Mechanisms of Arrhythmogenesis:
Focus on Long QT Syndrome (LQTS)

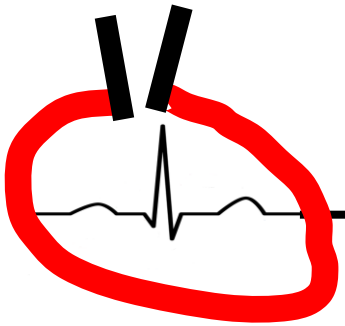
Craig T. January, MD, PhD
Division of Cardiovascular Medicine
University of Wisconsin-Madison

CSRC-HESI-FDA

Rechanneling the Current Cardiac Risk Paradigm: Arrhythmia Risk Assessment During Drug Development Without the Thorough QT Study

White Oak Facility, FDA. July 23, 2013

Disclosures



Cellular & Molecular Arrhythmia Research Program

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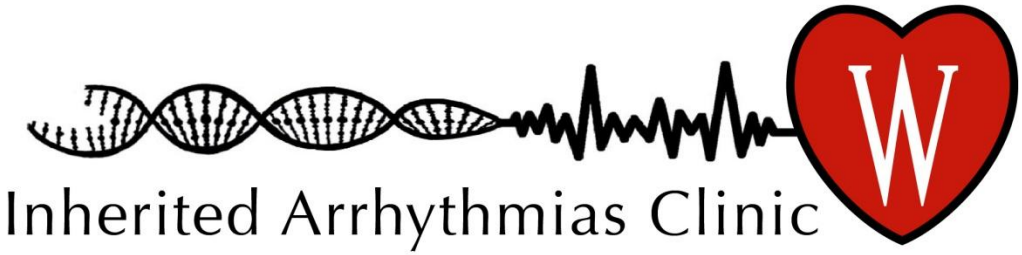
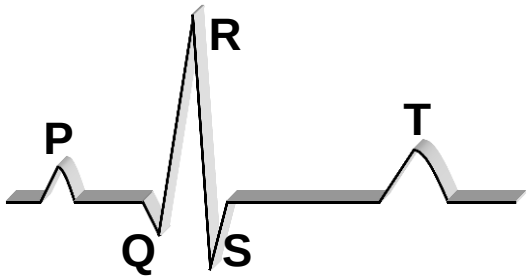
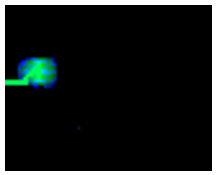
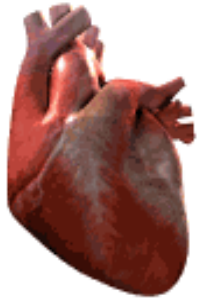


The Heart Beat: A Remarkable Feat!







- **Your heart is an electrically driven pump.**
- **It usually beats 60-80 times a minute,**

  or about 100,000 times a day,

  or about 35 *million* times a year,

  or about 3 *billion* times in a normal life span.

- **If the normal pumping <u>rhythm</u> or <u>function</u> is severely disrupted for more than a few minutes, irreversible multi-organ damage and death occur.**

Organization of Talk

- **Background**
  - **Congenital (Inherited) LQTS**
  - **Acquired (Drug-induced) LQTS**
    - **Anti-arrhythmic drugs**
    - **Non-cardiovascular drugs**
- **Cellular Mechanisms of Drug Action**
  - **Effects on ion channels**
  - **Effects on protein trafficking**
- **Cellular and Tissue Consequences**
- **Summary**

Definitions and History

- **Cellular/tissue Mechanisms of Cardiac Arrhythmias**
  - **Triggered activity**
    - **Early afterdepolarizations (EADs): Trigger for Torsades de Pointes**
    - **Delayed afterdepolarizations (DADs): Ca^{2+} overload**
  - **Reentry (most common arrhythmia mechanism)**
    - **Monomorphic (fixed circuit): The more common reentrant mechanism**
    - **Polymorphic (varying circuit): LQTS related Torsades de Pointes**
  - **Abnormal (accelerated) automaticity**
  - **Parasystole (rare)**

