"Drug challenges in the diagnosis of inherited arrhythmias: friends or foes?"

Orhan Uzun
University Hospital Of Wales

Clinical Use of Drug Challenges

• Unmask Brugada syndrome or LQTS, but also less often in CPMVT
• Ajmaline challenge in suspected Brugada syndrome
• Epinephrine challenge in suspected LQTS and CPMVT
Fainting After A Game

- 10 year old boy, healthy, no previous problems
- No family history of SIDS, SCD, LQT or Brugada
- Mother and father both have normal QTc
Fainting After A Game

*Epinephrine Challenge*

- QTc prolonged from 440 to 540 on Shimizu
- Placed on Beta Blockers and restrictions
Asymptomatic Child

- 8 year old girl with previous VSD surgical closure
- Incidental finding of type-2 ST elevation
- No family history of SIDS, SCD, LQT or Brugada
Mother of Asymptomatic Child

**Ajmaline Challenge**

- Parents referred to cardiology baseline ECG type2?
- Ajmaline produced further ST elevation Type 1?
Loss of Consciousness

- 37 year old fit active man
  - Arose from bed, toilet, just finished urinating, developed prodromal light-headedness. Prompt LOC with minor injury
- PMH is remarkable for LOC aged 9 in Assembly
- No family history of SID, SCD, Brugada or LQTS

![Baseline ECG](image1.png)

![5 min ECG](image2.png)
Brugada Syndrome

- Autosomal dominant and common in men
- Prevalence of 1:2000 in the world and 1:1000 in Japan, 1:500 Singapore, Thailand
- Youngest patient 2 days old, oldest 84 year
- ~4% of all sudden deaths and 20% of sudden deaths in patients with structurally normal hearts
- Type 2-ECG prevalence varies between 0.2 and 0.6 in European population
Brugada ECG Types

AD with incomplete penetrance and variable expression
Defects in alpha-subunit of cardiac Na channel
Reduction in Na current accentuates epicardial AP notch leading to ST-segment elevation

Type I Diagnostic
- Coved

Type 2
- Saddle Back

Type 3
- Non Diagnostic

RBBB pattern with ST elevation in leads V1-V3
Brugada Diagnostic Criteria

- A type-1 ECG (coved-type), spontaneously or after Na-channel blocker
- Plus 1 of the following is also required:
  - Ventricular fibrillation or PM-VT
  - Family history of sudden death less than 45 yr
  - Coved-type ECGs in family members
  - Inducibility of VT with PES
  - Syncope, or nocturnal agonal respiration

Bangungot (in the Philippines), Pokkuri (in Japan), or Lai Tai (in Thailand)

Heart Rhythm 2005;2:429–40
Drug Challenges in Brugada Syndrome

- ECG features of Brugada syndrome - RBBB pattern with ST elevation in leads V1-V3 can be produced by blocking cardiac sodium channels using:
  - Ajmaline 1 mg/kg over 5 min
  - Flecainide 2 mg/kg over 10 min (400 mg PO)
  - Procainamide 10 mg/kg over 10 min
  - Pilsicainide 1 mg/kg over 10 min

_Circulation_ 2005;111;659-670
Ajmaline or Flecainide Protocol

• Ajmaline given 1 mg/kg over 5 min bolus
  – ECG printed every minute for 5 minutes during infusion, then
  – Every minute for 5 minutes after infusion and
  – At any time when ST elevation is noted

• Flecainide 2mg/kg IV over 10 minutes
  – ECG printed every minute for 10 minutes during infusion, then
  – Every minute for 10 minute after infusion, and
  – Any time when ST elevation is noted

*Circulation 2005;111;659-670*
Positive Test Brugada Syndrome

• 2mm ST elevation in one or more RV leads of V1-V3 with Type 1 COVED ECG

• If positive, 12 lead ECG is continued every 2 minutes until ECG normalises

• Patient monitored for at least 30 minutes if the test is negative and for 60 minutes if the test is positive or equivocal
# Power of Ajmaline Challenge

<table>
<thead>
<tr>
<th>Description</th>
<th>Negative test</th>
<th>Positive test</th>
</tr>
</thead>
<tbody>
<tr>
<td>677 pts, retrospective, 4 centers, unselected group, Familial Brugada, type 2 ECG, syncope</td>
<td>415 pts negative test (61%)</td>
<td>262 pts positive test (39%)</td>
</tr>
<tr>
<td>Total 382 pts genotyped for SCN5A (56%)</td>
<td>144 pts with –ve test genotyped</td>
<td>238 pts with +ve test genotyped</td>
</tr>
<tr>
<td>76 pts SCN5A Positive (20%)</td>
<td>18/144</td>
<td>58/238</td>
</tr>
<tr>
<td>Veltmann et al. Europace 2009;11:1345-1352</td>
<td>FALSE 13% Negative test</td>
<td>(24%)</td>
</tr>
<tr>
<td>Despite positive genotype</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IC-SCN5A</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veltmann 2009</td>
<td>76%</td>
<td>43%</td>
<td>24%</td>
<td>88%</td>
</tr>
<tr>
<td>Hong 2004</td>
<td>80</td>
<td>94</td>
<td>93</td>
<td>83</td>
</tr>
<tr>
<td>Meregalli 2006</td>
<td>77</td>
<td>80</td>
<td>96</td>
<td>36</td>
</tr>
<tr>
<td>(Flecainide)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Circulation 2004;110:3023

