multiplied by the QT-interval. The **SVG** has a magnitude and orientation in 3-dimensional space expressed as azimuth and elevation coordinates (Figure 1):

$$\begin{aligned} \text{SVG Magnitude} &= \sqrt{\text{SVG}_x^2 + \text{SVG}_y^2 + \text{SVG}_z^2} \\ \text{SVG Azimuth} &= \arctan \frac{\text{SVG}_z}{\text{SVG}_x} \\ \text{SVG Elevation} &= \arccos \frac{\text{SVG}_y}{|\mathbf{SVG}|}. \end{aligned} \tag{3}$$

Spatial QRST angle is the 3-dimensional angle between the area QRS- and area T-vectors [11] (Figure 1):

$$\text{QRST angle} = \arctan \frac{|\mathbf{QRS} \times \mathbf{T}|}{\mathbf{QRS} \cdot \mathbf{T}}, \tag{4}$$

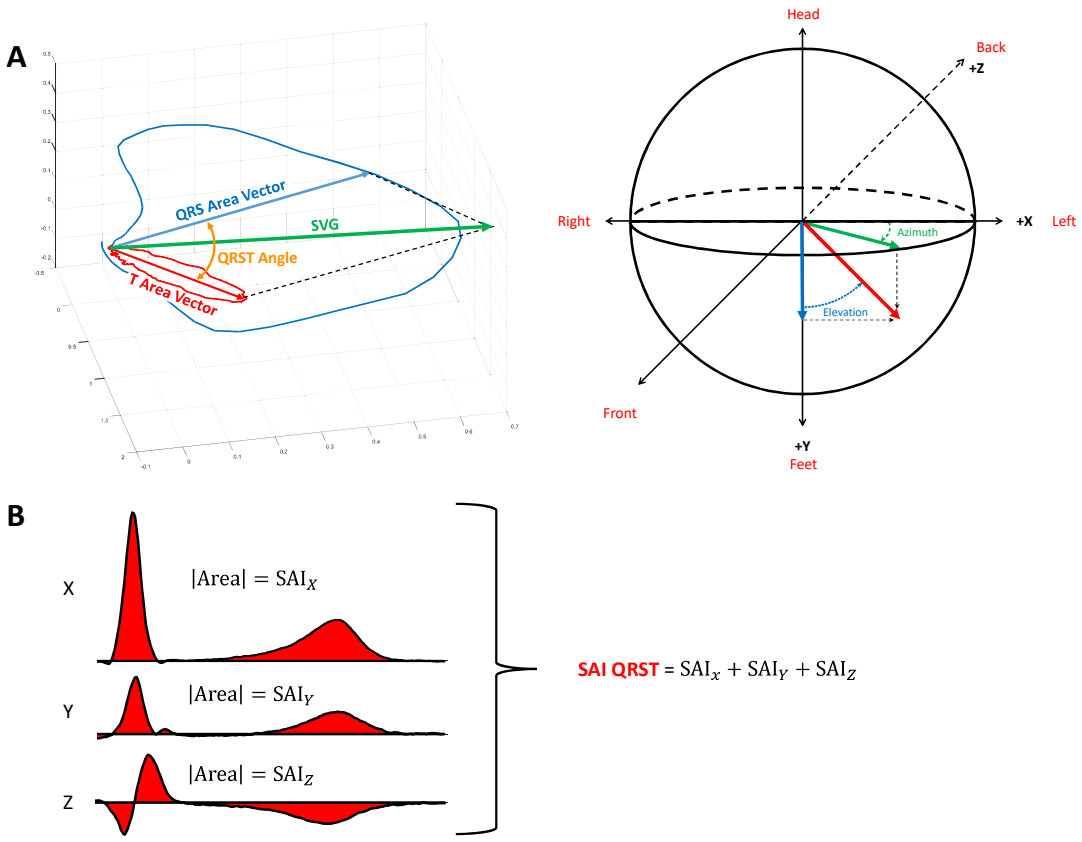
where **QRS** and **T** are defined as in equation 2.

SAI QRST = $\text{SAI}_x + \text{SAI}_y + \text{SAI}_z$, where

$$\text{SAI}_x = \int_{\text{QRS}_{\text{beg}}}^{\text{T}_{\text{end}}} |X(t)| \, \mathrm{d}t, \text{etc.} \tag{5}$$

where $X(t)$ is the voltage in the corresponding VCG lead at time t (see Figure 1) [32, 33].

The SVG-QRS peak angle is the three-dimensional angle between the **SVG** and $\mathbf{QRS_{peak}}$ vectors. $\mathbf{QRS_{peak}}$ is the vector originating from the origin of the coordinate system (0,0,0) to the point furthest from the origin in the QRS vector loop. The SVG-QRS peak angle describes the spatial relationship between the **SVG** and the principal electrical axis of the heart during depolarization. It is calculated similarly to the QRST angle (equation 4).



