Role of the ECG in Risk Assessment of the Poisoned Patient

Alex Manini, MD, MS
Division of Medical Toxicology
Mount Sinai School of Medicine

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Disclosures

- No commercial disclosures

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- I do not know how to correctly pronounce “Torsades” so I will go with “TdP”…..
Lecture Goals

1. Review common cardiac rhythms and how the action potential is generated
2. Understand how toxins modify the cardiac action potential
3. Identify “classic” ECG signs of toxicity
4. Know how certain ECG findings dictate management of the poisoned patient
The Basics

Cardiac conduction system:

- Sinus node
- Internodal pathways
- AV node
- Bundle of His
- Right bundle branch
- Left bundle branch
- Bachmann's bundle

P-QRS-T complex

Normal sinus rhythm
Action Potential → ECG Waveform

**1. Na⁺, K⁺, Ca²⁺, K⁺**

**2. qrs**

**3. qt**

**4. p, pr, t, st**
Sinus Tachycardia

Pathophysiology:

- None: Physiologic response to stress
  - Anxiety, hypoxia, pain, fever, etc.
- Normal impulse formation/conduction
  - Conduction blocker unlikely (e.g., digoxin)

Typical HR range 100-200
Bradycardia with Heart Block

1st Degree:
- Conduction slowed *(AV node)*; more physical sign

3rd Degree
- AV dissociation
- Multiple locations

Differential
- BB/CCB, digoxin, imidazolines, cholinergics
Digoxin

- PVCs
  - Most common
- “Classic” ECG findings:
  - Bi-directional VT
  - Atrial tachycardia, variable/slow ventricular response
  - Accelerated junctional

- “Dig-effect”
  - Not marker of toxicity

- ECG Pearl:
  - “Toxicity can produce any rhythm EXCEPT rapid 1:1 conduction thru AV node”
Delayed after-depolarization (DAD)

- Spontaneous M cell depolarization after repolarization complete:
  - Phase 4 (rest)
  - Cardioactive steroid (i.e. digoxin)
  - Mechanism:
    - High intracellular Ca → Transient Na influx
  - ECG Manifestation:
    - PVC (usually)
    - VT (rarely)
Myocardial Sensitization

Altered substrate

Triggered event

Nelson LS, J Toxicol Clin Toxicol 2002
Sodium channel blockade

Na\(^+\) K\(^+\) Ca\(^{2+}\) K\(^+\)

1

0

2

3

4

qrs

qt

p

t

pr

st
Na channel blockade

- **Class IA**: e.g., quinidine, TCAs
  - Moderate Na⁺-channel blockade
  - ↑ ERP
- **Class IB**: e.g., lidocaine
  - Weak Na⁺-channel blockade
  - ↓ ERP
- **Class IC**: e.g., flecainide
  - Strong Na⁺-channel blockade
  - → ERP

**Fast-Response Action Potential** (e.g., ventricular myocyte)

- ERP
- Na⁺ in
- Ca⁺⁺ in
- K⁺ out

**Ventricular Action Potential**

- IC
- IA
- IB
Rate-dependent Sodium channel blockade

Goodman and Gilman’s, Pharmacological Basis of Therapeutics, 11th ed. 2006.
Rate-dependent Sodium channel blockade

Sasyniuk BI et al.. 1986.
Diagnosis: Use of lead aVR

Positive predictive value = 81%
Negative predictive value = 94%

Example in real patient

Harrigan RA and Brady WJ. 1999.
QRS > 100 ms

- Serum Alkalinization*
- Sodium Bicarbonate
  - 1-2 mEq/kg IV boluses
  - serum pH no greater than 7.55
- Continuous infusion at 1.5 times maintenance IV fluid rate
  - 150 mEq sodium bicarbonate in 1 L D5W
- Controlled ventilation (if hypoventilating)

* Boehnert and Lovejoy, NEJM 1985
Wide Complex Tachycardia

- **Serum Alkalization**

- **Consider Lidocaine:** *
  - **Dose:** 1 mg/kg IV bolus, infusion (20-50 μg/kg/min)
  - **Mechanism:** Narrows ERP

* 2010 ACC/ECC ACLS “special populations”
Non-randomized ED overdoses with QRS > 100 ms