J Cardiovasc Electrophysiol 2006;17:857–6
# Power of Ajmaline Challenge

<table>
<thead>
<tr>
<th></th>
<th>Negative test</th>
<th>Positive test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>41 pts with –ve test</td>
<td>30 pts with +ve test</td>
</tr>
<tr>
<td></td>
<td>(58%)</td>
<td>(42%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>FALSE Negative test</th>
<th>Positive test</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 pts (20%)</td>
<td>28 patients with</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Despite +ve genotype</td>
<td>(80%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Negative test</th>
<th>FALSE Positive test</th>
</tr>
</thead>
<tbody>
<tr>
<td>34/36 (94%)</td>
<td>2/36 (16%)</td>
<td></td>
</tr>
<tr>
<td>Hong at al 2004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circulation 2004;110:3023-7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SCN5A</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hong 2004</td>
<td>(28/35) 80%</td>
<td>(34/36) 94%</td>
<td>(28/30) 93%</td>
<td>(34:41) 83%</td>
</tr>
</tbody>
</table>

Test increased penetrance from 32% to 78%
# Power of Flecainide Challenge

<table>
<thead>
<tr>
<th>159 pts with syncope, aborted SCD</th>
<th>Negative Flecainide test</th>
<th>Positive Flecainide test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>95 (60%)</td>
<td>64 (40%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>110 pts genotyped for SCN5A</th>
<th>Negative FCT</th>
<th>Positive FCT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>51 Negative FCT</td>
<td>59 Positive FCT</td>
</tr>
<tr>
<td></td>
<td>7 pts SCNA5 +ve (14%)</td>
<td>23 pts SCNA5 +ve (39%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>From 12 SCN5A +ve families 35 pts selected</th>
<th>7 False –ve test (63%)</th>
<th>1 False +ve test (4%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Of 11 pts -ve FCT</td>
<td>Of 24 pts +ve FCT</td>
</tr>
<tr>
<td></td>
<td>+ 7/11 SCNA5 (63%)</td>
<td>+ 23/24 SCNA5 (96%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IC-SCN5A</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meregalli 2006 (Flecainide)</td>
<td>77%</td>
<td>80%</td>
<td>96%</td>
<td>36%</td>
</tr>
</tbody>
</table>

Failure of flecainide in genotype positive patients (32%) may be due to greater inhibition of Ito by flecainide which may make it less effective.
Intermittent Brugada ECG
Test Reproducibility

Initial ECG with Flecainide challenge

Negative test in the follow up
Flecainide Reproducibility

After Event

Initial

2 weeks later
Safety of Ajmaline Challenge

- Ventricular tachyarrhythmias was reported to be very low 0.3%.
- 1 of 677 patients 0.15% had sustained VF which was terminated by a single external DC shock.
- In 2.4% of the patients test was stopped due to QRS prolongation or the occurrence of PVCs.
Conclusion

- Na channel blocking test is a safe and valuable tool in the diagnosis of SCN5A carriers.
- The sensitivity and specificity of ajmaline is superior compared to Flecainide, Procainamide and Pilsicainide.
- A negative INa blocking test does not exclude Brugada Syndrome.
- Negative responses can change to a positive one if the test is repeated another day.
BS Risk is Decreasing

- Brugada Registry – Asymptomatic Patients
  - 1998 – 10% VT/VF per year
  - 2002 – 3.5% VT/VF per year
  - 2005 – 1.7% VT/VF per year
  - 2009 – 0.9% VT/VF per year

Brugada HRS Boston May 2009  Courtesy of PO’C
## Risk Stratification

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Low Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Syncope</td>
<td>Normal basal ECG</td>
</tr>
<tr>
<td>Abnormal basal ECG</td>
<td>Non-inducible</td>
</tr>
<tr>
<td>Inducible VT/VF ??</td>
<td></td>
</tr>
</tbody>
</table>

EPS has a high negative predictive value

+/- FHx  Sudden death has no predictive value!
**Spontaneous Type 1 ECG**

**Symptomatic**
- Aborted SCD
  - Syncope
  - Seizure
  - NAR

  Evaluate for clear extracardiac cause
  - ICD (class I)
    - EPS recommended for assessment of supraventricular arrhythmias
      - ICD (class I)
      - Close Follow-up
    - ICD (class IIa)
      - Close Follow-up

**Asymptomatic**
- Family History of SCD suspected to be due to BS
  - EPS (class IIa)
    - +
      - ICD (class IIa)
      - Close Follow-up
    - -
      - EPS justified (class IIa)
    - -
      - ICD (class IIa)
      - Close Follow-up

