QT/RR Hysteresis in QT Prolongation Studies

Exemplarily for a new MR Contrast Agent

APF-Workshop: EKG/QT Klinischen Studien

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Carsten Schwenke and Jörg Kaufmann
Schering AG, Berlin
Overview

1. Hysteresis
2. ICH E14
3. Example
4. Correction for hysteresis effect
5. Conclusions
Hysteresis

What is hysteresis?
A delayed adaptation of the QT after HR changes.

Piotrovsky (2005):
In humans, ”the QT interval adapts to the changes in HR rather slowly (90% of the adaptation requires ~2 minutes), and this causes the phenomenon known as QT/RR hysteresis“.
ICH E14

3.1.2 Correction Formulae Derived from Within-Subject Data

As adaptation of the QT/QTc interval to changes in heart rate is not instantaneous, care should be taken to exclude ECG recordings collected during times of rapid heart rate changes due to this QT/RR hysteresis effect.

=> hysteresis not mentioned anywhere else in E14
ICH E14

2.2.2 Dose-Effect and Time Course Relationships in the "Thorough QT/QTc Study"

"An adequate drug development program should ensure that the dose-response and generally the concentration-response relationship for QT/QTc prolongation have been characterized, including exploration of concentrations that are higher than those achieved following the anticipated therapeutic doses."

2.2.3 Timing of ECGs in the "Thorough QT/QTc Study"

"...care should be taken to perform ECG recordings at time points around the Cmax."
But...

*What about drugs inducing rapid HR changes after administration close to Cmax?*

**Example: Contrast agents for MRI**

Fast administration of liquid into the arteries or veins

=> rapid change in HR at Cmax after administration of the contrast agent

=> increased change in HR with increased dose (higher volume)

=> change in HR happens at the timepoint of interest for QT prolongation
Example: MRI Contrast Agent

Thorough QT-Study

5-period Williams-cross-over study
- concurrent placebo control
- positive control (assay sensitivity)
- three dose groups
  (low dose, therapeutic dose, supratherapeutic dose)
- patient population and study design according to ICH E14
Example: Study Results

Average change in QTcF of first 15 minutes post injection

- Moxi - Placebo: -3.0, 2.3, 10.7, 16.1
- Dose3 - Placebo: 1.5, 6.9
- Dose2 - Placebo: 0.1, 5.5
- Dose1 - Placebo: 2.3
Example: Study Results (2)

Slight increase in QTcF seen with higher doses

However...

<table>
<thead>
<tr>
<th></th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Dose 3</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTcF avg</td>
<td>2.3</td>
<td>5.4</td>
<td>6.8</td>
<td>2.6</td>
</tr>
<tr>
<td>QT avg</td>
<td>-1.1</td>
<td>-1</td>
<td>-6.9</td>
<td>2.7</td>
</tr>
<tr>
<td>HR avg</td>
<td>1.4</td>
<td>3.3</td>
<td>6.8</td>
<td>0</td>
</tr>
</tbody>
</table>

(baseline corrected)
Characterization of QT/RR Hysteresis

Non-linear method of QT dynamics assessment from non-steady-state recordings (Neilson 1998):

First step:
- compensate for QT lag by resynchronizing the variations in QT and RR

Second step:
continuous calculation of the QT/RR slope inside 5-min windows during periods of strong correlation of QT and RR (R>0.8)

\[ QT_{cj} = QT \_ (RR) - J \]

where \( J = S(RR/QT) \) varies over time.
mean(\( J \))=0.32 in healthy subjects (Sredniawa 2005)
Characterization of QT/RR Hysteresis (2)

QT Interval adaptation by weighted averages of RR intervals (Pueyo et al. 2004):

Aim:
Optimum subject-specific RR averaging window for QT/RR hysteresis (profile and duration)

Approach:
(1) fixed window profile of RR average
   - estimation of profiles of moving-window averages to obtain $\bar{RR}$
   - linearly weighted or exponentially weighted
Characterization of QT/RR Hysteresis (3)

(2) Individualized Profiles of RR average
- assessment of individual window duration L by global optimization algorithm
- assessment of RR interval averaging weights by regression
  - ten different models used:
    linear, hyperbolic, parabolic log/log, logarithmic, shifted logarithmic, exponential, arcus tangent, hyperbolic tangent, arcus hyperbolic sine, arcus hyperbolic cosine.
  - optimum defined, where regression residual of fitting [QT, \overline{RR}] data minimal
Characterization of QT/RR Hysteresis (4)

(3) Effective RR history
- estimation of window length $L$, where preceding cardiac cycles have effect on QT
- $L$ estimated as a function of average RR and number of beats with influence on the respective QT

(4) Heart rate correction
- all ten regression models converted into HR correction formula projecting QT interval onto $\overline{RR} = 1 \text{ sec}$
- optimum for each subject selected by golden cut search
  $\Rightarrow$ Pearson corr. coefficient between QT$c$ and RR $= 0$
Correction for Hysteresis and Heart Rate

Pueyo et al. provide a method for hysteresis characterization but not for hysteresis correction.

Prof. M. Malik further advanced this method and expanded the approach towards correcting the QTc interval for a combination of heart rate and hysteresis.

He developed this correction recently in cooperation with Schering AG on animal and clinical data.

Results are not published yet.
Correction for Hysteresis and Heart Rate (2)

Ongoing activities:

Pilot analysis on thorough QT study of new MRI contrast agent

=> new ECG reading and analysis done by Prof. M. Malik

=> correction for hysteresis and heart rate as addition to original analysis
Conclusions

Without correction for hysteresis effect:

=> artificial effect on corrected QT possible
=> direction of bias of QTc depends on direction of change in HR

Therefore

- with stable HR, no correction for hysteresis needed
- in presence of rapid changes in heart rate around Cmax, correct for hysteresis effect
References


References


Vielen Dank !