- **Long QT syndromes first characterized >50 yrs ago**
  - **Autosomal recessive congenital LQTS with deafness (Jervell and Lange-Nielsen, 1957)**
  - **Autosomal dominant congenital LQTS (Romano et al, 1963; Ward, 1964)**
  - **Quinidine syncope with drug-induced LQTS (Selter and Wray, 1964)**
  - **Ventricular arrhythmia Torsades de Pointes – TdS (Dessertenne, 1966)**

Background: Proarrhythmia and Antiarrhythmic Drugs

Block of Na^+ channels: Not LQTS related

- **CAST I: Encainide & Flecainide arms stopped due to ↑mortality and nonfatal cardiac arrests.** *NEJM*, 1989.
- **CAST II: Moricizine arm stopped for same.** *NEJM*, 1992.

Block of K^+ channels: Proarrhythmia associated with QT interval lengthening

- **Mixed channel blockers (Quinidine, etc) shown in 1960-70's to cause ↑APD, ↑QRS, ↑QT, and EADs and TdS. Meta-analyses later showed ↑mortality.** *Circ,* 1991.
- **Selective I_{Kr} blockers developed in 1980-90's caused ↑APD and ↑QT, to trigger EADs and TdS. Clinical trials showed increased or neutral impact on mortality.** *Lancet,* 1996 (d-sotalol). *NEJM,* 1999, (dofetilide).

Proarrhythmia and Non-antiarrhythmic Drugs

The "founder" drug terfenadine (Seldane)

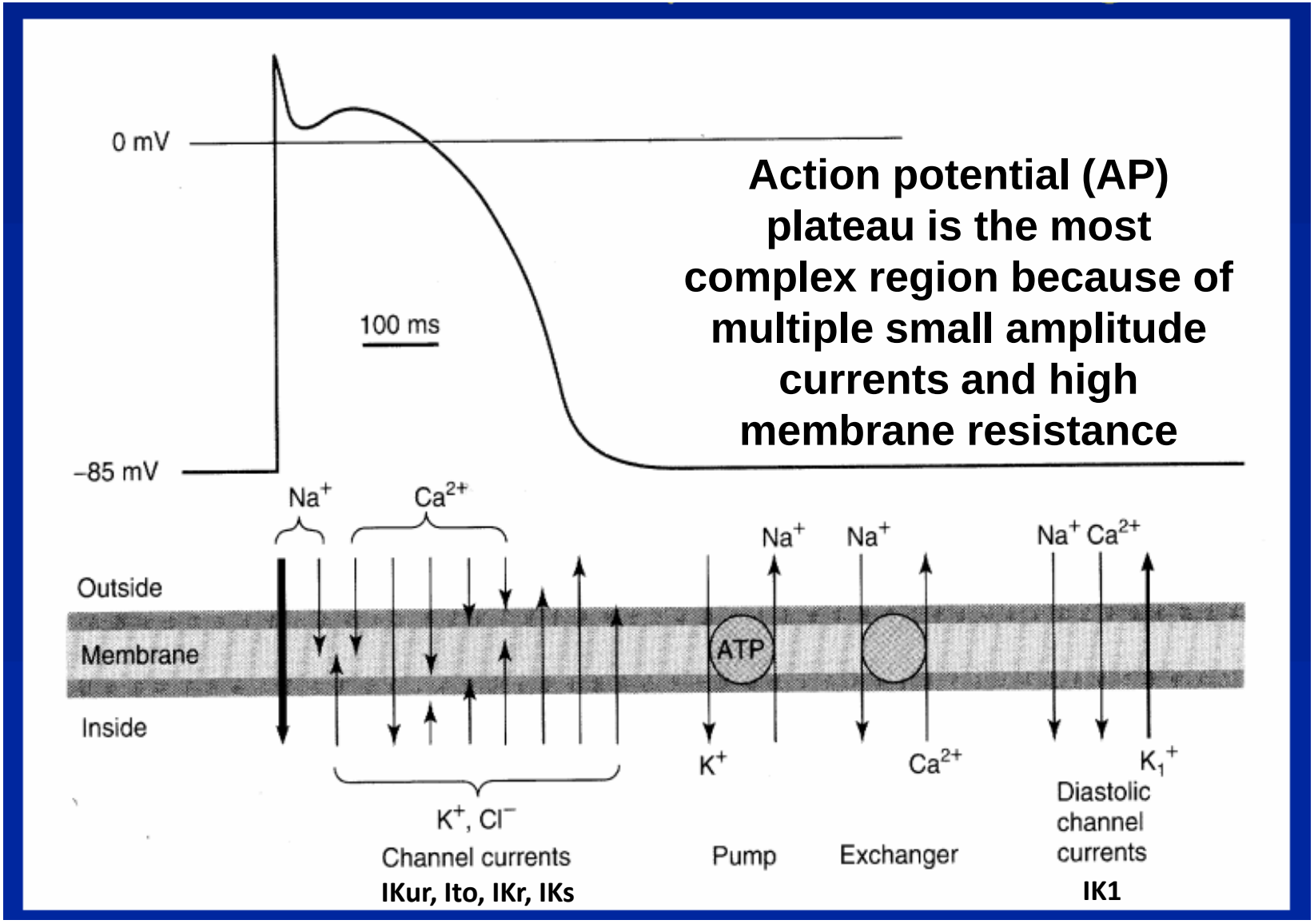
- **Monahan BP, Ferguson CL, Killeavy ES, Lloyd BK, Troy J, Cantilena LR Jr. Torsades de pointes occurring in association with terfenadine use. First report of overdose.** *JAMA. 1990. 264:2788-2790.*