589 ODs Screened

89 Included
(mean age 45, 64% male, mean QRS 113)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No Bicarb (%)</th>
<th>Bicarb (%)</th>
<th>RR (95% CI)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>79</td>
<td>10</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ACVE*</td>
<td>7 (8.8)</td>
<td>3 (30)</td>
<td>3.4 (1.1-11.0)</td>
<td>0.043</td>
</tr>
<tr>
<td>VTVF</td>
<td>1 (1.2)</td>
<td>2 (20)</td>
<td>15.8 (1.6-158)</td>
<td>0.019</td>
</tr>
</tbody>
</table>

* Defined as shock, MI, VTVF, CPR
† z-statistic

ACVE = Adverse cardiovascular event

K⁺ Channel Blockade

- Prolonged Repolarization
- $\text{IK}_r$ Interference

$I\text{K}_r$ = Potassium rectifier current
Normal baseline QT

Rate: 80 bpm

QT interval: 0.36 sec
(within QTc range of 0.32 – 0.39 sec for a heart rate of 80 bpm)

Prolonged QT due to drug toxicity

Rate: 80 bpm

QT interval: prolonged, 0.45 sec (above normal QTc range for a heart rate of 80 bpm)
Computer “Calipers”: Improved QT Algorithms

Hnatkova K (GE Healthcare) PACE 2006
# QT Correction (QTc)

<table>
<thead>
<tr>
<th>Name</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bazett’s Correction</td>
<td>$QTc = \frac{QT}{RR^{0.5}}$</td>
</tr>
<tr>
<td>Fridericia’s Correction</td>
<td>$QTc = \frac{QT}{RR^{0.33}}$</td>
</tr>
<tr>
<td>Framingham Correction</td>
<td>$QTc = QT + 0.156 \times (1 - RR)$</td>
</tr>
</tbody>
</table>

$QT$ in ms and $RR$ in s.
Drug-Induced QT Prolongation: A Moving Target

- Healthy subjects
- Ibutilide injection
- Holter monitors

Azie NE (Pfizer), Ann Noninv Electro 2004
Drug-Induced Long QT

- Magnesium sulfate* (Class IIa, Level B)
  - 2 gm iv bolus, may start drip 2 gm/hr
- Potassium Repletion (Class IIb, Level C)
  - to > 4.5 mEq/L
  - Risk if < 3.0 mEq/L

* Mechanism unknown
Racial Differences in Poisoning: QT Prolongation

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Prolonged QTc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.53</td>
</tr>
<tr>
<td>Black</td>
<td>2.2</td>
</tr>
</tbody>
</table>

* Model included significant co-variates: age, heart rate, and serum potassium.

Torsades de Pointes (TdP)

Defining Criteria per ECG Key:
- QRS complexes display “spindle-node” pattern – VT amplitude increases then decreases in regular pattern (creates the “spindle’)

ACLS
- Immediate DC cardioversion (non-terminating TdP or VF)

Magnesium 2g bolus*
- Regardless of Serum Magnesium Conc.

Overdrive pacing
  - Chemical: Isoproterenol
  - Electrical: transcutaneous vs. transvenous (set to >70 bpm)

* Mechanism unknown
Methadonians, QT, and TdP

MGH\(^1\)  

John Hopkins\(^2\)  

Australia\(^3\)

<table>
<thead>
<tr>
<th>Methadone Dose (mg)</th>
<th>Continuing Methadone Therapy</th>
<th>QTc Interval (ms) at Baseline</th>
<th>QTc Interval (ms) on Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>260</td>
<td>0</td>
<td>450</td>
<td>660</td>
</tr>
<tr>
<td>200</td>
<td>+</td>
<td>392</td>
<td>680</td>
</tr>
<tr>
<td>92.5</td>
<td>+</td>
<td>460</td>
<td>540</td>
</tr>
<tr>
<td>120</td>
<td>0</td>
<td>480</td>
<td>640</td>
</tr>
<tr>
<td>70</td>
<td>+</td>
<td>N/A</td>
<td>643</td>
</tr>
<tr>
<td>200</td>
<td>+</td>
<td>420</td>
<td>510</td>
</tr>
<tr>
<td>600</td>
<td>+</td>
<td>427</td>
<td>540</td>
</tr>
<tr>
<td>90</td>
<td>+</td>
<td>N/A</td>
<td>690</td>
</tr>
</tbody>
</table>