- No Family History
Brugada Management Guide

Sodium Channel Block-induced Type 1 ECG

**Symptomatic**
- Aborted SCD
- Syncope
- Seizure
- NAR

Evaluate for clear extracardiac cause

- ICD (class I)
- ICD (class IIa)
- Close Follow-up

- EPS recommended for assessment of supraventricular arrhythmias

**Asymptomatic**
- Family History of SCD suspected to be due to BS
- No Family History

EPS justified (class IIb)

- Close Follow-up

- ICD (class IIb)
- Close Follow-up
Risk Stratification

Type-1 ECG after Class I

Spontaneous Type-1 ECG

Free of SD or VF

0 12 24 36 48 60
Months Follow-up

p=0.046
Brugada in Childhood

- Brugada syndrome can manifest during childhood
- Symptoms may appear during febrile illness
- Symptomatic patients with a spontaneous type-1 ECG may be at a high risk of cardiac events in a short period of follow-up (48 months)
- ICD may be considered only in symptomatic cases with baseline Type 1 ECG
- Quinidine could be an option in particularly the youngest patients

Circulation 2007;115;2042-2048
Progress in Cardiovascular Diseases 2008; 51(1): 1-22
Long QT Syndrome

- Uncommon genetic disorder 1:3000-5000
- QTc normal range 350-440ms
- ECG QTc interval prolonged
  - ≥ or > 450ms in males (AHA/ACCF/HRS)
  - ≥ or > 460ms in females (AHA/ACCF/HRS)
  - ≥ or > 470 in both sexes sensitivity
- 25-30% of carriers will have QTc 420-460ms
QT interval Distribution

![Graph showing the distribution of QT intervals for non-genetically affected and genetically affected patients. The x-axis represents 20 ms QTc clusters ranging from 320 to 700, and the y-axis represents the number of patients. The bars for non-genetically affected patients are colored light gray, and the bars for genetically affected patients are colored dark gray.](image-url)
Need For Provocation Tests?

- 25-30% of carriers have QTc 420-460ms
- 10-15% of carriers <440 “concealed LQTS"
Table 2 Detection rates (DRs) at various rate corrected QT (QTc) cut off points for long QT syndrome along with respective false positive rates (FPRs) and odds of being affected given a positive result (OAPRs)

<table>
<thead>
<tr>
<th>QTc cut off level (≥)</th>
<th>DR (%)</th>
<th>FPR (%)</th>
<th>OAPR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.41</td>
<td>99.2</td>
<td>69.1</td>
<td>1:3500</td>
</tr>
<tr>
<td>0.42</td>
<td>98.1</td>
<td>50</td>
<td>1:2550</td>
</tr>
<tr>
<td>0.43</td>
<td>96</td>
<td>32.6</td>
<td>1:1700</td>
</tr>
<tr>
<td>0.44</td>
<td>92.4</td>
<td>17.9</td>
<td>1:970</td>
</tr>
<tr>
<td>0.45</td>
<td>86.4</td>
<td>8.1</td>
<td>1:470</td>
</tr>
<tr>
<td>0.46</td>
<td>78.2</td>
<td>3.1</td>
<td>1:200</td>
</tr>
<tr>
<td>0.47</td>
<td>67.7</td>
<td>0.9</td>
<td>1:66</td>
</tr>
<tr>
<td>0.48</td>
<td>55.6</td>
<td>0.2</td>
<td>1:18</td>
</tr>
<tr>
<td>0.49</td>
<td>42.5</td>
<td>0.10</td>
<td>1:12</td>
</tr>
<tr>
<td>0.50</td>
<td>30.5</td>
<td>&lt;0.01</td>
<td>&gt;1:1.5</td>
</tr>
</tbody>
</table>

*At a prevalence of 1:5000.
Sensitivity and Specificity

Panel A

Panel B

§ Performance of the gender-specific cut offs
i.e. QTc > 440 for males and QTc > 460 for females

Circulation 2003;108:IV-363
Detection rate DNA Analysis

DNA positive
- 200 Children with LQTS
- DR = 50%
- FPR = 0.01%
- 100 Children true positives
- 100 Children false positives
- OAPR 1:1

ECG positive
- 200 Children with LQTS
- DR = 30.5%
- FPR = 0.01%
- 61 Children true positives
- 100 Children false positives
- OAPR 1:1.6