- **Zimmermann M, Duruz H, Guinand O, Broccard O, Levy P, Lacatis D, Bloch A. Torsades de Pointes after treatment with terfenadine and ketoconazole. First report of drug-drug interaction.** *Eur Heart J. 1992. 13:1002-1003.*

- **Antihistamines were the first non-cardiovascular agents linked to drug-induced QT interval prolongation and TdS.**

- **FDA first became concerned in 1991 about non-sedating antihistamines (primarily terfenadine but also astemizole).**

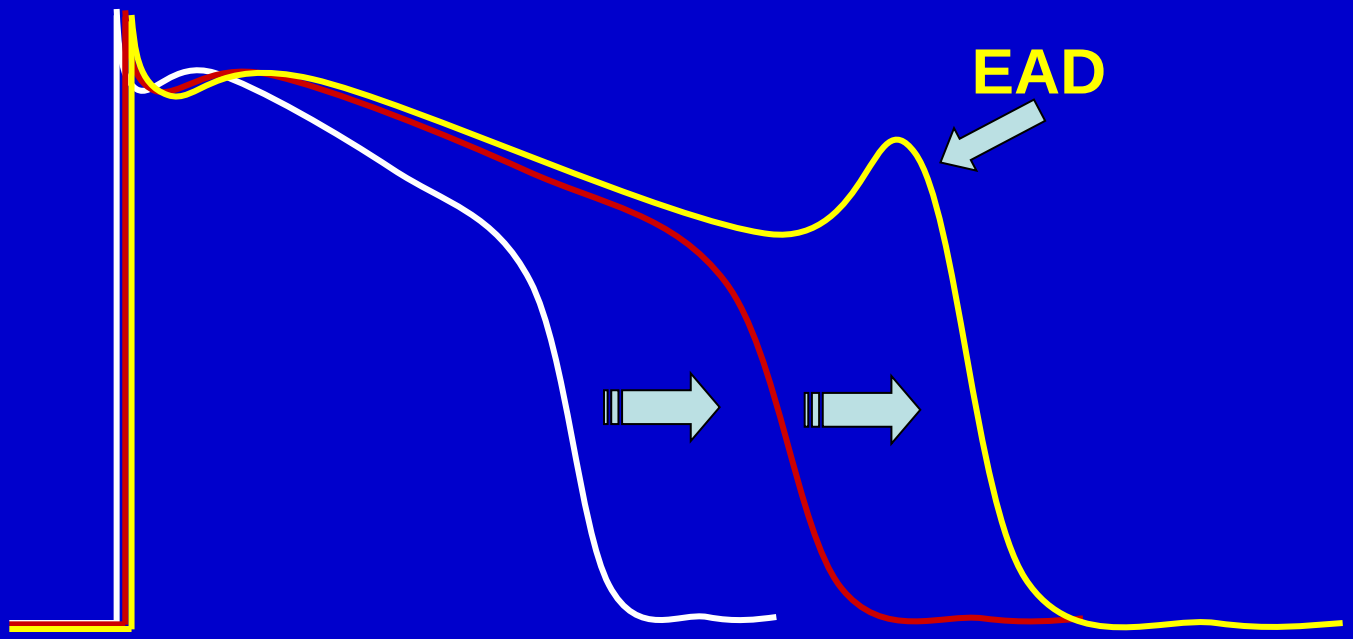
Cardiac Myocyte Ionic and Exchanger Currents



