Meaning and Determination of the QT-Interval : Clinical Aspects

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Background of the QT-interval

- QT interval is used as a surrogate marker for the prediction of serious adverse drug effects like:
  - VT/ TDP
  - syncope
  - sudden cardiac death

- HR is an important factor affecting QT. Drugs may independently affect QT and HR and the successful treatment of a disease may itself change the HR
Background LQTS

• Molecular genetic aspects: Channelopathy
  - 7 genes have been linked to LQTS
  - mutations of the fast and slow K⁺-channel (loss of function, reduces repolarizing K⁺ currents)
  - mutations of the Na⁺-channel (gain of function, increases inward INa currents)

  prolongation of the repolarization

• congenital QT-syndrome
• acquired QT-syndrome (drug induced)
Background LQTS: Genetic

- 7 Genes on chromosomes 3, 4, 7, 11 and 21 identified
- Most frequent are mutations on KCNQ1-gene (LQT1 30%) and on KCNH2-gene (LQT2 30%).

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Channel Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1-Syndrom:</td>
<td>KCNQ1</td>
<td>mutations slow K-channel</td>
</tr>
<tr>
<td>LQT2-Syndrom:</td>
<td>KCNQ2</td>
<td>mutations fast K-channel</td>
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<tr>
<td>LQT3-Syndrom:</td>
<td>SCN5A</td>
<td>mutations Na-channel</td>
</tr>
<tr>
<td>LQT4-Syndrom:</td>
<td>ankyrin B</td>
<td>mutations unknown</td>
</tr>
<tr>
<td>LQT5-Syndrom:</td>
<td>KCNQ1</td>
<td>mutations slow K-channel</td>
</tr>
<tr>
<td>LQT6-Syndrom:</td>
<td>KCNQ2</td>
<td>mutations fast K-channel</td>
</tr>
</tbody>
</table>
LQTS
1:7000 bis 1:10000 all newborn

Congenital (60 %)

Romano Ward (99%)
Autosomal dominant
LQT1 (25%), LQT2 (25%), LQT3 (10%)
Mild-severe
LQT5 (1%), LQT6 (1%)
Mild
Autosomal rezessiv
LQT1-3 (1%)
severe

Jervell-Lange-Nielsen-syndrome (<1%)
Autosomal rezessiv
LQT1 (75%), LQT5 (25%)

Sporadic (40 %)

New mutations (LQT1-3)

Anderson-syndrome
Autosomal dominant with extracardiac involvement
LQT7
Typical episode of drug induced VT or TDP associated with QT-prolongation
Measurement of the QT-interval guidelines

- manually measured by using one of the limb leads
- Beginning of QRS – end of T – wave (3-5 beats)
- U-wave only included if large and merging with T-wave
- Measured during peak plasma levels of the QT prolonging drugs
- QT interval should be adjusted for heart rate

Al Khatib et al., JAMA 2003: 289; 2120-2127
ECG in LQTS \((QTc \ 550ms)\)
Measurement of the QT-interval

- SR vs atrial fibrillation
- narrow QRS vs wide QRS vs pacemaker QRS

Figure. Measuring the QT Interval in Different Clinical Scenarios

Bazett Formula (60-100 bpm)

\[
\text{QTc} = \frac{\text{QT}}{\sqrt{\text{RR}}}
\]

Fridericia Formula (> 80-100 bpm)

\[
\begin{align*}
\text{QTc}_1 &= \frac{\text{QT}_1}{\sqrt{\text{RR}_1}} \\
\text{QTc}_2 &= \frac{\text{QT}_2}{\sqrt{\text{RR}_2}} \\
\text{QTc} &= \frac{\text{QTc}_1 + \text{QTc}_2}{2}
\end{align*}
\]
Interpretation of the QT-interval

• QT interval > 500 ms is commonly regarded as conferring an increased risk

• QTc Interval > 450 ms in male
• QTc interval > 460 ms in female

• However, in family members of pts with LQTS (registry) 5 % had TDP or SCD with QTc < 440 ms as QT interval is inconstant

• Exercise testing: no reduction of QT duration during HR increase
Typical ECG findings in LQTS

- QT-prolongation, QT-dispersion
- T wave changes, U-wave
- Bradycardia
- polymorphic VT/TDP
<table>
<thead>
<tr>
<th>Criteria for the diagnosis of LQTS</th>
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</thead>
<tbody>
<tr>
<td>• QTc interval</td>
</tr>
<tr>
<td>- &gt; 480 ms</td>
</tr>
<tr>
<td>- 460 - 470 ms</td>
</tr>
<tr>
<td>- 450 ms</td>
</tr>
<tr>
<td>- TDP</td>
</tr>
<tr>
<td>- T-wave alternas</td>
</tr>
<tr>
<td>- incision in T wave in 3 leads</td>
</tr>
<tr>
<td>- bradycardia</td>
</tr>
<tr>
<td>- syncope</td>
</tr>
<tr>
<td>- during exercise</td>
</tr>
<tr>
<td>- without exercise</td>
</tr>
<tr>
<td>- deafness</td>
</tr>
<tr>
<td>- Family history for LQTS</td>
</tr>
<tr>
<td>- SCD &lt;30 yrs of age</td>
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</tbody>
</table>

