Acquired QT Prolongation and Clinical Implication

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OBJECTIVES

- Background
- Target population
- Natural history of acquired QT prolongation
- Clinical risk factors
- Therapeutic strategies
- Underlying mechanisms
- Future directions
Congenital Long QT Syndrome

- Abnormalities of ion channels that result in long QT intervals (prolongation of phase III-time for repolarization) and predispose to polymorphous ventricular tachycardia (“Torsade de Pointe”)
- Common cause of sudden death in children and young adults
- 1:7000 births
- In the US it causes ~ 5% of the SCD/year
- Symptoms include syncope or SCD usually with physical activity or emotional stress
# Drugs Which Prolong the QTc

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsants</td>
<td>Fosphenytoin; Felbamate</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Azelastine; Clemastine</td>
</tr>
<tr>
<td>Anti-Infectives</td>
<td>Amantadine; Clarithromycin; Chloroquine; Foscarnet; Erythromycin; Halofantrine; Mefloquine; Moxifloxacin; Pentamidine; Sparfloxacin; Quinine; Trimethoprim-Sulfamethoxazole; Ketoconazole</td>
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<tr>
<td>Antineoplastics</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>Cardiovascular: Antiarrhythmics</td>
<td>Amiodarone; Bretylium; Disopyramide; Flecaïnide; Ibutilide; Procainamide; Quinidine; Sotalol; Dofetilide</td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td>Bepridil; Irsapridine; Nicardipine</td>
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<tr>
<td>Diuretics</td>
<td>Indapamide; Moxipril/HCTZ</td>
</tr>
<tr>
<td>Hormones</td>
<td>Octreotide; Vasopressin</td>
</tr>
<tr>
<td>Immunosuppressives</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Migraine: Serotonin Receptor Agonists</td>
<td>Zolmitriptan; Naratriptan; Sumatriptan</td>
</tr>
<tr>
<td>Muscle Relaxant</td>
<td>Tizanidine</td>
</tr>
<tr>
<td>Narcotic Detoxification</td>
<td>Levomethadyl</td>
</tr>
<tr>
<td>Psychotherapeutics: Antidepressants</td>
<td>Amitriptyline; Desipramine; Fluoxetine; Imipramine; Venlafaxine</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>Chlorpromazine; Haloperidol; Pimozide; Quetiapine; Risperidone; Thioridazine</td>
</tr>
<tr>
<td>Antianxiety</td>
<td>Doxepin</td>
</tr>
<tr>
<td>Antimanic</td>
<td>Lithium</td>
</tr>
<tr>
<td>Respiratory: Sympathomimetics</td>
<td>Salmeterol</td>
</tr>
<tr>
<td>Sedative/Hypnotics</td>
<td>Choral hydrate</td>
</tr>
</tbody>
</table>

[http://www.dml.georgetown.edu/depts/pharmacology/torsades.html](http://www.dml.georgetown.edu/depts/pharmacology/torsades.html)
[http://www.hc-sc.gc.ca/hpb-dgps/therapeut/cfiles/english/publicat/adrv8n1_e.html](http://www.hc-sc.gc.ca/hpb-dgps/therapeut/cfiles/english/publicat/adrv8n1_e.html)
Drug-Induced Long QT Syndrome

Mean Change of QTc Duration
(Degree of outliers equally important)

- < 5 msec  - probably no concern
- 5 - 10 msec  - increasing concern
- 10-20 msec  - uncertain concern
- > 20 msec  - definite concern

BUT DEPENDS ON RISK-BENEFIT OF THERAPY
Suggested Risk-Stratification Scheme for ACA or SCD in LQTS Patients

- Risk stratification categories for LQTS patients based on published event rates.
- Kaplan-Meier (K-M) estimates are based on a series of 869 LQTS patients (52).
- CPR = cardiopulmonary resuscitation; TdP = torsades de pointes.

- Acquired QTc prolongation is an independent risk factor for sudden cardiac death

- Increased risk of torsades de pointes as QTc interval increases - not all cases had QTc >500 msec

- Drug-induced
  - Primary: Drug effect (Ik block)
  - Secondary: Effect Modifiers
    - Bradycardia
    - Hypokalemia
    - Heart disease (LVH or CHF)
    - Atrial fibrillation
    - Female gender
    - Form Fruste HERG mutation
    - Metabolic inhibitors (pK); overdose
    - Concomitant Ik blockers (pD)
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**Moderate-to-severe** sleep apnea is independently associated with a large increased risk of all-cause mortality, incident stroke, and cancer incidence and mortality in this community-based sample.

Survival Based on AHI

Survival free of fatal or resuscitated sudden cardiac death (SCD) in the total study population, based on the apnea-hypopnea index (AHI) threshold determined by classification and regression tree analysis (AHI <20 vs. AHI ≥20). Hazard ratio: 1.60, 95% confidence interval: 1.14 to 2.24; p = 0.007.
Patients with OSA had longer QTc interval than those without OSA:
492±38 vs 475±39, p=0.001

In OSA patients with a prolonged QTc, mean (±SD) QTc:
- 501±26ms in men (range 452~561ms)
- 519±35ms in women (range 473~567ms)

From 2010 to 2014, patients who had implantable cardioverter-defibrillator (ICD) procedures were screened.