Many drugs interact with I_{Kr} but other channels/currents may also be important

Action Potential Prolongation (AP)

- Lengthens Refractoriness (>Purkinje, M-cell)
- Increases Heterogeneity of Repolarization
- Induce Early Afterdepolarizations (EADs)



EAD mechanism: Recovery of L-Ca^{2+} channel window current at the AP plateau voltage range.

January and Riddle. *Circ Res*, 1989.

Acquired (*Congenital*) LQTS: APD/EAD/QT Interval Prolonging Models

Drug (*Gene Defect*)	Principal Target
Veratridine, ATX II, anthopleurin A, alfuzosin, (*mutations in Na^+ channels*)	Enhance late I_{Na}
Bay K 8644 (*mutations in Ca^{2+} channels*)	Enhance $I_{Ca\text{-}L}$ (mode 2)
Cs^+, quinidine, procainamide, bepridil	Suppress K^+ currents
E-4031, dofetilide, ibutilide, sotalol, terfenadine, astemizole, desmethylastemizole, cisapride, haloperidol, droperidol, halofantin, erythromycin, fluoxetine, etc. (*mutations in hERG/Kv11.1 K^+ channels*)	Suppress I_{Kr}
Chromanol 293B (*mutations in KCNQ1/Kv7.1 K^+ channels*)	Suppress I_{Ks}
Depolarizing current	No direct channel effects
Ischemia, reperfusion, acidosis, hypertrophy	Multiple effects

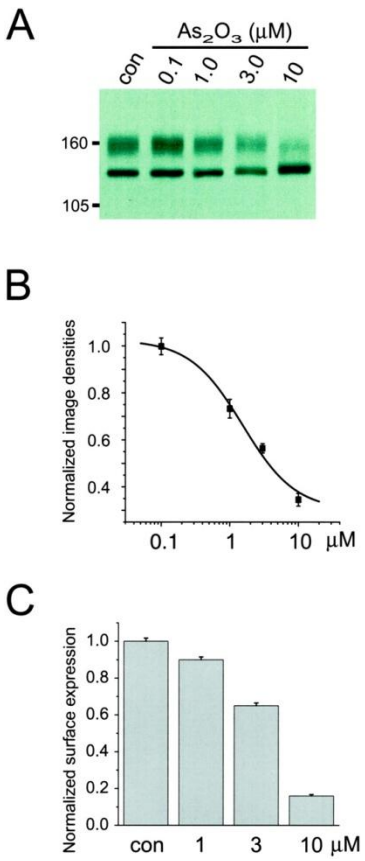
Conclusions:

- **Congenital LQTS: Multiple channels but K^+ channels dominant**
- **Acquired LQTS: Most drugs cause rapid direct channel block of I_{Kr}**