< 1 point probability low; 2-3 points moderate, > 4 points high
Clinical aspects for the different forms of LQTS
Genotype-phenotype correlations and risk stratification

<table>
<thead>
<tr>
<th></th>
<th>LQT1</th>
<th>LQT2</th>
<th>LQT3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction</strong></td>
<td>Exercise, physical activity, swimming</td>
<td>Emotional stress, acoustic stimuli</td>
<td>Sleep, rest</td>
</tr>
<tr>
<td><strong>T-wave</strong></td>
<td>Prolonged, QT not shortened by exercise</td>
<td>Small</td>
<td>delayed</td>
</tr>
<tr>
<td><strong>Cardiac event until 40 yrs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 1 event (%)</td>
<td>62</td>
<td>46</td>
<td>18</td>
</tr>
<tr>
<td>≤ 1 event (%)</td>
<td>37</td>
<td>36</td>
<td>5</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>4</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>Mean age at 1. event</td>
<td>9 yrs.</td>
<td>12 yrs.</td>
<td>16 yrs.</td>
</tr>
</tbody>
</table>
Survival free events in LQTS

Priori et al., N Engl J Med 2003: 348; 1866-1874
Survival free events in LQTS according to QT-durations

Priori et al., N Engl J Med 2003: 348; 1866-1874
Survival free events in LQT1 according to sex and QTc

Priori et al., N Engl J Med 2003: 348; 1866-1874
Survival free events in LQT2 according to sex and QTc

Priori et al., N Engl J Med 2003: 348; 1866-1874
Survival free events in LQT3 according to sex and QTc

Priori et al., N Engl J Med 2003: 348; 1866-1874
Incidence of first event before the age of 40 yrs in different forms of LQTS

Priori et al., N Engl J Med 2003: 348; 1866-1874
QTc duration is associated with the event rate in the LQTS

Priori et al., N Engl J Med 2003: 348; 1866-1874
Risk stratification for LQTS

High Risk

> 50%

QTc ≥ 500 msec
- LQT1, LQT2
- Male sex, LQT3

Intermediate Risk

(30-49%)

QTc < 500 msec
- Female sex, LQT2
- Female sex, LQT3
- Male sex, LQT3

Low risk

< 30%

QTc < 500 msec
- Male sex, LQT2
- LQT1

Priori et al., N Engl J Med 2003: 348; 1866-1874
• In the past decade the single most common cause of the withdrawal or the restriction of the use of drugs that have already been marketed has been the prolongation of the QT-interval

• QT interval prolongation is associated with polymorphic VT or TDP.

• Current predictors of this serious side effect are imperfect, both for individual pts and for populations of pts who are exposed to a given drug
Drugs that may cause TDP

• **Drugs commonly involved** (Loss of function K+)
  • by more than 50 ms, risk for TDP 2-4%, monitoring required
    - Quinidine
    - Sotalol
    - Dofetilide
    - Ibutilide
    - Disopyramide
    - Bepridil
    - Amiodarone (risk for TDP < 1%)

• **Other drugs**
  • mean increase about 5-20 ms. risk for TDP < 1%
    - Cisapride (gain of function)
    - Antiinfective agents: claritromycin, erythromycin
    - antiemetic agents: domperidone, droperidol
    - antipsychotic agents: chlorpromazine, haloperidol etc
    - Methadone
Risk factors for drug induced TDP

- female gender
- family history of SCD
- Hypokalemia
- Bradycardia
- Recent CV of atrial fibrillation in SR (e.g., AAD)
- congestive heart failure
- digitalis therapy
- High drug concentrations (exception quinidine)
- rapid iv infusion with a QT prolonging drug
- baseline QT prolongation
- ion channel polymorphisms
- severe Hypomagnesemia
Hereditäre Susceptibility for a subclinical LQTS

- subclinical SCN5A-mutation, which manifests after Cisaprid administration
- sotalol unmasks drug induced QT prolongation

Kääb et al., European Heart Journal 2003:24; 649-657
Precautions if QT prolonging drug is administered

• minimal program
  - carefully taken history for risk predictors
  - ECG

• Patient should be informed to report promptly the new-onset of symptoms like
  - palpitations
  - near syncope
  - syncope

• or intercurrent conditions or therapies that can cause hypokalemia

• Control ECG during treatment
Treatment options

• No/withdrawal of QT prolonging drugs

• betablocker (recurrence rate 25%, SCD 10%) plus pacemaker

• contraindication for BB: Ca-antagonist (EAD)

• pacemaker (increase of the intrinsic heart rate)

• ganglion stellatum blockade

• ICD

• acute treatment if VT/TDP persists after KV
  - withdrawal of QT prolonging drugs
  - Mg 2 iv in 2 min (2x) K > 4.5 mmol/l
  - BB, Lidocain, Ca-antagonist
Recomodations for clinical practice

• Physicians have to be informed about the problem with QT-prolonging drugs (not only cardiologists)

• adequate dosage of the drug, reduce dosage, if renal or hepatic failure

• use potassium saving diuretics, if necessary

• control the ECG, E‘lyte
Weighing risk and benefits

- **Drug effectiveness in an otherwise fatal disease**
  - Arsenic trioxide. acute promyelocytic leukemia
  - Antiarrhythmic drug

- A drug that causes even a very low incidence of TDP would be unacceptable if safer alternative were available or if the indication were not itself serious.