QT/QTc

Individual Heart Rate Correction for QTi

Steve Weldon, René Kubiak

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QT\text{i} or QT interval

\begin{itemize}
  \item Parameter measured during ECG measurements

  Electrocardiogram (ECG): A graphical tracing of the electrical forces produced by the atria and ventricles during the cardiac cycle as recorded at the body surface

  \item Time from the beginning of QRS complex to end of T wave

  Indirect measure of ventricular-action potential including ventricular repolarization which occurs by outward movement of potassium through specific channels in myocardial cell membranes
\end{itemize}
Measurement of ECG Waveform

Frank G. Yanowitz, M.D., copyright 1997

http://medlib.med.utah.edu/kw/ecg/mml/ecg_533.html
Safety issues

- No drug induced prolongation
- Compare QTi values of placebo and dose group
Data

- 10 data sets
- 1 placebo group / 3 dose groups
- Same 4 dogs are used in each dose group
- 13 predefined 30-second intervals for each dose – Median used
- 52 QTi medians for each group and animal
Single Values for Dog 1344

Symbols: Placebo Dose 1 Dose 2 Dose 3

Symbols: ○ ○ Placebo ■ ■ Dose 1 ▲ ▲ Dose 2 *** Dose 3

Hours: -6 -4 -2 0 2 4 6 8 10 12 14 16 18

QT interval (msec): 100 150 200 250 300 350 400
Problem

• QTi cannot be analyzed independently RRi
• RRi and QTi are strongly correlated
• Correlation example: Non-Drug Data
• Correlation example: All Groups
• Correction formula $\Rightarrow$ uncorrelated QTc-RRi relationship
Measured QTi Values

Symbols:  Placebo  Dose 1  Dose 2  Dose 3

RRi (msec)

QTi (msec)
Traditional Correction Formulae

• Bazett: \[ QTc_{\text{(Bazett)}} = \frac{QTi}{(RRi)^{1/2}} \]

• Fridericia: \[ QTc_{\text{(Fridericia)}} = \frac{QTi}{(RRi)^{1/3}} \]

• BUT:
  Bazett’s overcorrects for HRs > 60 bpm and undercorrects for HRs < 60 bpm

• Fridericia’s correction is typically better than Bazett’s correction but still not optimal
Bazett’s Correction

Symbols:
- Placebo

QTc Bazett (msec)

RRi (msec)
Fridericia’s Correction

Symbols:  Placebo
Correction Formulae

- Formulae are derived from observed QTi-RRi relationships
  - Bazett (n = 39 in 1920)  Fridericia (n = 50 in 1920)

- These QTi-RRi relationships are used for
  - all kinds of species
  - all kinds of trials
  - all kinds of individuals
Correction Formulae

• It can be doubt that a universal correction formula that provides the best fit for all species, trials, individuals, in all circumstances exists.

• Each individual has its particular QTi-RRi relationship.

• Each individual has its particular correction formula.
Two-Step Procedure

1. Step:

Fit curve that describes the QTi:RRi relationship for placebo data

2. Step:

Use curve to correct QTi values Non-Drug All Groups
Uncorrected Placebo Values

Model Arcsin: \( QT_i = 288.29 -37.89 \cdot \text{arcsinh}(RR_i - 2.764) \)

Symbols: ○ ○ Placebo  ■ Fitted curve
Used Functions to Find Best Fit

- Function 1  \( Q_{Ti} = \alpha + \beta \cdot \text{arcsinh}(RR_{i\gamma}) \)
- Function 2  \( Q_{Ti} = \alpha + \beta \cdot \text{arctg}(RR_{i\gamma} - \text{tg}(1)) \)
- Function 3  \( Q_{Ti} = \alpha + \beta \cdot \exp(-RR_{i\gamma}) \)
- Function 4  \( Q_{Ti} = \alpha + \beta \cdot \ln(1+RR_{i\gamma}) \)
- Function 5  \( Q_{Ti} = \alpha + \beta \cdot \ln(RR_{i\gamma}) \)
- Function 6  \( Q_{Ti} = \alpha + \beta \cdot \tgh(RR_{i\gamma}) \)
- Function 7  \( Q_{Ti} = \alpha + \beta \cdot RR_{i\gamma} \)
- Function 8  \( Q_{Ti} = \alpha + \exp(\beta \cdot RR_{i\gamma}) \)
Used Functions to Find Best Fit

• Functions recommended by

Katerina Hnatkova, Marek Malik
Optimum Formulae for Heart Rate Correction of QTi
Pace, Vol. 22, November 1999

“It is known that the general shape between QTi and RR interval is best fitted by curves having approximately hyperparabolic shape.”

• Additional functions with similar shape are also used
Uncorrected Placebo Values

Symbols: ○ ○ Placebo  - - Fitted curve

Model Arcsin: \[QT_i = 288.29 - 37.89 \cdot \text{arcsinh}(RR_i - 2.764)\]
Corrected Values

Symbols: ○ ○ Placebo

Model Arcsin: QTc = 288.29 - 37.89 * arcsinh(RRi - 2.764)
# Coefficient of Correlations

<table>
<thead>
<tr>
<th>Data set</th>
<th>Model</th>
<th>Individual</th>
<th>Bazett</th>
<th>Fridericia</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>I</td>
<td>-0.06</td>
<td>-0.71</td>
<td>-0.08</td>
</tr>
<tr>
<td>02</td>
<td>IV</td>
<td>-0.01</td>
<td>-0.68</td>
<td>-0.03</td>
</tr>
<tr>
<td>03</td>
<td>I</td>
<td>-0.06</td>
<td>-0.70</td>
<td>-0.16</td>
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<tr>
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<td>V</td>
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<td>-0.80</td>
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<tr>
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<td>I</td>
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<tr>
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<tr>
<td>08</td>
<td>I</td>
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<tr>
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<td>VIII</td>
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<td>-0.76</td>
<td>-0.33</td>
</tr>
<tr>
<td>10</td>
<td>IV</td>
<td>-0.05</td>
<td>-0.88</td>
<td>-0.70</td>
</tr>
</tbody>
</table>
Corrected Values

Model Arcsin: $Q_T = 288.29 - 37.89 \times \text{arcsinh}(\text{RRI} - 2.764)$

Symbols:  
- ○ ○ Placebo  
- □ □ Dose 1  
- ▲ ▲ Dose 2  
- ★ ★ Dose 3

QTc data based (msec)
Individual Correction

- Individual QTc values are differences between expected placebo value (estimated curve) and observations (placebo and dose).
- Easy to interpret
- Independent from RRi
Use of Individual Correction

QTi-RRi-relationship:
Variability within individual < Variability between individuals

• Cross-over design
  ⇒ Correction for each individual or placebo group

• Parallel Design
  ⇒ Correction for species (general or historical)

• The more individual the fitted curve the better
Assumption

• Placebo RRi range must cover the dose RRi range
Summary

- QT\(i\) are correlated with RR\(i\)
  => QT\(i\) cannot be analyzed independently from RR\(i\)

- Bazett’s and Fridericia’s corrections does not work well
  => QT\(i\) cannot be analyzed independently from RR\(i\)

- QT\(c\) (data-based) works
  => QT\(i\) can be analyzed independently from RR\(i\)