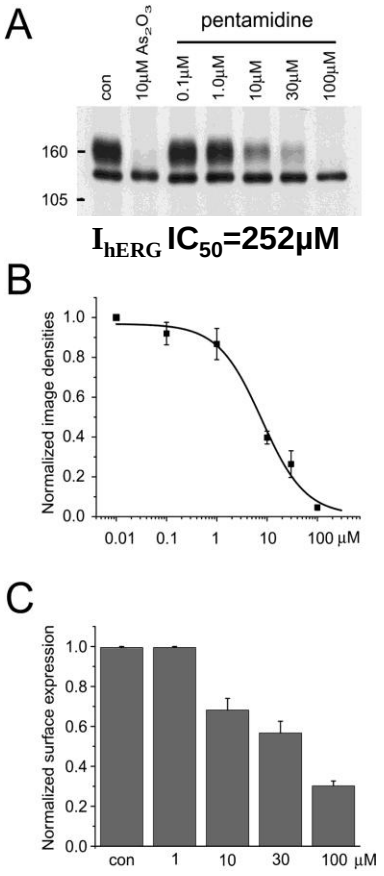
hERG/I_{Kr} Channel Protein Trafficking: Indirect mechanism to reduce I_{Kr}

Drug-induced disruption of WT hERG channel protein trafficking

I. As_2O_3

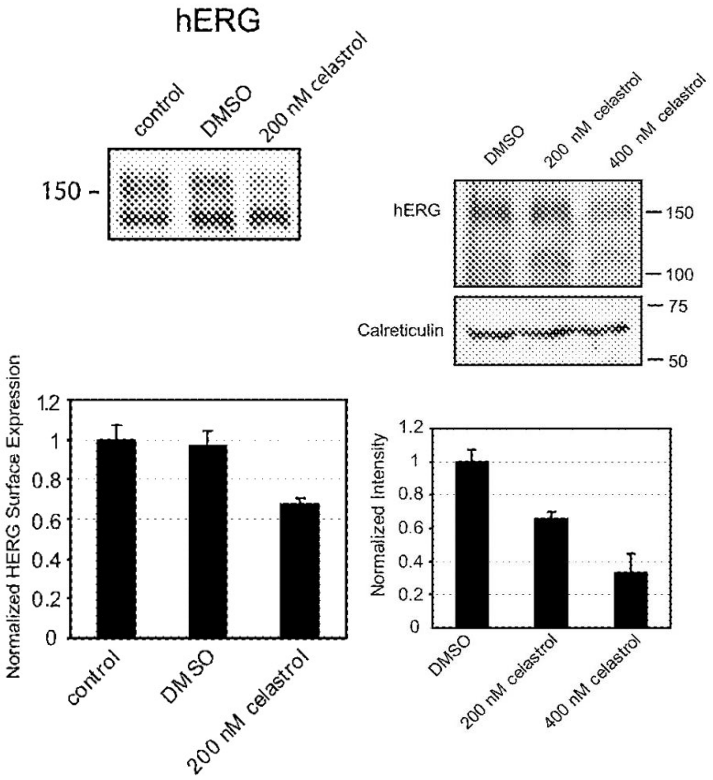


II. Pentamidine



I_{hERG} IC_{50}=252μM

III. Celastrol



Yang et al, *JBC.* 2006

Ficker et al, *Molec Pharm*. 2004 Kuryshev et al, *Molec Pharm*. 2005

Direct vs Indirect hERG Effects: Complex Drug Interactions to Reduce I_{Kr}

DRUG	EFFECT
• Probucol	trafficking only
• Cardiac glycosides	trafficking only (↑conc)
• Arsenic trioxide	trafficking > block
• Celastrol	trafficking > block
• Pentamidine	trafficking > block
• Fluoxetine	trafficking ~ block
• Ketoconazole	trafficking ~ block
• Thioridazine	block > trafficking
• Verapamil	block > trafficking (↑conc)
• Cisapride	block only
• E-4031	block only

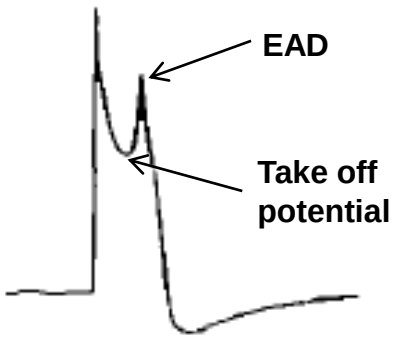
Findings support separate drug binding domains for direct and indirect block