Research sites: Rhode Island Hospital, The Miriam Hospital, Brown University

Patients with OSA had longer QTc interval than those without OSA.
OSA is an Independent Risk Factor for Acquired QT Prolongation

- OSA patients more frequently had co-morbidities, such as HF, NIDCM, CVD, DM and HTN.
- ECG revealed more atrial fibrillation/flutter and abnormal intraventricular conduction.
- Further analysis showed QTc interval was associated with OSA, history of ventricular tachycardia, left ventricular ejection fraction, potassium level, creatinine, and the use of diuretics or beta blockers.
- OSA, ejection fraction, and potassium level might be independent predictors for QT prolongation.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>P value</th>
<th>Significance</th>
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<tbody>
<tr>
<td>Obstructive sleep apnea</td>
<td>0.004</td>
<td>Yes</td>
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<tr>
<td>History of ventricular tachycardia</td>
<td>0.001</td>
<td>Yes</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.039</td>
<td>Yes</td>
</tr>
<tr>
<td>BUN</td>
<td>0.027</td>
<td>Yes</td>
</tr>
<tr>
<td>LVEF</td>
<td>&lt;0.0001</td>
<td>Yes</td>
</tr>
<tr>
<td>Potassium</td>
<td>0.015</td>
<td>Yes</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>0.005</td>
<td>Yes</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>0.01</td>
<td>Yes</td>
</tr>
<tr>
<td>Diuretics</td>
<td>0.033</td>
<td>Yes</td>
</tr>
<tr>
<td>Abnormal conduction</td>
<td>&lt;0.0001</td>
<td>Yes</td>
</tr>
<tr>
<td>QRS</td>
<td>&lt;0.0001</td>
<td>Yes</td>
</tr>
</tbody>
</table>
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VB is a 68 years lady with sleep apnea. Since 2003, she has frequent admissions which end up with an ICD in her chest (Feb. 2014) as well as 218 ECGs in the medical records.
QTc prolonged progressively over time
From 2003 to 2014, A → B → D → E → G → H
QTc prolonged significantly under stress/acute event (B → C, E → F)
Partially recovered after acute event (C → D, F → G)
But did not return back to baseline (D>B, G>E).
It took > 6 years for QTc to reach high normal end (450-470ms), but only 2 years from 450ms to 560ms (accelerated phase), concurrently the medical condition has been worsening which requires more frequent hospital stay.
Natural History of Acquired QT Prolongation

- QTc prolonged progressively over time.
- QTc prolonged significantly under stress/acute event. Partially recovered after acute event, but did not return back to baseline.
- The QT interval became progressively longer until the point of “accelerated phase”, concurrently the medical condition had been worsening which required more frequent hospital stay and more intensive management.
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Several Risk Factors Identified as the Most Common Cause with the Use of QTc Prolonging Drugs

- **Organic Heart Disease**
  - Congenital Long QT syndrome
  - Ischemic Heart Disease
  - Congestive Heart Failure
  - Dilated Cardiomyopathy
  - Hypertrophic Cardiomyopathy
  - Myocarditis
  - Kawasaki Syndrome

- **Metabolic Abnormalities**
  - Hypokalemia (most common)
  - Hypocalcemia
  - Hypomagnesemia

- **Bradycardia, Atrioventricular & Sinoatrial blocks**
- **Recent conversion from Atrial Fibrillation especially with QT-prolonging drug**

- **Drug related factors**
  - Narrow therapeutic window
  - Multiplicity of pharmacological actions
  - Inhibition & induction of cytochrome P450 enzymes
  - Polypharmacy

- **Female Preponderence**
- **Hepatic Impairment**
- **Digitalis therapy**
- **High Drug Concentrations (with exception of quinidine)**
- **Rapid rate of IV infusion with QT-prolonging drug.**
- **Base-line QT prolongation**
- **Subclinical long-QT syndrome**
- **Ion-channel polymorphisms**
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LQTS: Facts

- With treatment, can lower the mortality from 10% at 10 years to <1%
- BB prevent symptoms is 70% of patients
- ICD’s are indicated for those who have not responded to BB
- TdP: Acutely need to treat with defibrillation, IV magnesium, consider temporary pacing if bradycardic, and remove offending drugs
- Need to avoid drugs which can further prolong the QT
  www.qtdrugs.org
- If a QT-prolonging drug has been administered and the corrected QT interval (QTc) is greater than 500 msec or has increased by 60 msec or more, the offending drug should be discontinued, because this is a risk factor for torsades de pointes.
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Currents of Sodium, Calcium and Potassium Channels Underlie the Atrial and Ventricular Action Potential