Supplemental Figure 1: Illustration of GEH parameters. **A:** The spatial ventricular gradient (SVG) is defined as the vector sum of the QRS-area vector and the T-area vectors. The SVG vector has magnitude (vector length), elevation, and azimuth. Elevation can have values between 0 and 180 degrees, with 0 pointing downwards towards the feet, and 180 degrees pointing upwards towards the head. Azimuth can have values between -180 and 180 degrees; positive azimuth values between 0 to +180 degrees are oriented posteriorly, and negative azimuth values between 0 to -180 degrees are oriented anteriorly. QRST angle is the 3-dimensional angle between the QRS-area vector and the T-area vector. **B:** Sum absolute QRST integral (SAI QRST) is defined as the sum of areas under the absolute values of the X, Y, and Z leads. Reproduced with permission from Stabeneau et al. [14].

Supplemental Table 1: Detailed characteristics of study population. Abbreviations: AF=atrial fibrillation, CAD=coronary artery disease, MI=myocardial infarction, HTN=hypertension. Rightmost column indicates which medication triggered episode of torsade de pointes.

Age	Gender	AF	CAD	MI	HTN	Medication
Cases						
39	F	Yes	No	No	Yes	Sotalol
47	F	Yes	No	No	Yes	Diuretic
72	F	No	No	No	Yes	Unknown
54	F	Yes	No	No	No	Sotalol
77	F	Yes	Yes	Yes	Yes	Sotalol
61	F	No	No	No	No	Bisacodyl
64	F	No	No	No	Yes	Sotalol
72	F	No	No	No	No	Cipramil
75	F	Yes	No	No	Yes	Sotalol, Cipramil, Furosemide
58	M	Yes	No	No	No	Sumatriptane
55	M	Yes	Yes	Yes	No	Amiodarone
70	M	Yes	Yes	Yes	No	Erythromycin
64	M	Yes	No	No	No	Sotalol
63	M	Yes	No	No	No	Sotalol
39	M	No	No	No	No	Imipramine
52	M	Yes	No	No	Yes	Amiodarone
40	M	No	No	No	No	Clarithromycin
Controls						
47	F	Yes	No	No	Yes	
60	F	Yes	No	No	No	
67	F	Yes	No	No	Yes	
70	F	No	Yes	Yes	Yes	
61	F	Yes	No	No	Yes	
65	F	Yes	No	No	No	
70	F	Yes	No	No	No	
64	F	Yes	No	No	Yes	
62	F	Yes	No	No	No	
82	F	Yes	Yes	No	Yes	
70	F	Yes	Yes	No	Yes	
73	F	Yes	No	No	Yes	
63	M	Yes	No	No	No	
56	M	Yes	No	No	Yes	
36	M	Yes	No	No	No	
54	M	Yes	No	No	No	
37	M	Yes	No	No	No	

Supplemental Table 2: Mean values and standard deviation (σ) of other GEH measurements for cases and controls. p-values computed using two-sample t-test. See Methods for details. Abbreviations: SAI QRST=sum absolute QRST integral, SVG=spatial ventricular gradient.

	Cases		Controls		
GEH Parameter	Mean	σ	Mean	σ	p
Area QRST Angle (deg)	90.0	51.5	63.8	40.6	0.11
SVG-QRS Angle (deg)	6.0	4.8	4.2	2.6	0.17
SAI QRST (mV$\cdot$ ms)	121.7	35.7	120.6	49.2	0.94

Supplemental Table 3: Univariable logistic regression. Odds ratios are given per unit measurement. SVG azimuth (Az) is adjusted for the mean azimuth of the control group, that is, Adj Az = |Az − 22.0| deg. Abbreviations: SVG=spatial ventricular gradient, SAI QRST=sum absolute QRST integral, MI=myocardial infarction, CAD=coronary artery disease, HTN=hypertension, AFib=atrial fibrillation. QTc is computed via Fridericia's formula.

Variable	OR	p	95% CI
Adjusted SVG Azimuth (deg)	1.04	0.02	1.01 – 1.08
SAI QRST (mV*ms)	1.00	0.94	0.98 – 1.02
SVG Magnitude (mV*ms)	0.99	0.46	0.96 – 1.02
SVG Azimuth (deg)	0.99	0.40	0.98 – 1.01
SVG Elevation (deg)	1.00	0.93	0.97 – 1.03
QRST Angle - Area (deg)	1.01	0.11	1.00 – 1.03
QRST Angle - Peak (deg)	1.01	0.13	1.00 – 1.03
Age (yrs)	0.99	0.62	0.93 – 1.04
QTc (ms)	1.02	0.10	1.00 – 1.05
Male	2.13	0.29	0.52 – 8.76
History of MI	3.43	0.31	0.32 – 36.83
History of CAD	1.00	1.00	0.17 – 5.83
History of HTN	0.62	0.49	0.16 – 2.42
History of AFib	0.11	0.06	0.01 – 1.09