1- Patel AM, Am J Cardiol 2008; 2- Ehret GB, JAMA 2006; 3- Calver J Addiction Med 2012
QTc Prediction of TdP

Bazett’s QTc

QTc > 500ms

- Sensitivity = 93.8%
- Specificity = 97.2%

QT Nomogram

Extrapolated, 6-lead median*

- Sensitivity = 96.9%
- Specificity = 98.7%

* Kappa ~ 0.8

 Chan, Isbister, et al, QJM 2007
High Risk ECG Features:

- Each 10-ms increase QTc → 5-7% exponential increase TdP risk
- QTc > 500 ms → 2-3 fold higher TdP risk
- TdP triggered after pause (e.g., ectopic beat)
- No recommendation to use QT nomogram

Drew BJ, et al. AHA, Circulation 2010
Drug-Induced QT Prolongation – Indications for Cardiac Monitoring:
- if the QTc exceeds 500 ms
  - or -
- If there has been an increase of at least 60 ms compared with baseline
  Especially when accompanied by other ECG signs of impending TdP (eg ectopy)

Appropriate actions:
- Admit to unit with unit with the highest possible ECG monitoring surveillance
- Withhold qt drugs, institute alternative pharmacotherapy if necessary
- Assess for:
  - Potentially aggravating drug-drug interactions
  - Bradyarrhythmias
  - Electrolyte abnormalities
- Ready availability of an external defibrillator
- Patients should not be transported from the monitoring unit for diagnostic or therapeutic procedures
Myocardial Sensitization

Altered substrate

Triggered event

Nelson LS, J Toxicol Clin Toxicol 2002
Early After-Depolarization (EAD)

- Spontaneous M cell depolarization before repolarization complete:
  - Normal QT → EAD → PVC
- When substrate exists, leads to “R on T”
  - Long QT → EAD → PVC/ VT/ VF/ TdP
Mythology...

Long QT

EAD

"Worry exclusively about TdP and only TdP"
Not just TdP...

Long QT

EAD

PVC/ VT/ VF/ TdP
QT Risk Categories: Acute Drug Overdose

- Undifferentiated acute drug overdoses
- Risk of CV events
  - Shock
  - MI
  - VT/VF
  - Cardiac Arrest

- Normal QTc
  - Lowest Risk 3.8%

- Long QTc (but <500 ms)
  - High Risk 26%

- Severe QTc ≥ 500 ms
  - Highest Risk >38%

QT Dispersion

**STEP 1:** Measure raw QT all 12 leads

**STEP 2:** Calculate

\[
QTD = (\text{Longest QT}) - (\text{Shortest QT})
\]

**QTD prediction of ACVE:**

\[AUC = 0.66 \ (CI \ 0.55-0.76)\]

- **Optimal cutpoint = 70 ms**
  - **Sensitivity = 59%**
  - **Specificity = 68%**

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2- Manini AF, J Med Tox 2010
“Epidemiological studies are required to document the incidence rate of cardiac events secondary to drug toxicity”

“Tox” ACLS

- Benzos (Flumazenil)
- BB/CCB (glucagon, HIE, calcium, ECLS)
- Cyclic antidepressants (Sodium Bicarbonate)
- Cocaine (phentolamine, benzos, ccb, nitro)
- Digoxin (Fab)
- Local Anesthetic Toxicity (IV lipid emulsion)*
- Carbon Monoxide (HBO)
- Cyanide (Hydroxocobalamin)

* ACMT Position Paper
* Geib AJ et al, JMT 2011
Incidence of Adverse CV Events (ACVE) From Drug Overdose

Answering the ACLS/AHA’s Call
– Can we move from detection (toxidrome) to prediction (prevention)

Prospective cohort study (12 months)*
– Consecutive adult ED acute drug ODs
– ACVE incidence
  - Overall = 5.8% (CI 3.6-9.3%)
  - Admissions = 10.7% (CI 6.6-16.9)

