Global Electrical Heterogeneity and Sudden Cardiac Death

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• In general population SCD incidence is low, but absolute number of SCD events is high
• SCD is the first manifestation of CVD in > 60% of SCD victims

Myerburg R J , and Junttila M J Circulation 2012;125:1043
Table 17-3. Survival After Out-of-Hospital Cardiac Arrest in US Sites of the Resuscitation Outcomes Consortium

<table>
<thead>
<tr>
<th></th>
<th>Survival to Discharge (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMS assessed</td>
<td></td>
</tr>
<tr>
<td>Any age</td>
<td>6.3 (5.9–6.7)</td>
</tr>
<tr>
<td>Adults</td>
<td>6.4 (6.0–6.8)</td>
</tr>
<tr>
<td>Children</td>
<td>7.2 (4.3–10.2)</td>
</tr>
<tr>
<td>Unknown age</td>
<td>0.5 (0.0–1.3)</td>
</tr>
<tr>
<td>EMS treated</td>
<td></td>
</tr>
<tr>
<td>Any age</td>
<td>12.0 (11.3–12.7)</td>
</tr>
<tr>
<td>Adults</td>
<td>12.1 (11.3–12.8)</td>
</tr>
<tr>
<td>Children</td>
<td>9.8 (5.8–13.7)</td>
</tr>
<tr>
<td>Unknown age</td>
<td>6.7 (0.0–19.3)</td>
</tr>
<tr>
<td>VF</td>
<td></td>
</tr>
<tr>
<td>Any age</td>
<td>32.6 (30.2–34.9)</td>
</tr>
<tr>
<td>Adults</td>
<td>32.5 (30.1–34.8)</td>
</tr>
<tr>
<td>Children</td>
<td>40.0 (15.2–64.8)</td>
</tr>
<tr>
<td>Bystander-witnessed VF</td>
<td></td>
</tr>
<tr>
<td>Any age</td>
<td>38.6 (35.4–41.8)</td>
</tr>
<tr>
<td>Adults</td>
<td>38.2 (35.0–41.4)</td>
</tr>
<tr>
<td>Children</td>
<td>71.4 (38.0–100)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; EMS, emergency medical services; and VF, ventricular fibrillation.

Resuscitated SCA Survival to hospital discharge remains low

Focus on prediction and prevention of SCD
Goal: Understand SCD Mechanisms

Disease substrate/pathology

Electrophysiological substrate

Sudden Cardiac Death

HTN, CHD, DM, HF, Fibrosis

?DM

?CHD

?HTN

?Fibrosis

ECG

Asystole, PEA, VF

Goal: Understand and Characterize EP substrate of SCD
Vectorcardiogram

Frank VCG

Images from website bem.fi

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Spatial Ventricular Gradient Vector

Spatial ventricular gradient (SVG) = vector to point the direction along which non-uniformity in Total Recovery Time is the greatest and the duration of the TRT is the shortest.

- Frank Wilson, 1934
- Burger, 1954
- Plonsey, 1979
- Geselowitz, 1983
- Van Oosterom, 2004

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SVG properties and dispersion in total recovery time

1. Points the direction along which non-uniformity in both activation and recovery (Total Recovery Time) is the greatest (perpendicular to the line of block).

2. Points towards the area where the total recovery time is the shortest.

3. Depends on heterogeneity of action potential morphology across the entire myocardium.

4. Characterizes the degree of heterogeneity of total recovery time across the ventricles.

5. Steepness of the gradient determines the magnitude of SVG. Close proximity of areas with min-max TRT gives largest SVG.
ECG Global Electrical Heterogeneity #1-3:
Spatial Ventricular Gradient Magnitude, Azimuth, Elevation

- Spatial Ventricular Gradient represents a vector in three-dimensional space defined by the vectorial sum of the QRS-vector and the T-vector.
- The (1) magnitude, (2) azimuth and (3) elevation of the SVG vector are measured.

Waks et al, Circulation 2016
Global Electrical Heterogeneity #4: spatial QRS-T angle

Spatial QRS-T angle is defined as the three-dimensional angle between the spatial QRS-vector and the spatial T-vector.

Waks et al, Circulation 2016
Global Electrical Heterogeneity #5: SAI QRST

Sum Absolute QRST integral (SAI QRST) is a scalar analogue of the Spatial Ventricular Gradient. It is calculated as the absolute value of the area under the QRS complex and T-wave.

\[ \text{SAI QRST} = X(62.3) + Y(30.1) + Z(56.8) = 149.2 \text{ mV.ms} \]

Waks et al, Circulation 2016
Association of GEH with SCD in Cox Regression (per 1 SD of continuous variable)

