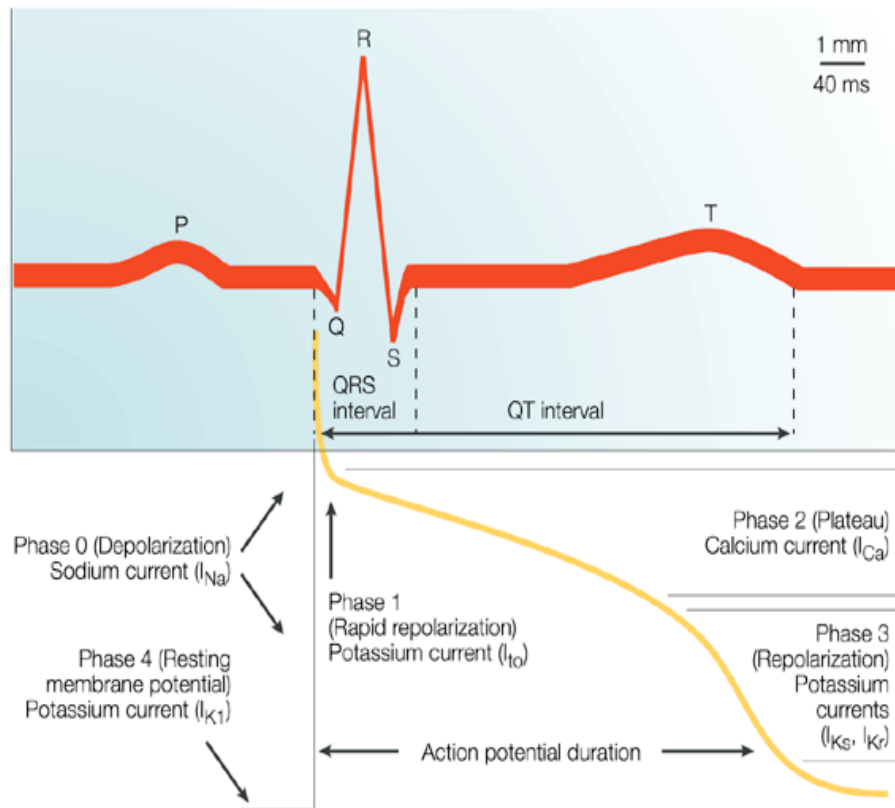


Article #2 2009 Tox LLSA

Kao LW, Furbee RB. Drug-induced Q-T
prolongation. *Med Clin N Am.*
2005;89:1125-1144.



Pathophysiology



- Action potential correlates with QRS
- Phase 0 – fast Na in
- Phase 1&2 – calcium in, slow K out
- Phase 3 – fast K out
- Phase 4 – Na in

From: Fermini B & Fossa AA. The Impact of Drug Induced QT Prolongation on Drug Discovery and Development. Nature Reviews Drug Discovery 2, 439-447 (June 2003)