* Manini AF, Acad Emerg Med 2012 (In press)
ECG Predictors: CV Events

Case Control Study
Acute drug ODs

CV Events:
- Shock
- Cardiac arrest
- VT/VF
- MI

ECG Predictors:
- Ectopy
- Non-Sinus Rhythm
- QTc

Manini et al. JMT 2010
Future Research: Role of ECG

- Risk Prediction using ECG
  - “Toxicologic” cardiac risk?
- “Go where the money is”
  - Worst prescription drug epidemic of all time
  - PEA/ VT > VF >> TdP
- Interventions based on ECG findings
  - “Tox” ACLS
  - Adaptive clinical trials
  - Pre-hospital interventions
Take Home Points

1. Role of the ECG for the poisoned patient continues to evolve

2. Action potential $\rightarrow$ ECG waveform
   - QRS/Na, QT/K, etc

3. TdP = least of our worries in toxicology

4. ECG findings guide clinical management
Thank You For Your Attention

– alex.manini@mountsinai.org
Lipid Resuscitation Therapy

- Use of IV fat emulsion for resuscitation of drug-induced cardiac arrest
- ACMT Position Paper 2011
  - Supports use for HD instability due to “lipophilic xenobiotics” even in absence of cardiac arrest
- Initial Clinical Experience (ToxIC)*
  - 55% survival rate
  - Significant adverse effects

T Wave Morphology: The Future?

\[ MCS = \text{Asymmetry} + \text{Notch} + 1.6 \times \text{Flatness} \]

Graff C, Drug Safety 2009
Amiodarone

Chronic amiodarone prolongs the QT interval, yet it is very rarely associated with TdP.

It has been postulated (although as yet unproven) that unlike high-risk drugs that selectively prolong repolarization in myocytes located in the mid myocardium (M cells), amiodarone uniformly delays repolarization in all layers of the myocardial wall.

- As a result, there is only QT prolongation and no transmural heterogeneity of repolarization, which is the necessary substrate for the development of a reentrant arrhythmia.

Another theory regarding the low TdP risk nature of amiodarone suggests that the drug also inhibits the physiological late sodium currents that ultimately produce the arrhythmia.

Magnesium

Therapeutic mechanism to prevent VT/VF/TdP in the setting of long QT is unknown....

- Decrease repolarization time
- L-type Ca dependent
- Suppresses EADs

Bailie DS, Circulation 1988
IKr Blockade → Action Potential

Validation of ECG Predictors

**FIGURE 1: STUDY ENROLLMENT DIAGRAM**

- **Subjects Screened**: 238
- **Included**: 157
  - 48% female
  - Mean age 40.8
  - 14% prior coronary disease
- **Excluded**: 81
  - 30 age <18
  - 41 no ECG
  - 2 alternate dx
  - 8 lack data

**ELECTROCARDIOGRAM (ECG) FINDINGS ASSOCIATED WITH ACVE**

<table>
<thead>
<tr>
<th>ECG Features:†</th>
<th>No event (%)</th>
<th>ACVE (%)</th>
<th>OR (CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemia by ECG*</td>
<td>19 (13)</td>
<td>7 (64)</td>
<td>15.2 (3.6-64)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Non-sinus rhythm</td>
<td>6 (4)</td>
<td>3 (27)</td>
<td>8.6 (1.8-41)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Ectopy</td>
<td>4 (3)</td>
<td>2 (18)</td>
<td>7.4 (1.2-46)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td><strong>TOTALS</strong></td>
<td><strong>146 (100)</strong></td>
<td><strong>11 (100)</strong></td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Ischemia and infarction defined according to AHA/ criteria.
† ECG interpreted by a blinded cardiologist.

Other sodium channel blockers

- Quinidine
- Procainamide
- Lidocaine
- Phenytoin
- Carbamezepine
- Diphenhydramine
Peri-Arrest/ Pulseless Rhythms in Poisoning

**Ventricular Fibrillation (VF):**
- **Rate/QRS complex:** unable to determine

**Ventricular Tachycardia (VT):**
- **Rate:** ventricular rate >100 bpm; typically 120 to 250 bpm

**Pulseless Electrical Activity (PEA):**
- **Any** “organized” rhythm without a pulse
- **5 H’s and 5 T’s (“tablets”)**