<table>
<thead>
<tr>
<th>Model</th>
<th>SAI QRST</th>
<th>QRS-T angle</th>
<th>SVG magnitude</th>
<th>SVG elevation</th>
<th>SVG azimuth</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.26(1.20-1.33)</td>
<td>1.55(1.43-1.68)</td>
<td>1.03(0.95-1.13)</td>
<td>1.26(1.15-1.37)</td>
<td>1.30(1.20-1.42)</td>
</tr>
<tr>
<td>2</td>
<td>1.21(1.15-1.28)</td>
<td>1.30(1.20-1.41)</td>
<td>1.10(1.01-1.20)</td>
<td>1.19(1.09-1.29)</td>
<td>1.14(1.05-1.24)</td>
</tr>
<tr>
<td>3</td>
<td>1.16(1.07-1.25)</td>
<td>1.21(1.10-1.32)</td>
<td>1.09(1.00-1.19)</td>
<td>1.11(1.02-1.22)</td>
<td>1.01(0.92-1.11)</td>
</tr>
<tr>
<td>4</td>
<td>1.16(1.07-1.25)</td>
<td>1.29(1.17-1.43)</td>
<td>1.15(1.05-1.25)</td>
<td>1.01(0.92-1.11)</td>
<td>1.05(0.95-1.17)</td>
</tr>
<tr>
<td>w/o EF</td>
<td>1.34(1.15-1.55)</td>
<td>1.15(0.98-1.36)</td>
<td>1.24(1.08-1.43)</td>
<td>0.98(0.85-1.14)</td>
<td>0.97(0.82-1.16)</td>
</tr>
<tr>
<td>+ LVEF</td>
<td>1.30(1.12-1.51)</td>
<td>1.12(0.95-1.32)</td>
<td>1.23(1.07-1.42)</td>
<td>0.99(0.85-1.14)</td>
<td>0.99(0.83-1.18)</td>
</tr>
</tbody>
</table>

Sensitivity analyses evaluated the effect of adding LVEF into fully-adjusted and time-updated models in 4,954 CHS participants.

Model 1 adjusted for demographic characteristics (age, sex, race, study center/cohoot).
Model 2 additionally adjusted for prevalent CVD (CHD, HF, stroke, AF, use of BB) and traditional cardiovascular risk factors (BMI, HTN, s, DM, smoking, alcohol, cholesterol, HDL, triglycerides, physical activity index).
Model 3 further adjusted for ECG parameters associated with SCD (heart rate, QRS,QTc, sex-specific Cornell product).
Model 4 additionally adjusted for time-updated traditional ECG measurements, and time-updated incident non-fatal cardiovascular events (AF, HF, CHD, and stroke).

Waks et al, Circulation 2016
GEH is an independent EP substrate of SCD

Global Electrical Heterogeneity Sudden Cardiac Death Risk Score Calculator

Enter patient information in the yellow cells below.
The model calculates the estimated 10-year risk of sudden cardiac death.

Clinical Characteristics:
- Age: 76 yrs
- Female: 1 (1=yes, 0=no)
- White: 1 (1=yes, 0=no)
- Diabetes: 0 (1=yes, 0=no)
- Hypertension: 0 (1=yes, 0=no)
- CHD: 0 (1=yes, 0=no)
- Stroke: 0 (1=yes, 0=no)

Low-risk Threshold: 1%

GEH ECG Parameters:
- SAI QRST: 70 mv*ms
- QRST angle: 45 deg
- SVG elevation: 40 deg
- SVG azimuth: 10 deg

CIF(t | x) = 1 - (1-CIF(t|0)) \exp(x \beta)

N=20,177 participants of prospective study.
Adjudicated sudden cardiac death.
GEH is associated with SCD independent of stroke, its risk factors, and other.

10 year SCD risk:
- Clinical Only Model: 0.65%
- Clinical + GEH Model: 0.39%

Patient Low-Risk for SCD

WWW.ecgpredictscd.org
SCD risk stratification capacity and reclassification rate in a low risk population. Low risk ≤ 0.5% High risk ≥ 5%

N = 20,177

N=49 (10%) are appropriately reclassified from intermediate to High risk; N=1 (0.2%) from low to medium

Waks et al, Circulation 2016
SCD risk stratification capacity and reclassification in BBB/IVCD.
Low risk \(\leq 0.5\%\)  High risk \(\geq 5\%\)

30\% are appropriately Reclassified
From Intermediate To High Risk;
64\% of SCDs occurred in high Risk group

Waks et al, Circulation 2016
Longitudinal Time-Updated Analyses

1. Does GEH change over time?
Patient-specific (mixed effect) models

Mixed effect models (participant nested within study center nested within cohort), adjusted by age, sex, and race. Change in GEH ECG parameter over each time interval of median 2.8 (interquartile range 1.0-3.2) years of follow-up.

<table>
<thead>
<tr>
<th>SAI QRST, mV*ms</th>
<th>QRS-T angle, deg</th>
<th>SVG magnitude, uV</th>
<th>Sqrt SVG elevation</th>
<th>Sqrt abs SVG azimuth</th>
</tr>
</thead>
<tbody>
<tr>
<td>+0.63 (0.51 to 0.76)</td>
<td>+0.36 (0.29 to 0.42)</td>
<td>-4.02 (-5.05 to -3.00)</td>
<td>+0.035 (0.032 to 0.037)</td>
<td>+0.008 (0.003 to 0.012)</td>
</tr>
</tbody>
</table>

Waks et al, Circulation 2016
Longitudinal change in EP substrate

Fast worsening of GEH → SCD
Slow worsening of GEH → LV dysfunction

SVG azimuth changes

Healthy aging

SCD outcome

ABNORMAL GEH

NORMAL GEH

Time, years

1987

2013

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Biering-Sørensen et al, CircAE, 2018
GWAS of GEH: 10 independent loci

- We tested 22-26 million genotyped and imputed variants in African American (AA, N=3,057) and European American (EA, N=10,769)
- Adjusted linear regression models were constructed with each GEH parameter as an outcome.
GEH-loci: syndromes

Larisa G. Tereshchenko et al. J Am Heart Assoc 2018;7:e008160
Summary

• GEH is an independent EP substrate of SCD
• GEH provides unique insight into mechanisms of SCD and cardiac arrhythmias
• GEH ECG risk score of SCD improves reclassification beyond clinical-only SCD predictors
Thank you!

https://physionet.org/physiotools/geh/
www.ecgpredictscd.org
www.tereshchenkolab.org
https://github.com/Tereshchenkolab