<table>
<thead>
<tr>
<th>Type</th>
<th>Gene</th>
<th>Protein</th>
<th>Chromosomal Locus</th>
<th>Comment</th>
<th>Frequency, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Romano-Ward (autosomal dominant)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LQT1</td>
<td>KCNQ1</td>
<td>kvLQT1 (Kv7.1 a)</td>
<td>11p15.5</td>
<td>Trigger: Stress. Decreased IKs</td>
<td>30-35</td>
</tr>
<tr>
<td>LQT2</td>
<td>KCNH2</td>
<td>hERG (Kv11.1 a)</td>
<td>7q35-q36</td>
<td>Trigger: Noise. Decreased IKr</td>
<td>25-30</td>
</tr>
<tr>
<td>LQT3</td>
<td>SCN5A</td>
<td>Nav1.5 a</td>
<td>3p24-p21</td>
<td>Trigger: Sleep, rest. Beta blocker therapy seems to be the less effective. Increased plateau INa</td>
<td>5-10</td>
</tr>
<tr>
<td>LQT4</td>
<td>ANK2</td>
<td>Ankyrin-B</td>
<td>4q25-q27</td>
<td>Production of defective accessory protein Ankyrin-B. Polyphasic T waves. AF, SND. Decreased N/K and Na/Ca-X</td>
<td>less than 1</td>
</tr>
<tr>
<td>LQT5</td>
<td>KCNE1</td>
<td>MinK b</td>
<td>21q22.1</td>
<td>Associated to the Jervell, Lange-Nielsen syndrome (congenital deafness). Decreased IKs</td>
<td>less than 1</td>
</tr>
<tr>
<td>LQT6</td>
<td>KCNE2</td>
<td>MIRP1 b</td>
<td>21q22.1</td>
<td>Triggers: certain drugs, exercise. Decreased IKr.</td>
<td>less than 1</td>
</tr>
<tr>
<td>LQT7</td>
<td>KCNJ2</td>
<td>Kir2.1 a</td>
<td>17q23</td>
<td>Associated to the Andersen-Tawil Syndrome. Decreased IK1.</td>
<td>less than 1</td>
</tr>
<tr>
<td>LQT8</td>
<td>CACNA1C</td>
<td>Cav1.2 a1c</td>
<td>12p13.3</td>
<td>Associated to the Timothy Syndrome. Increased L type Ca current.</td>
<td>less than 1</td>
</tr>
<tr>
<td>LQT9</td>
<td>CAV3</td>
<td>Caveolin-3</td>
<td>3p25</td>
<td>Mutations of CAV3 also associated to muscle diseases. Increased plateau INa.</td>
<td>less than 1</td>
</tr>
<tr>
<td>LQT10</td>
<td>SCN4B</td>
<td>Nav1.5 β4</td>
<td>11q23.3</td>
<td>So far, only found in one single family. Increased plateau INa.</td>
<td>less than 1</td>
</tr>
<tr>
<td>LQT11</td>
<td>AKAP9</td>
<td>AKAP9/yotiao</td>
<td>7q21-q22</td>
<td>Decreased IKs</td>
<td>less than 1</td>
</tr>
<tr>
<td>LQT12</td>
<td>SNTA1</td>
<td>α1-syntrophin</td>
<td>20q11.2</td>
<td>Increased plateau INa. Asymmetrical T waves.</td>
<td>less than 1</td>
</tr>
<tr>
<td><strong>Jervell, Lange-Nielsen (autosomal recessive)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JLN1</td>
<td>KCNQ1</td>
<td>kvLQT1 7.1 a</td>
<td>11p15.5</td>
<td>Deafness autosomal-recessive homozygous Decreased IKs</td>
<td>more than 90.5</td>
</tr>
<tr>
<td>JLN2</td>
<td>KCNE1</td>
<td>MinK b</td>
<td>21q22.1</td>
<td>Deafness, compound heterozygous, autosomal-recessive. Decreased IKs</td>
<td>less than 0.5</td>
</tr>
</tbody>
</table>
# Schwartz Criteria

## ECG

<table>
<thead>
<tr>
<th>Condition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc &gt;480 ms</td>
<td>3</td>
</tr>
<tr>
<td>QTc 460-470 ms</td>
<td>2</td>
</tr>
<tr>
<td>QTc 450 ms males</td>
<td>1</td>
</tr>
<tr>
<td>Torsade de pointes</td>
<td>2</td>
</tr>
<tr>
<td>T-wave alternans</td>
<td>1</td>
</tr>
<tr>
<td>Notched T wave in 3 leads</td>
<td>1</td>
</tr>
<tr>
<td>Low heart rate for age with</td>
<td></td>
</tr>
<tr>
<td>less than second percentile</td>
<td>0.5</td>
</tr>
</tbody>
</table>

## Clinical History

<table>
<thead>
<tr>
<th>Condition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope with stress</td>
<td>2</td>
</tr>
<tr>
<td>Syncope without stress</td>
<td>1</td>
</tr>
<tr>
<td>Congenital deafness</td>
<td>0.5</td>
</tr>
</tbody>
</table>

## Family History

<table>
<thead>
<tr>
<th>Condition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family members with definite LQTS</td>
<td>1</td>
</tr>
<tr>
<td>Unexplained sudden death among immediate family members younger</td>
<td>0.5</td>
</tr>
</tbody>
</table>

## Interpretation

1 point, low probability

2 or 3 points, intermediate probability: sensitivity 59% and specificity 100%

>4 points, high probability sensitivity: 53% and specificity 100%
Sensitivity and specificity of QTc duration


Science 1991;252:704–706
Diagnostic Dilemma

[Bar chart showing probabilities of having LQTS (%)]

- General Population: <<0.1%
- 4-day-old Infant, QTc ≥ 440 ms: <1%
- Asymptomatic Female QTc ≥ 440 ms: <0.1%
- Asymptomatic Female QTc = 480 ms: 4%
- Asymptomatic child of parent with LQT1, QTc = 440 ms: ~50%
- 16 yo with TdP while swimming, QTc ≥ 500 ms: 100%

