Repolarization Morphology
and Cardiac Safety

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Rochester, NY
T Wave Morphology

Benhorin J et al.
Circulation 1990;82:521-7
T-wave morphology and LQTS mutations


Transmural Heterogeneity of Repolarization

Antzelevitch C and Shimizu W. Curr Opin Cardiol 2002;17:43-51
<table>
<thead>
<tr>
<th>Variable</th>
<th>LQT1</th>
<th>LQT2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc</td>
<td>488±26</td>
<td>496±26</td>
<td>0.098</td>
</tr>
<tr>
<td>QTpc</td>
<td>385±27</td>
<td>371±52</td>
<td>0.483</td>
</tr>
<tr>
<td>TpTo</td>
<td>95±17</td>
<td>117±48</td>
<td>0.016</td>
</tr>
<tr>
<td>T wave complexity</td>
<td>0.18±0.08</td>
<td>0.27±0.13</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>N=84</th>
<th>N=43</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tbody>
</table>
T Wave Morphology in LQT2 Carriers and Noncarriers
### I$_{kr}$-related Repolarization Abnormalities from Surface ECGs

<table>
<thead>
<tr>
<th>HERG mutation, LQT2</th>
<th>Sotalol</th>
<th>Moxifloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject non-carrier of HERG mutation RR=1000 msec, QTc=415 msec</td>
<td>Healthy subject RR=845 msec, QTc=383 msec</td>
<td>Baseline, RR=1072msec, QTc=425 msec</td>
</tr>
<tr>
<td><img src="image" alt="ECG Trace" /></td>
<td><img src="image" alt="ECG Trace" /></td>
<td><img src="image" alt="ECG Trace" /></td>
</tr>
<tr>
<td>Patient carrier of HERG mutation RR=1002 msec, QTc=428 msec</td>
<td>Healthy subject after sotalol dose (1430ng/ml) RR=845 msec, QTc=417 msec</td>
<td>Moxifloxacin, RR=1038msec, QTc=433 msec</td>
</tr>
<tr>
<td><img src="image" alt="ECG Trace" /></td>
<td><img src="image" alt="ECG Trace" /></td>
<td><img src="image" alt="ECG Trace" /></td>
</tr>
<tr>
<td>(2 hours after 400 mg dose)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- HERG: Human Ether-à-go-go Related Gene
- LQT2: Long QT Syndrome Type 2
Scalar T-wave measurements, HR Dependency and LQTS Mutations

**T-wave Magnitude (Lead II)**

- **LQT1**
- **LQT2**

**TpTe (lead II)**

- **RR bins (msec)**
QTc distribution in LQT2 (KCNH2 mutation)

Couderc et al. Heart Rhythm Journal 2006
Figure 2. ECG registration of T wave alternans at baseline before the almokalant infusion in TdP patient 3 (see Table II). The registration shows shifting polarity of the T waves, most visible in leads V3-V5.
Distribution of QTc by Categories in 443 LQT2 Gene Carriers
(mean age: 26 ± 20 years; 57% females)

- normal QTc (<440ms)  n= 62 (14%)
- borderline QTc (440-500ms)  n= 264 (60%)
- definitely prolonged QTc (>500ms)  n= 117 (26%)
T Wave Morphology Classification

- bifid/notched
- broad/slow
- flat
- normal
T wave morphology and ACA or Death in LQT2 Patients with QTc 440-500 ms

Unadjusted $P = 0.005$
Percent Change in QT, JT interval and QT, JT Dispersion in Female vs. Male Rabbits after Dofetilide or Placebo

Different electrophysiology of the myocardial layers accounts for changes in QT-T wave with various lesions

“TDR” = Transmural dispersion of repolarization
Spatial (Interlead) Heterogeneity
Transmural (Interlayer) Heterogeneity
QTpeak/QTend
Temporal (Dynamic) Heterogeneity

