QT Variability: Application to Drug Studies

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No relationships to disclose
Figure 1 The ventricular action potential

Ability to recruit outward current to meet the challenge of inward current = “Repolarization Reserve”
hERG blockade destabilizes QT in dog

Van der Linde J Pharmacol Toxicol Methods. 2005
QT Variability is significantly increased in LQTS
Representative ECG tracings and associated Poincare plots of the QT and RR intervals: QT variability is significantly increased in survivors of drug induced TdP

QT variability increased in subjects at risk for drug-induced TdP

Table 2 Electrocardiographical characteristics of dLQTS patients and age- and sex-matched controls

<table>
<thead>
<tr>
<th></th>
<th>dLQTS</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group size</td>
<td>20</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>59 ± 17</td>
<td>63 ± 18</td>
<td>0.57</td>
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<tr>
<td>RR, ms</td>
<td>909 ± 166</td>
<td>873 ± 131</td>
<td>0.45</td>
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<tr>
<td>QRS, ms</td>
<td>96 ± 13</td>
<td>92 ± 9</td>
<td>0.62</td>
</tr>
<tr>
<td>QT, ms</td>
<td>408 ± 47</td>
<td>391 ± 30</td>
<td>0.025</td>
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<tr>
<td>QTc, ms</td>
<td>428 ± 25</td>
<td>421 ± 34</td>
<td>0.026</td>
</tr>
<tr>
<td>STV_{QT}, ms</td>
<td>8.1 ± 3.7</td>
<td>3.6 ± 1.3</td>
<td>0.001</td>
</tr>
<tr>
<td>STV_{RR}, ms</td>
<td>15 ± 11</td>
<td>19 ± 16</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Hinterseer EHJ 2008
QT Variability Index (QTVI)

Time series of QT and HR generated

Berger, et al.
Circulation. 1997;96:1557-1565
QT Variability Index

\[ QTVI = \log \left( \frac{QTV}{\text{mean } QT^2} \right) \div \left( \frac{HRV}{\text{mean } HR^2} \right) \]

QT Variability Normalized

\[ QTVN = \left( \frac{QTV}{\text{mean } QT^2} \right) \]
QTVN and Appropriate ICD Therapy in 476 subjects

QTVN = (QTV/mean QT^2)

QTVI and Cocaine

Haigney et al., JCE 2006
Program interface
Conclusions

• Hypothesis: Increased QT variability may be a more accurate indicator of depressed repolarization reserve
  – Prior to drug
  – On drug

• The utility of QT (or T wave) variability to assess the risk of drug-induced proarrhythmia has not been adequately tested

• The ideal method for measuring in vivo repolarization instability unclear
  – ?Include the U wave?
  – Normalize for heart rate/HRV?
**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 V4-V5.

Houltz et al. PACE 1998
Induction of Short-term Variability in MAP Predicts TdP

Thomsen et al Cardiovascular Res 2007