Additional potential drug mechanisms: Drug transporters, signaling & adrenergic pathways, secondary genes/proteins, genomic associations

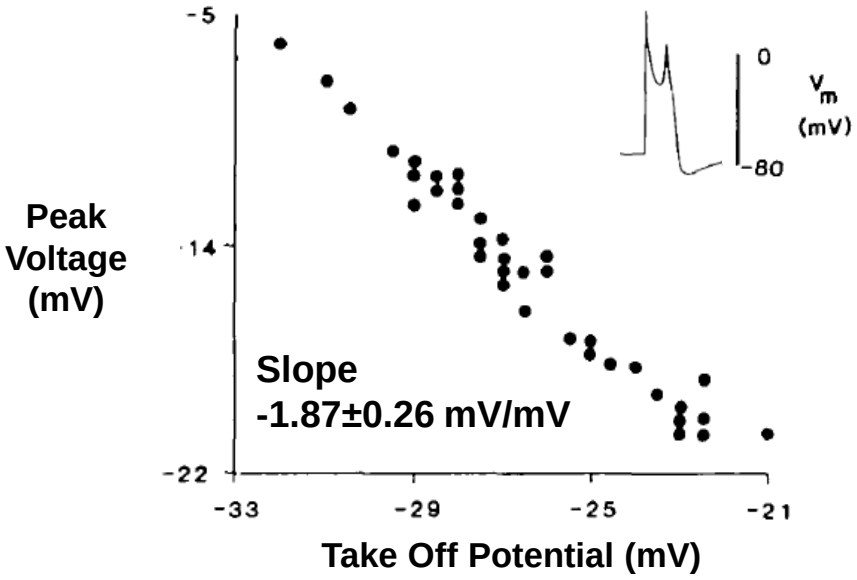
EAD Mechanism: The same in iPS-CMs

EAD amplitude varies inversely with its take off potential

Adult Canine Purkinje Fiber APs

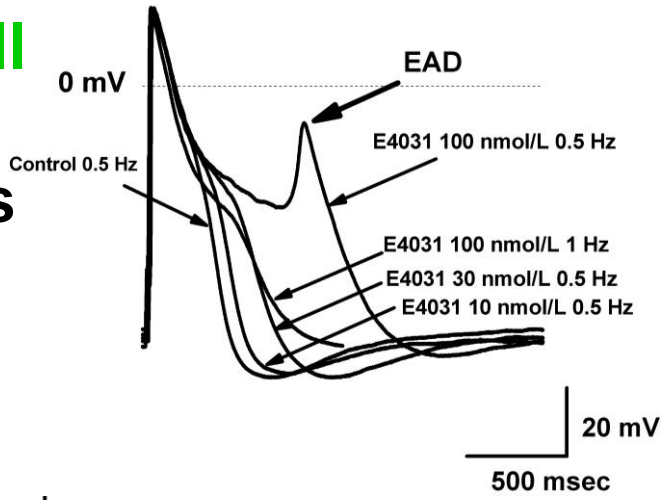


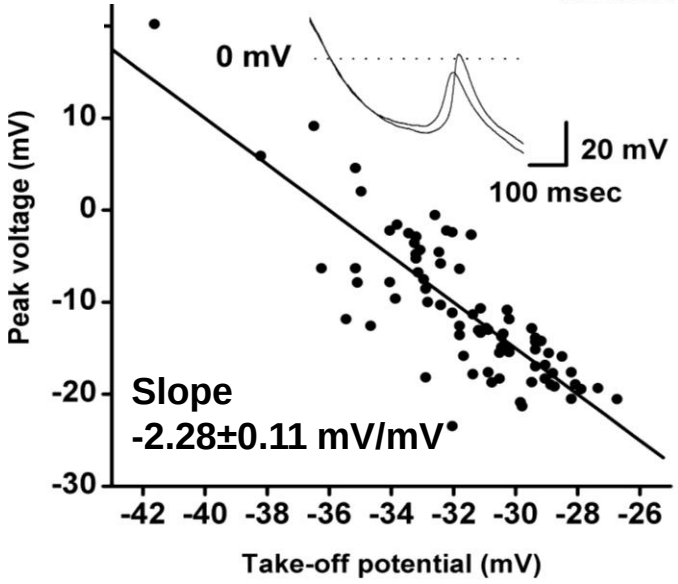
Bay k 8644



January et al, *Circ Res*, 65:570+, 1988

iCell CM APs

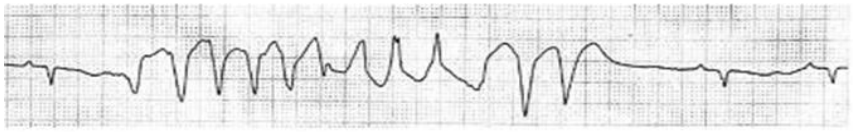


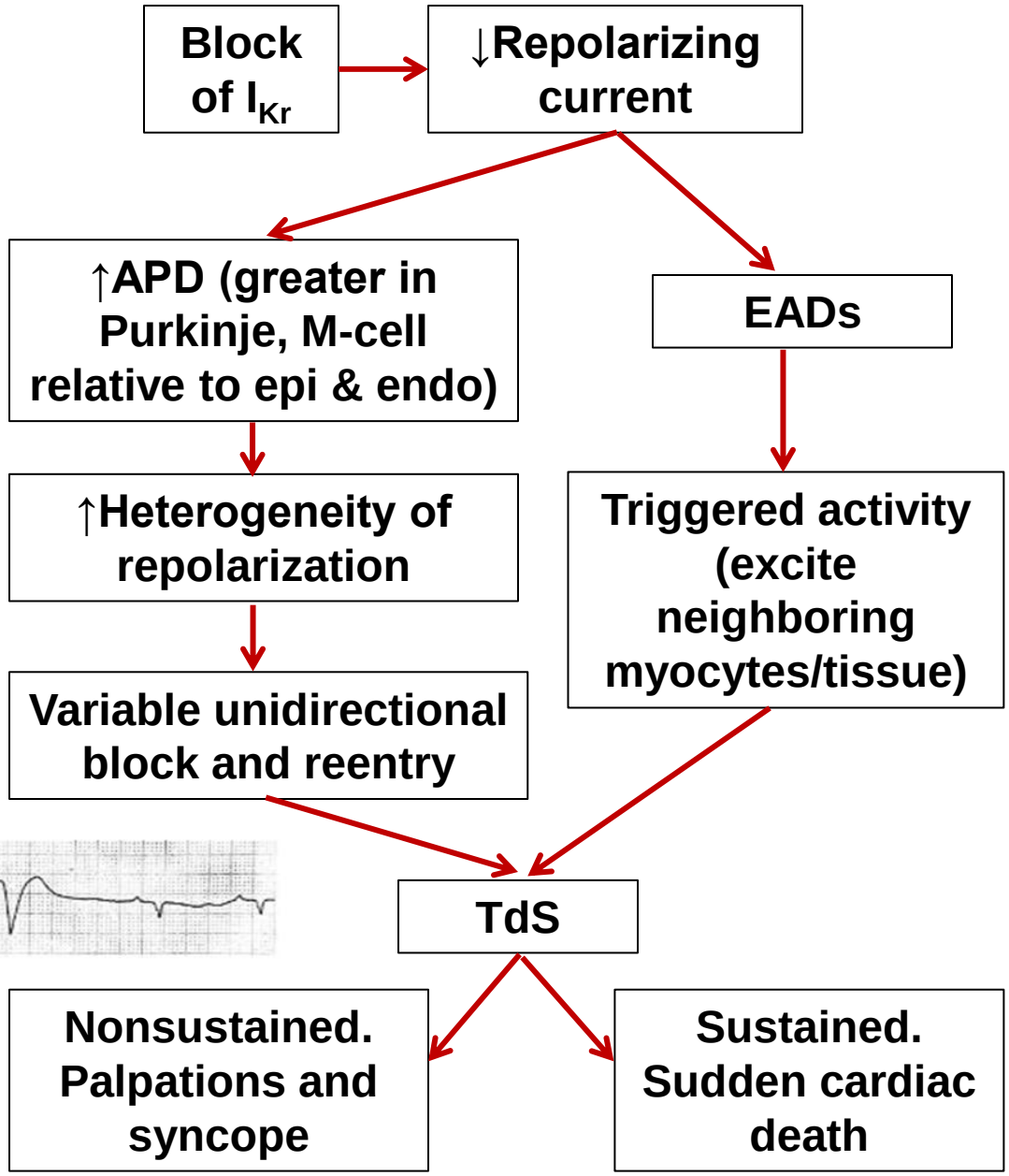


