T-wave Morphology Restitution Predicts Cardiovascular Risk in the UK Biobank Cohort

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Motivation

- **Cardiovascular** mortality is one of the main causes of death in the general population
  

- Prediction of cardiovascular mortality remains **challenging**

- Need of complementary and **strong** cardiovascular risk **predictors**
Restitution of ventricular repolarization

- Response of repolarization times to changes in CL.
Restitution heterogeneity

- **Restitution dynamics**: heterogeneous along the ventricle: Dispersion of repolarization restitution  

- **Increments** of dispersion of repolarization restitution: **Increased** arrhythmic risk.  
  *Nash MP. Et al., Exp Physiol, 2006.*

- **Main limitation**: Its quantification requires **invasive** procedures.  
  *Yue AM. Et al., J Am Coll Cardiol, 2005.*
T-wave morphology restitution

- **T-wave** reflects the spatio-temporal repolarization heterogeneity of the ventricular myocardium. *Burgess MJ. et al., Am J Physiol, 1979*

- **Hypothesis:** T-wave Morphology Restitution: dispersion of repolarization restitution.
T-wave morphology restitution

- Original study:
  - 650 CHF consecutive patients
  - 52 SCD victims
  - ECG Holter recordings
- Its predictive value needs validation in an independent study

\[ TMR = \frac{d_w}{\Delta RR} \text{ [a.u.]} \]

Ramírez et al. J Am Heart Assoc 2017
Objective

To investigate the predictive value of TMR in the general population
Materials: UK Biobank

- Prospective study
- ~95,000 participants invited for moderate exercise test between 2006-2010
- Raw ECG recordings available in 58,161
- Extensive follow-up from hospital episode statistics

- UK Biobank application number 8256
Materials: Exercise test
Materials: UK Biobank

- Study exclusion criteria
  - Myocardial infarction
  - Cardiac arrhythmias or conduction disorders
  - Pacemaker
  - Heart failure
  - Calcium channel blockers medication
  - $\Delta RR < 10$ms

- UK Biobank application number 8256
Materials: UK Biobank

• 58,161 individuals in the study
• Population characteristics:
  • 26,998 men (46.4%)
  • Median (IQR) age of 58 (13) years old
  • Median (IQR) BMI of 26.4 (5.4) kg/m².

• UK Biobank application number 8256
ECG analysis

Pre-processing

Selection of T-waves

Quantification of T-wave morphological differences

Computation of TMR
ECG analysis

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\[ \frac{\sum_{i=1}^{n} x_i}{n} \]
Methods

Pre-processing

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Methods

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**Methods**

- **Pre-processing**
- **Selection of T-waves**
- **Quantification of T-wave morphological differences**
- **Computation of TMR**

Mathematically:

\[ TMR^{ex} = \frac{d_{w}^{ex}}{\Delta RR^{ex}} \text{[a. u.]} \]

\[ TMR^{rec} = \frac{d_{w}^{rec}}{\Delta RR^{rec}} \text{[a. u.]} \]

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Methods

• Study end-points

• Primary:
  • Death or hospital admission due to major adverse cardiovascular event

• Secondary:
  • Death or hospital admission due to ventricular arrhythmia
Death or hospitalization due to major adverse cardiovascular event

\[ p < 0.0001 \]
Death or hospitalization due to ventricular arrhythmias

(a) \( p = 0.628 \)

(b) \( p = 0.008 \)
# Prognostic value of TMR for cardiovascular events

## Univariate

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender [men]</strong></td>
<td>2.39 (2.18 – 2.62)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Age [per 1 SD increment]</strong></td>
<td>1.78 (1.69 – 1.88)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>BMI [per 1 SD increment]</strong></td>
<td>1.24 (1.20 – 1.29)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>2.22 (1.91 – 2.58)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>SBP [per 1 SD increment]</strong></td>
<td>1.34 (1.23 – 1.46)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>( \overline{HR}_{ex} ) [per 1 SD increment]</td>
<td>1.11 (1.06 -1.15)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>( \overline{HR}_{rec} ) [per 1 SD increment]</td>
<td>1.11 (1.06 -1.16)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>( \Delta HR_{ex} ) [per 1 SD decrement]</td>
<td>1.15 (1.10 – 1.21)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>( \Delta HR_{rec} ) [per 1 SD decrement]</td>
<td>1.20 (1.14 – 1.26)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>( TMR_{ex} ) [per 1 SD decrement]</td>
<td>1.14 (1.10 – 1.18)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>( TMR_{rec} ) [per 1 SD decrement]</td>
<td>1.28 (1.05 – 1.57)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

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Cardiovascular events survival curves

- TMR = 0.04: Cut-off value to risk-stratify CHF patients according to SCD risk

Ramírez et al. J Am Heart Assoc 2017

\[
TMR^{ex} < 0.04 \quad \text{and} \quad TMR^{ex} \geq 0.04
\]

\[
TMR^{rec} < 0.04 \quad \text{and} \quad TMR^{rec} \geq 0.04
\]
Conclusions

• We have demonstrated the association between the T-wave morphology restitution index, TMR, and cardiovascular events in a large (~58,000) general population
  • Predictive value during the recovery stage > exercise stage

• TMR was independent from demographic and heart rate information.
  • Higher values (increased T-wave morphology variations per RR increment) → increased cardiovascular risk.

• Future work:
  • Investigate the underlying biological mechanisms
  • Combine multiple risk predictors to improve prediction
Thank you for your attention!

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