Global Surface ECG Phenomena
Local AP Heterogeneity

V1 V2 V3 V4 V5 V6

Spatial (Interlead) Heterogeneity

Transmural (Interlayer) Heterogeneity

QTpeak/QTend

Temporal (Dynamic) Heterogeneity

Epi
M cell
Endo
TpTe Interval and Dispersion of Repolarization

Opthof et al. Heart Rhythm 2007;4:341-8
Scalar Repolarization Morphology

T-wave Loop Repolarization Parameters

Sotalol-Induced T-Wave Impairment

Example of ECG tracings illustrating the T-wave amplitude impairment to heart rate induced by sotalol, healthy male subject
Sotalol and T-amplitude Dependency to HR
Moxifloxacin-Induced Repolarization Changes

<table>
<thead>
<tr>
<th></th>
<th>Median difference vs. placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT offset (msec)</td>
<td>13.6</td>
<td>0.020</td>
</tr>
<tr>
<td>T magnitude (mV)</td>
<td>-0.03</td>
<td>0.023</td>
</tr>
<tr>
<td>(\alpha_L) ((\mu)V/ms)</td>
<td>-0.36</td>
<td>0.007</td>
</tr>
<tr>
<td>(\alpha_R) ((\mu)V/ms)</td>
<td>0.58</td>
<td>0.011</td>
</tr>
<tr>
<td>TpTe (msec)</td>
<td>-0.5</td>
<td>0.41</td>
</tr>
<tr>
<td>(\lambda_2/\lambda_1)</td>
<td>0.01</td>
<td>0.41</td>
</tr>
<tr>
<td>Planarity ((\lambda_3))</td>
<td>-0.05</td>
<td>0.14</td>
</tr>
<tr>
<td>ERD(_{30%}) (msec)</td>
<td>11.1</td>
<td>0.001</td>
</tr>
</tbody>
</table>

All measurements are corrected for HR using pooled-formula
Moxifloxacin-induced Repolarization Abnormalities

Simulated ECG tracings
Moxifloxacin-induced Repolarization Abnormalities
# Ability to Identify TdP Patients at Baseline Before and After Drug Challenge

<table>
<thead>
<tr>
<th></th>
<th>Before: Baseline (absolute values)</th>
<th>P value (baseline)</th>
<th>After: Sotalol challenge (sotalol induced changes)</th>
<th>P value (challenge)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(-) TdPs N=17</td>
<td>(+) TdPs N=16</td>
<td>(-) TdPs N=17</td>
<td>(+) TdPs N=16</td>
</tr>
<tr>
<td>QTc*</td>
<td>425.7±35.6</td>
<td>451.0±39.3</td>
<td>0.06</td>
<td>79.0±47.4</td>
</tr>
<tr>
<td>TpTe</td>
<td>104.7±30.6</td>
<td>108.2±30.5</td>
<td>0.74</td>
<td>8.2±23.7</td>
</tr>
<tr>
<td>ERD30%</td>
<td>34.8±8.6</td>
<td>43.7±12.6</td>
<td>0.02</td>
<td>11.3±14.2</td>
</tr>
<tr>
<td>ERD50%</td>
<td>55.9±14.6</td>
<td>71.4±22.1</td>
<td>0.02</td>
<td>23.3±28.7</td>
</tr>
<tr>
<td>LRD30%</td>
<td>27.7±4.9</td>
<td>35.2±17.5</td>
<td>0.12</td>
<td>3.8±3.5</td>
</tr>
<tr>
<td>LRD50%</td>
<td>42.8±5.5</td>
<td>55.5±31.9</td>
<td>0.14</td>
<td>5.2±5.7</td>
</tr>
<tr>
<td>LRD70%</td>
<td>65.3±10.6</td>
<td>86.0±43.7</td>
<td>0.08</td>
<td>8.4±13.2</td>
</tr>
</tbody>
</table>
Repolarization Reserve

A schematic diagram showing the changes in Ca2+ handling and contractility and the potential compensatory function of ion-channel remodelling that causes action potential (AP) duration (APD) prolongation in congestive heart failure.
Age- and Sex-adjusted Hazard Ratios of Cardiac Death in a Population-based Cohort of 5,815 Older (>55 years) Men and Women

- ST depression
- Diabetes
- Angina
- T wave inv.
- Bord. T loop
- Bord. T axis
- Prior MI
- Abn T axis
- Abn. T loop

HR

p<0.05 for all HR

Predictive Value of T Wave Morphology in Postinfarction Patients