- **Inward currents**
  - $I_{Na}$: Nav1.5, SCN5A
  - $I_{Ca,L}$: Cav1.2, CACNA1C

- **Outward currents**
  - $I_{Ko}$: Kv4.3, KCND3
  - $I_{Kur}$: Kv1.5, KCNA5
  - $I_{Kr}$: Kv11.1 (hERG), KCNH2
  - $I_{Ks}$: Kv7.1 (KvLQT1), KCNQ1
  - $I_{K1}$: Kir2.1-2.3, KCNJ2/12/4
  - $I_{K,ACH}$: Kir3.1/3.4, KCNJ3/5
  - $I_{K,ATP}$: Kir6.2, KCNJ11
Correlation of the Expression of Baseline Potassium Channels with Hypoxia

<table>
<thead>
<tr>
<th></th>
<th>KCNQ1</th>
<th>KCNH2</th>
<th>KCNE1</th>
<th>KCNE2</th>
<th>KCNJ2</th>
<th>KCNA5</th>
<th>KCNJ11</th>
<th>KCND3</th>
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<tr>
<td><strong>Log\textsubscript{10} AHI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( r )</td>
<td>-0.486</td>
<td>-0.437</td>
<td>-0.567</td>
<td>0.002</td>
<td>-0.442</td>
<td>-0.468</td>
<td>-0.329</td>
<td>-0.249</td>
</tr>
<tr>
<td>( p )</td>
<td>0.007</td>
<td>0.016</td>
<td>0.001</td>
<td>0.993</td>
<td>0.015</td>
<td>0.009</td>
<td>0.076</td>
<td>0.184</td>
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<tr>
<td><strong>Log\textsubscript{10} ODI4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>( r )</td>
<td>-0.404</td>
<td>-0.416</td>
<td>-0.465</td>
<td>-0.021</td>
<td>-0.349</td>
<td>-0.326</td>
<td>-0.296</td>
<td>-0.285</td>
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<tr>
<td>( p )</td>
<td>0.027</td>
<td>0.022</td>
<td>0.010</td>
<td>0.912</td>
<td>0.059</td>
<td>0.079</td>
<td>0.112</td>
<td>0.127</td>
</tr>
<tr>
<td><strong>Nadir O\textsubscript{2}</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( r )</td>
<td>0.27</td>
<td>0.27</td>
<td>0.34</td>
<td>0.18</td>
<td>0.27</td>
<td>0.15</td>
<td>0.02</td>
<td>0.37</td>
</tr>
<tr>
<td>( p )</td>
<td>0.15</td>
<td>0.15</td>
<td>0.06</td>
<td>0.35</td>
<td>0.15</td>
<td>0.44</td>
<td>0.92</td>
<td>0.04</td>
</tr>
</tbody>
</table>

- AHI: Apnea-hypopnea index.
- ODI4: the number of times per hour of sleep that the blood's oxygen level drops by 4 percent or more from baseline.
- Nadir O\textsubscript{2}: nadir arterial oxygen saturation levels.
Baseline Potassium Channel mRNA Expression Correlated with AHI

\[ r = -0.486, \ p = 0.007 \]

\[ r = -0.442, \ p = 0.015 \]
Baseline Potassium Channel mRNA Expression
Correlated with ODI4
CPAP improves KCNQ1 and KCNJ2 in patients with moderate OSA

- Of these channel genes, two were statistically significantly increased and five more showed trends toward an increase with CPAP therapy. These results suggest that hypoxemia may be mediating these changes.

- KCNQ1 and KCNJ2 were improved with CPAP but only in the moderate OSA group. This could be explained if correction of hypoxia were the major driver for improvements in channel levels.

- The presence of HIF-1α binding sites in the promoters of potassium channels may provide the mechanism by which systemic oxygen level affects the gene expression of potassium channels.
CPAP Withdrawal Led to a Recurrence of OSA, and a Significant Increase in the Length of the QTc.

European Heart Journal (2012) 33, 2206–2213
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Future Direction

- Redefine risk stratification including both genetic and clinical predictors

- Biomarkers of substantial Predictive value

- Regulators to reverse pathological process
  - HIFα
  - KCNE1
  - KCNE2
Acknowledgements

Cardiovascular Institute

- Samuel C Dudley Jr, MD, PhD
- Anyu Zhou, MD, PhD
- Hafiz Imran, MD
- Guangbin Shi, MD, MS
- Bahaa Kaseer, MD
- Vincent Siu, MD, MS
- Jharendra Rijal, MD

Lifespan Laboratories

- Susan Manzi, Manager, Outreach Services

Clinical Research Office

The Miriam Hospital

- Lori DeSimone, RN
- Catherine Gordon, RN
- Lina Felix, RA
- Jassira Gomes, RA

Rhode Island Hospital

- Kelly Franchetti, RN
- Emily Awopeju, RA
Thank you!