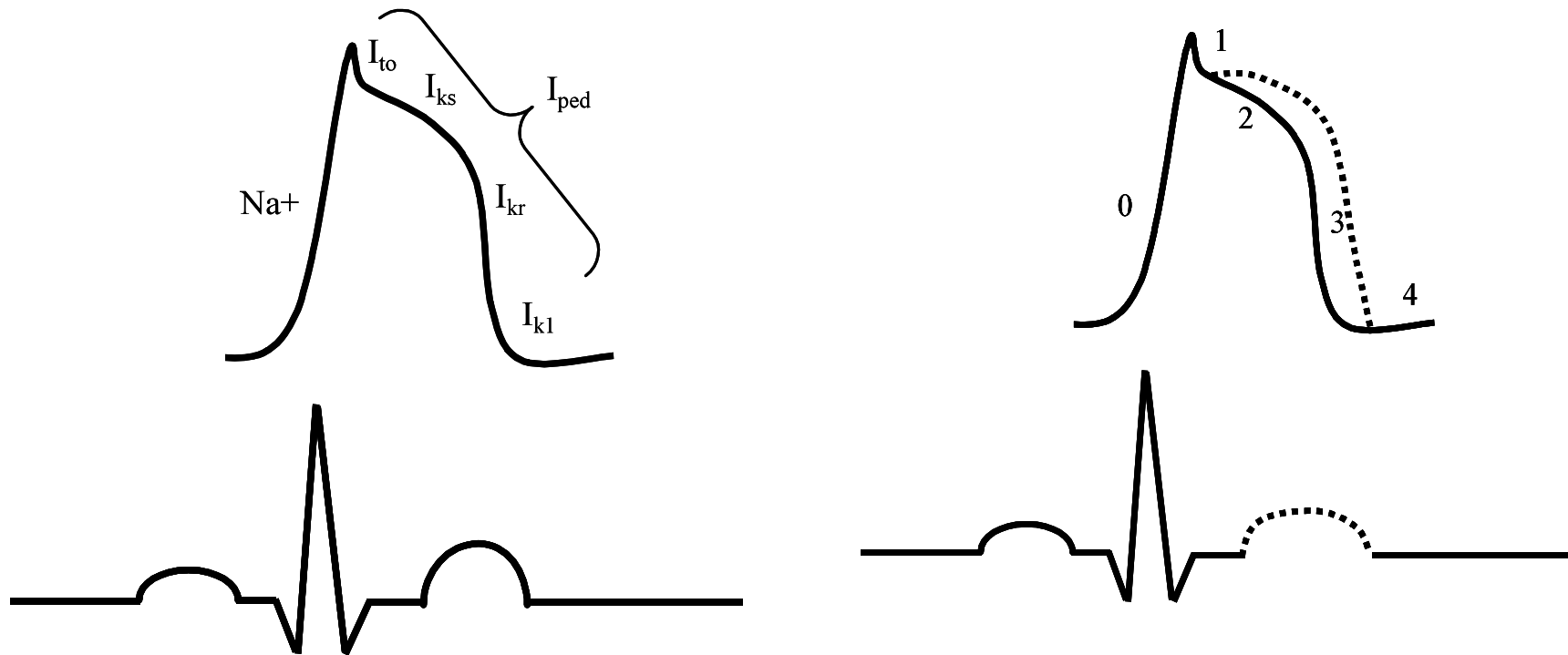


QT correction

- QT is most affected by RR interval
- Heart rate correction
 - Bazett's $QTc = QT/RR^{1/2}$
 - Friderica's $QTc = QT/RR^{1/3}$
 - More accurate at extremes of heart rate