Odds: 1:2500, 1:250, 1:2000, 1:25, 1:2, ~1:1

Approximately 80% of carriers demonstrate one of these patterns:

- **LQT3**: Discrete T after long ST
- **LQT2**: Wide base, double hump
- **LQT1**: Wide based, slow upstroke

Exercise QTc and T wave Morphology

LQT1: Wide based slow upstroke large T 43% normal 28%, late onset 25%
LQT2: Wide based shallow T double hump 58%, wide based slow upstroke large T 34%
Other Helpful Tests

- History low or intermediate probability
- Family history low or intermediate probability
- Genetic history high probability 50%
- Holter low yield QTc>500ms
- Exercise test QT hysteresis or T wave morphology
Basis For Epinephrine Challenge

• Even genetic test may have false positive rate?
  – 5% of healthy subjects show rare variants in KCNQ1 of uncertain functional significance
• Epinephrine may be helpful in concealed LQTS where QTc < 440ms
• Two protocols, Shimizu high dose and Mayo low dose prolonged infusion

*Heart Rhythm. 2004;1:600–607
Epinephrine Challenge

The Shimizu Protocol

• Epinephrine 0.1 mcg/kg IV bolus
• Followed by continuous infusion 0.1 mcg/kg/min
• ECG at baseline, every min for 5 mins during epinephrine infusion, at peak and steady state
• Peak effect occurs 1–2 min after the start when the RR interval at its shortest
• Steady state effect of epinephrine on RR and QT intervals occurs usually 2–3 min after the start
• Positive test: > 35 msec prolongation of QTc recorded from average of chest leads during steady state or induction of Torsades

Eur Heart J, 2002; 23: 975–983
Shimizu Interpretation

- LQT1: Mean QTc, QTc(peak), and QTc(peak-end) are higher at peak and remain prolonged at steady state.
- LQT2: Mean QTc and QTc(peak) also prolong at peak, but they return to baseline at steady state but QTc(peak-end) unchanged with epinephrine.
  - G2 notched T waves during low-dose epinephrine may unmask concealed LQT2.
- LQT3: Mean QTc and QTc(peak) slightly prolonged at peak and return to baseline at steady state. QTc(peak-end) remains unchanged with epinephrine.
### Epinephrine “Shimizu” Interpretation

**EHJ 2002;23: 975–983**

1-2 minutes or after bolus

3-4 minutes

<table>
<thead>
<tr>
<th></th>
<th>QTc Peak</th>
<th>QTc Steady</th>
<th>QTcp Peak</th>
<th>QTcp Steady</th>
<th>QTcp-e Peak</th>
<th>QTcp-e Steady</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>Prolonged</td>
<td>Prolonged</td>
<td>Prolonged</td>
<td>Prolonged</td>
<td>Prolonged</td>
<td>Prolonged</td>
</tr>
<tr>
<td>LQT2</td>
<td>Prolonged</td>
<td>Baseline</td>
<td>Prolonged</td>
<td>Baseline</td>
<td>Unchanged</td>
<td>Unchanged</td>
</tr>
<tr>
<td>LQT3 or Normal</td>
<td>Little change</td>
<td>Shortened</td>
<td>Little change</td>
<td>Shortened</td>
<td>Little changed</td>
<td>Shortened</td>
</tr>
</tbody>
</table>

**Baseline**

**Epinephrine (Peak)**

**Epinephrine (Steady-State)**

- **QTc ≥ 35 ms**
  - (Steady state – Baseline)
  - YES
  - NO

- **△ QTc ≥ 80 ms**
  - (Peak – Baseline)
  - YES
  - LQT1
  - NO
  - LQT2
  - LQT3 or Control

---

1. **LQT1**: Prolonged
2. **LQT2**: Prolonged
3. **LQT3 or Normal**: Little change

---

**Notes**

- **LQT1**: Prolonged QTc peak and QTc steady state.
- **LQT2**: Prolonged QTc peak, baseline QTc steady state.
- **LQT3 or Normal**: Little change in QTc peak, shortened QTc steady state.
Sensitivity and Specificity Epinephrine Test

- Group I: 19 mutation carriers QTc > 460
- Group II (in parenthesis): 15 mutation carriers with QTc < 460