Ma et al, *AJP:H&C*, 301:H2006+, 2011

Mechanism of Torsades de Pointes (TdS)

EADs excite polymorphic reentry in the ventricles

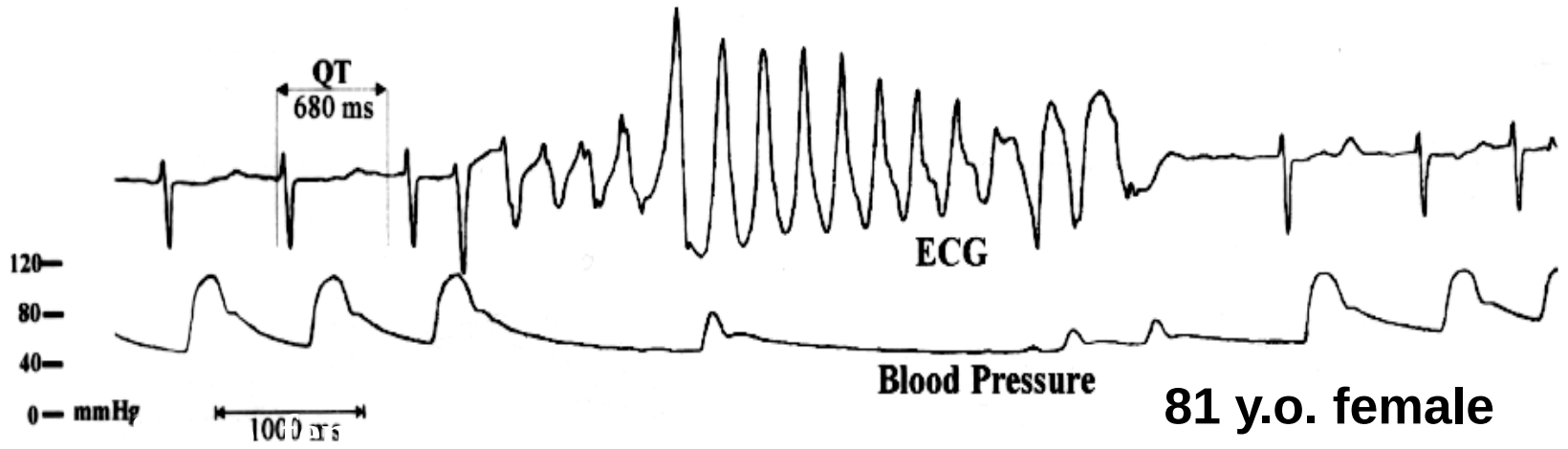




Modified from Yap and Camm. *Heart,* 2003

Long QT Syndrome (LQTS): A Long Journey

LQTS and Torsades de Pointes with the antihistamine astemizole (Hismanal®)



81 y.o. female

In 1999 Hismanal was withdrawn from the marketplace for drug-induced LQTS

Vorperian et al, *JACC,* 15:1556-1561, 1996

Summary

- **LQTS has been a “cardiology problem” for >50 years.**
- **AP prolongation lengthens refractoriness, increases tissue heterogeneity of repolarization, and triggers arrhythmogenic EADs to initiate Torsades de Pointes.**
- **Direct drug block of I_{Kr} (hERG channels) is the dominant mechanism for both cardiovascular and non-cardiovascular drug related LQTS.**
- **Additional channels and additional cellular mechanisms may infrequently also cause non-cardiovascular drug related LQTS.**
- **New screening approaches including iPS-derived human cardiomyocytes offer innovative ways forward.**