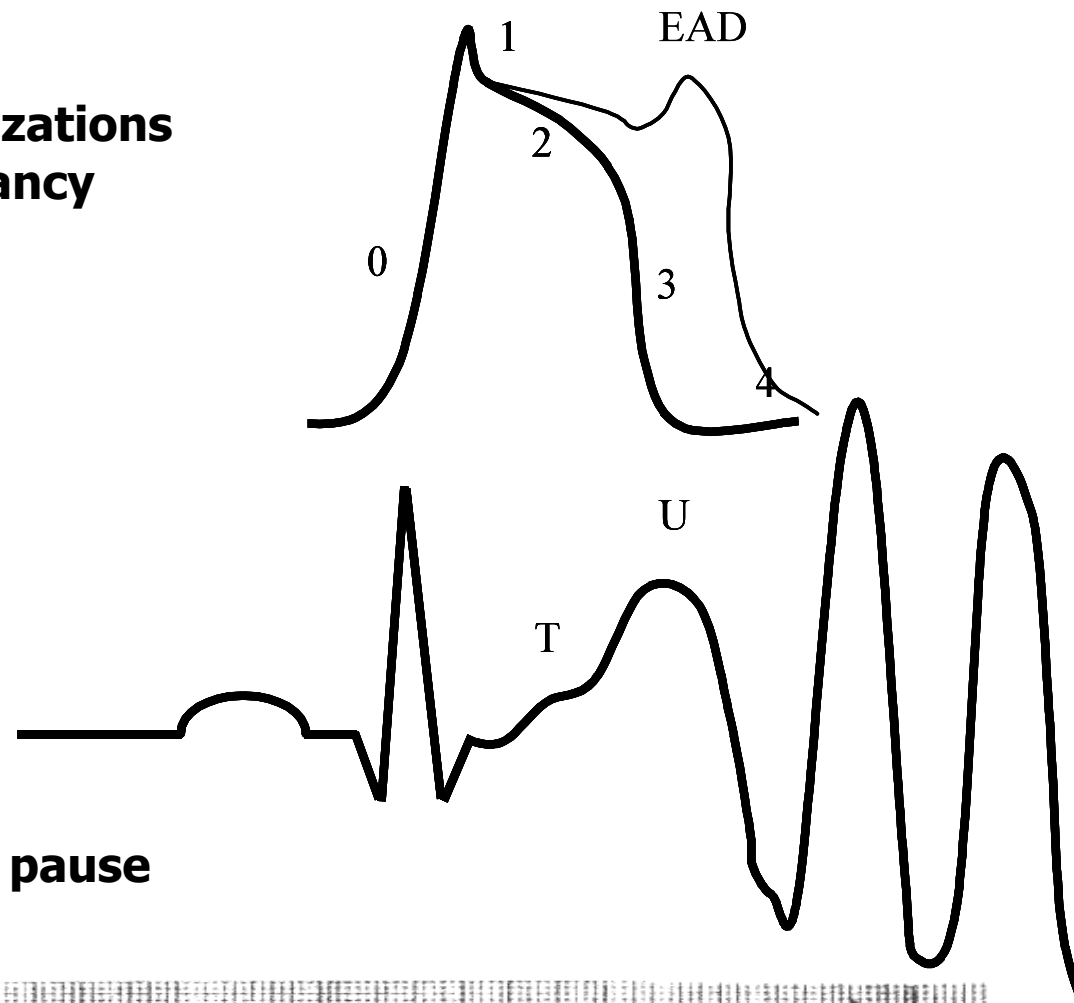
Potassium efflux blockade



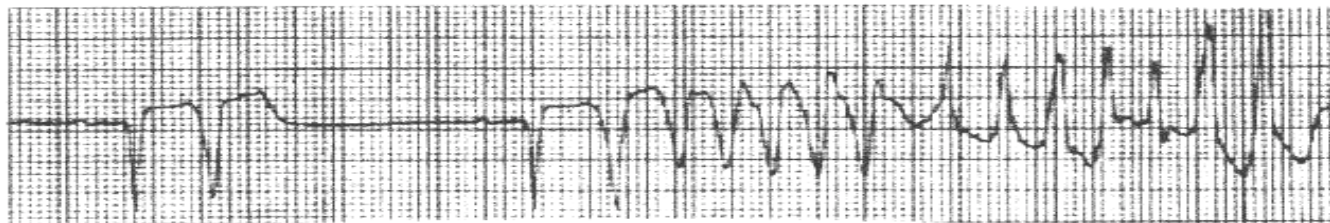
The various potassium currents during an action potential.
 I_{to} = Transient Outward current. I_{kr} , I_{ks} = Delayed rectifier.
 I_{k1} = Inward rectifying current.



**Early afterdepolarizations
May trigger abberancy
That leads to TdP**



**U wave and a long pause
Often precede TdP**



Inherited vs Acquired

■ Inherited

- Congenitally altered NA or K channels
- HERG mutations (I_{Kr})
- "Silent" gene carriers
- May be sympathetic triggered
 - Treat with beta blockers

■ Acquired

- Typically drug induced
- Usually blockade of I_{Kr}
- May be bradycardia triggered
 - Treat with overdrive pacing



Epidemiology

- LQTS – 3000-4000 deaths/yr in US
- 184,000 – 460,000 sudden deaths/yr
 - Some presumed due to TdP
- Associations
 - QT intervals and cardiac disease
 - Longer baseline QT intervals and mortality
 - Sudden death and prescribed medications

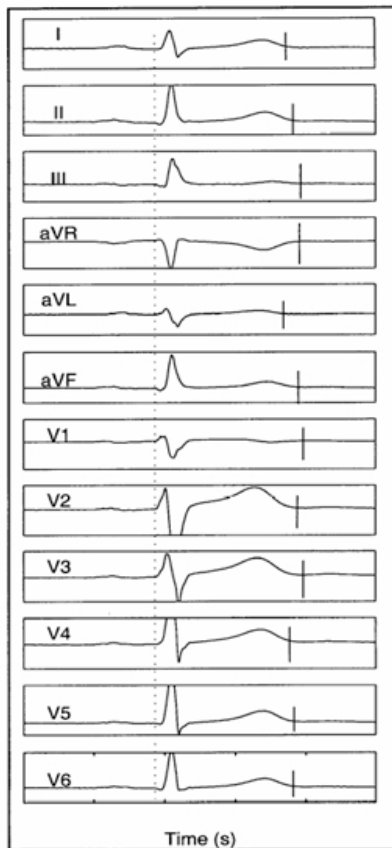


QT and Torsade de Pointes

- QT is a risk factor for TdP
- TdP may present as sudden death
- QT is only a surrogate marker
 - Not a 1:1 relationship
- Very hard to study



QT dispersion



- Difference between longest and shortest QT interval on 12 lead ECG
- Normal 40-60 msec
- Increased “dispersion” allows more potential for triggered activity
- Absolute values of 100 ms or 100% increase from baseline



Other risk factors for TdP

- Female sex
- Bradycardia
- Hypokalemia
- Hypomagnesemia
- Structural heart disease



Drug induced QT prolongation

- Mostly due to HERG blockade
- QT prolonging drugs not always associated with TdP ie amiodarone
- Antiarrhythmics ie sotalol
- Antipsychotics ie thioridazine
- Antihistamines ie terfenadine
- Anti-infectives ie erythromycin



Drug interactions

■ Pharmacodynamic

- Additive effects of two QT prolonging drugs
- Drugs causing hypokalemia or bradycardia

■ Pharmacokinetic

- One drug inhibits the other's metabolism
 - See chart
- Rapid IV infusion of drug



Repolarization reserve

- Individual genetic polymorphism to QT prolongation and arrhythmia
- May have normal screening ECG
- Trigger such as drug can “unmask” genetic predisposition
- Idiosyncratic and unpredictable



Clinical implications

- Weigh risks and benefits with drug rx
- Be aware of drug interactions
- Screening ECG at discretion
 - >500 msec prompts further evaluation
- Follow signs of syncope/presyncope



Treatment of TdP

- Magnesium 2 gm bolus
 - Repeat as needed
- Correct hypokalemia
- Pacing 90-140 bpm
 - Only for acquired
 - Avoid isoproterenol if poor LV function
- Defibrillation?
- Nicorandil (K channel opener) – experimental



New drug approvals

- New drug may take 3-10 years and cost \$100 million
- QT prolongation/TdP is #1 reason for recent drug warnings/withdrawals
- Preclinical HERG studies in channels, cells, isolated hearts, and animals
- Clinical studies
 - QT >500 msec or change of over 30-60 msec clearly bad
 - QT change of over 5 msec may require further study
 - QT change of over 20 msec may result in nonapproval
 - Drug interactions
- Postmarketing surveillance