- The sensitivity and specificity of QTc to identify mutation carriers were 59% (20/34) and 100% (27/27) before epinephrine.
- The sensitivity was improved to 91% (31/34) without the expense of specificity (100%, 27/27) after epinephrine.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG criteria (8)</td>
<td>20/34 (59%)</td>
<td>27/27 (100%)</td>
<td>31/34 (91%)</td>
<td>27/27 (100%)</td>
</tr>
<tr>
<td>(1/15 [7%])</td>
<td></td>
<td></td>
<td>(12/15 [80%])</td>
<td></td>
</tr>
<tr>
<td>Score ≥ 4 (9)</td>
<td>18/34 (53%)</td>
<td>27/27 (100%)</td>
<td>25/34 (74%)</td>
<td>27/27 (100%)</td>
</tr>
<tr>
<td>(0/15 [0%])</td>
<td></td>
<td></td>
<td>(6/15 [40%])</td>
<td></td>
</tr>
<tr>
<td>Score ≥ 2 (9)</td>
<td>20/34 (59%)</td>
<td>27/27 (100%)</td>
<td>31/34 (91%)</td>
<td>27/27 (100%)</td>
</tr>
<tr>
<td>(2/15 [13%])</td>
<td></td>
<td></td>
<td>(12/15 [80%])</td>
<td></td>
</tr>
<tr>
<td>ΔQTc ≥ 30ms</td>
<td>NA</td>
<td>NA</td>
<td>31/34 (91%)</td>
<td>27/27 (100%)</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td></td>
<td>(13/15 [87%])</td>
<td></td>
</tr>
</tbody>
</table>
T-wave Morphology Shimizu

• Low-dose epinephrine elicits G1 or G2 notching in > 50% of patients with LQT2
• G1 notching more common in LQT2 (25%), LQT1 (3%), controls (9%) but not clinically diagnostic
• G2 notching occurs in 18% of patients with LQT2 but not a sensitive marker
• A biphasic T-wave pattern seen in controls, LQT1 and LQT2 equally
Predictive Value Schimuzu

- They report a predictive value of a Delta-QTc of 35 milliseconds or greater at steady-state epinephrine as 90% or higher predictive of LQT1.
- Delta-QTc of 80 milliseconds or greater at peak epinephrine as 100% predictive of LQT2 phenotype.
- An estimated 5% of healthy subjects host rare variants in KCNQ1 of uncertain functional significance.
Epinephrine Mayo Protocol

- Epinephrine 0.025 mcg/kg/min, after 10 mins ECG
- Infusion increased to 0.05, 0.1, and 0.2 mcg/kg/min, ECG 5 minutes after each increase and 5 and 10 mins after infusion stopped

Circulation. 2006;113:1385-1392
Shimizu Protocol

- Termination criteria: SBP 200 mm Hg, NSVT or PM-VT, >10 PVC/min, TWA, or patient intolerance

- **Positive result:** QT interval change at 0.1mcg/kg dose >30ms
Safety of the Epinephrine QT Stress Test

- Epinephrine QT stress test is extremely safe
- Palpitations at the high doses (0.2 µg · kg⁻¹ · min⁻¹)
- Isolated PVC in 7% = 3/44 gene-negative, 10% = 4/40 of LQT1, 5/30 = 17% of LQT2 and 0/11 of LQT3
- Ventricular bigeminy in 2% = 1/44 of gene-negative, no LQT1, 10% = 3/30 LQT2, and 1 (9%) of 11 LQT3
- NS-VT in 2% = 1 gene-negative, 1 LQT1, and 1 LQT3
- A single patient (LQT1) developed macroscopic TWA.
- No VT, torsade de pointes, VF, or cardiac arrest
- No patients required defibrillation and no deaths
# Mayo Cohort

## TABLE 1. Demographics of Study Cohort

<table>
<thead>
<tr>
<th></th>
<th>Gene Negative (n=44)</th>
<th>LQT1 (n=40)</th>
<th>LQT2 (n=30)</th>
<th>LQT3 (n=11)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F), n</td>
<td>14/30</td>
<td>16/24</td>
<td>12/18</td>
<td>6/5</td>
<td>0.56</td>
</tr>
<tr>
<td>Age, y</td>
<td>16 (8–59)</td>
<td>26.5 (12–49)</td>
<td>27 (10–55)</td>
<td>26 (12–47)</td>
<td>0.19</td>
</tr>
<tr>
<td>Baseline heart rate, bpm</td>
<td>64 (44–96)</td>
<td>62.5 (43–90)</td>
<td>65.5 (52–95)</td>
<td>64 (52–74)</td>
<td>0.68</td>
</tr>
<tr>
<td>Baseline QT, ms</td>
<td>419.5 (356–642)</td>
<td>439.5 (360–550)</td>
<td>457.5 (380–656)</td>
<td>450 (420–542)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Baseline QTc, ms</td>
<td>444 (394–677)</td>
<td>456 (397–517)</td>
<td>486 (388–644)</td>
<td>473 (424–532)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak heart rate during test, bpm</td>
<td>92.5 (55–130)</td>
<td>88 (63–124)</td>
<td>96.5 (62–119)</td>
<td>80 (56–100)</td>
<td>0.005</td>
</tr>
<tr>
<td>Δ Heart rate, bpm</td>
<td>25.5 (5–46)</td>
<td>20.5 (0–41)</td>
<td>28.5 (5–59)</td>
<td>21 (–12 to 33)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Values are n or median (range).
Mayo Protocol Interpretation

- The median change in QT interval during epinephrine infusion is -23 ms in the gene negative group, +78 ms in LQT1, -4 ms in LQT2, and -58 ms in LQT3.
- The paradoxical QT prolongation >30 ms observed in 37/40 = 92% LQT1, 18% gene-negative, 13% LQT2, and 0% of LQT3.
Change in QTc With Epinephrine

Vyas, H. et al. Circulation 2006;113:1385-1392
Epinephrine Test Yield

• A paradoxical response characterized by >30ms QT lengthening rather than expected shortening pathognomonic for LQT1

• Paradoxical QT response has a sensitivity of 92.5%, specificity of 86%, positive predictive value of 76%, and negative predictive value of 96% for LQT1 status

• QTc change had sensitivity 40%, specificity of 92%, positive predictive value of 70%, and negative predictive value of 76% in detecting LQTS
False Positives

- QTc changes (no matter how long) with epinephrine challenge should not be used to make a Long QTS diagnosis
- Previously reported that epinephrine QTc values as high as 600 ms and a QTc changes exceeding 140 ms in healthy volunteers can occur

*Mayo Clin Proc. 2002;77:413–421*
## False Positive

<table>
<thead>
<tr>
<th>No</th>
<th>Sex</th>
<th>Genotype</th>
<th>Baseline QTc, ms</th>
<th>ΔQT, ms</th>
<th>Symptoms</th>
<th>Family History</th>
<th>Late Shortening of QT at Higher Epinephrine Doses*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28/F</td>
<td>Gene negative</td>
<td>508</td>
<td>95</td>
<td>Syncope</td>
<td>None</td>
<td>Yes (at 0.1)</td>
</tr>
<tr>
<td>2</td>
<td>18/F</td>
<td>Gene negative</td>
<td>414</td>
<td>96</td>
<td>Exercise-induced syncope</td>
<td>None</td>
<td>Yes (at 0.1)</td>
</tr>
<tr>
<td>3</td>
<td>16/F</td>
<td>Gene negative</td>
<td>427</td>
<td>90</td>
<td>Spells</td>
<td>+</td>
<td>Error of measurement—U-wave included</td>
</tr>
<tr>
<td>4</td>
<td>16/F</td>
<td>Gene negative</td>
<td>438</td>
<td>82</td>
<td>Presyncope</td>
<td>+</td>
<td>Yes (at 0.2)</td>
</tr>
<tr>
<td>5</td>
<td>8/F</td>
<td>Gene negative</td>
<td>461</td>
<td>84</td>
<td>Asymptomatic</td>
<td>+</td>
<td>Yes (at 0.2)</td>
</tr>
<tr>
<td>6</td>
<td>13/F</td>
<td>Gene negative</td>
<td>428</td>
<td>75</td>
<td>Asymptomatic (abnormal QTc on screening ECG)</td>
<td>None</td>
<td>Error of measurement—U-wave included</td>
</tr>
<tr>
<td>7</td>
<td>30/M</td>
<td>Gene negative</td>
<td>412</td>
<td>140</td>
<td>Asymptomatic</td>
<td>Abnormal QTc in incidental ECG in child</td>
<td>Error of measurement—U-wave included</td>
</tr>
<tr>
<td>8</td>
<td>23/F</td>
<td>Gene negative</td>
<td>448</td>
<td>100</td>
<td>Epinephrine-induced NSVT</td>
<td>None</td>
<td>Yes (at 0.2)</td>
</tr>
<tr>
<td>9</td>
<td>42/F</td>
<td>LQT2</td>
<td>505</td>
<td>76</td>
<td>Syncope</td>
<td>+</td>
<td>Absent, but test terminated at 0.05 due to ventricular bigeminy</td>
</tr>
<tr>
<td>10</td>
<td>34/F</td>
<td>LQT2</td>
<td>506</td>
<td>72</td>
<td>Syncope</td>
<td>+</td>
<td>Yes (at 0.1)</td>
</tr>
<tr>
<td>11</td>
<td>33/M</td>
<td>LQT2</td>
<td>454</td>
<td>53</td>
<td>Clearly vaso-vagal syncope, otherwise negative</td>
<td>+</td>
<td>Error of measurement—U-wave included</td>
</tr>
<tr>
<td>12</td>
<td>24/M</td>
<td>LQT2</td>
<td>490</td>
<td>30</td>
<td>Asymptomatic</td>
<td>+</td>
<td>Error of measurement—U-wave included</td>
</tr>
</tbody>
</table>
## False Negative

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Baseline QTc, ms</th>
<th>ΔQT, ms</th>
<th>Clinical Symptoms</th>
<th>Family History</th>
<th>Epinephrine Stress Test in Family Members</th>
<th>LQT1 Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34/F</td>
<td></td>
<td>483</td>
<td>10</td>
<td>None</td>
<td>(1) Sudden death in daughter (age 17 y) &lt;br&gt;(2) Another daughter with 1 syncopal episode, who carries the same mutation and had a positive epinephrine test</td>
<td>Positive (ΔQT 51 ms in surviving daughter)</td>
<td>W379R</td>
</tr>
<tr>
<td>2</td>
<td>40/M</td>
<td></td>
<td>456</td>
<td>28</td>
<td>None</td>
<td>(1) No sudden death &lt;br&gt;(2) Syncope in twin daughters of his sister &lt;br&gt;(3) Sister is asymptomatic mutation carrier &lt;br&gt;(4) Patient's 11-year-old son carries the mutation and is asymptomatic</td>
<td>Not done in other family members</td>
<td>Q530X</td>
</tr>
<tr>
<td>3</td>
<td>25/M</td>
<td></td>
<td>445</td>
<td>−20</td>
<td>None</td>
<td>(1) 7 other mutation carriers in family, all asymptomatic &lt;br&gt;(2) Index case was nephew with ALTE (age 7 weeks). Currently well. ALTE likely unrelated to LQTS.</td>
<td>(1) Patient's father: ΔQT 35 ms &lt;br&gt;(2) Patient's sister: ΔQT 62 ms</td>
<td>L191fs/90</td>
</tr>
</tbody>
</table>
Healthy individuals

- Absolute QT shortens slightly because of the relative increase of phase 3 potassium channel–mediated repolarisation force compared with the increased inward current activity via L-type calcium channels.
- The QTc may increase markedly depending on how brisk the chronotropic response is.
- If the QT interval shortens modestly but the RR interval decreases significantly, the Bazett’s equation–derived QTc increase.
LQT1

- Dysfunctional IKs channels prolong absolute (uncorrected) QT interval because the augmented inward calcium current is fully opposed by the dysfunctional IKs and unaffected IKr
- Prolongation of the QT interval >30ms with epinephrine infusion is referred to paradoxical QT response
- A paradoxical QT prolongation of 30 milliseconds or longer is both sensitive and specific as a marker for LQT1
LQT2

- LQT2 have dysfunctional IKr channels responsible for the very early part of phase 3 repolarization
- These individuals may show transient QT prolongation followed by QT shortening as the normally functioning IKs channels are utilised
- These individuals may show T-wave changes characterized by unusual notching patterns
LQT3

- LQT3 shortens QT interval with epinephrine infusion because of the recruitment of intact potassium channels
Catecholaminergic Polymorphic Ventricular Tachycardia
CPMVT = Coumel Tachycardia

- Coumel and Leenhardt described in 1978 and 1995
- AD and AR transmission with genetic heterogeneity
- Bidirectional and PM -VT during exercise
- VT frequently deteriorates into ventricular fibrillation and death
- Presents with recurrent syncope, seizures, or sudden death after physical activity or swimming or emotional stress and mortality 30% by age 30 years
- Mapped to 1q42–43 with missense mutations identified ryanodine receptor 2, calsequestrin 2, Kir2.1, AnkB
CPVT Clinical Types

1. Ryanodine receptor channel (*RYR2*) mutation: AD inheritance
   - *RYR2*: Intracellular Ca\(^{2+}\) release channel on SR that releases Ca\(^{2+}\) in response to Ca\(^{2+}\) entry through the membrane L-type Ca\(^{2+}\) channels during the action potential plateau

2. Mutation in the *CASQ2* gene: AR inheritance
   - Caused by homozygous mutation of *CASQ2* which encodes calsequestrin protein, serves as the major Ca\(^{2+}\) reservoir within the lumen of the SR
   - Symptoms more severe in *CASQ2* related CPVT, earlier age of onset, diagnosis more difficult because of the absence of a positive family history, due to the recessive nature of the disease.
CPMVT

- Major diagnostic tools exercise test or epinephrine challenge and Holter
- Characteristic sequence -- junctional tachycardia--PVCs with quadrigeminy—trigeminy—bigeminy--salvoes of bidirectional tachycardia--and bursts of rapid, irregular, and PMVT
- Depending on the intensity of the adrenergic stimulation, the disappearance occurs in the reverse order
- Bidirectional VT rapidly degenerates into PM VT-VF
- PES is not helpful in inducing VT but Isoprenaline infusion can reproduce VT
CPMVT adrenaline infusion
Total number of patients 26
2002-2007

- Ajmaline: 5
- Epinephrine: 7
- Flecainide: 14
Results

- Positive: 20
- Negative: 5
- Equivocal: 1

Legend:
- Positive
- Negative
- Equivocal
Positive tests

- Ajmaline: 3
- Epinephrine: 2
Complications while testing

• None of the patients had any symptoms or needed any interventions during and immediately after testing
Indications for testing

• F/H of sudden death/cardiac arrest
• F/H of Brugada syndrome
• F/H of long QT
• Episodes of dizziness and collapse with borderline or abnormal ECG
Resting ECG

- Normal resting ECG: 15
- Abnormal ECG: 11
Positive results-5/26

• 2/3 of them presented with syncopal/dizzy episodes with no specific family history and borderline QTc in resting ECG.
• 1/3- investigated for F/H of LQTS, had borderline resting ECG
• 2/2 had strong F/H of Brugada syndrome and their resting ECG showed partial RBBB with suspected ST elevation in the right precordial leads.
Conclusion

- Epinephrine QT stress and Ajmaline tests are safe
- Both tests are well tolerated with a low incidence of adverse events
- False positive and negative rates are reported
  - Shimizu protocol gives higher false positive rates
- Negative test does not exclude diagnosis