# TdP Mechanisms and CiPA


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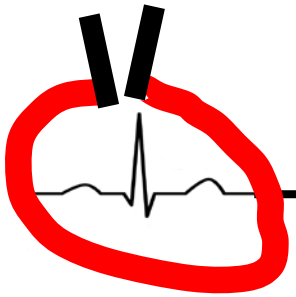
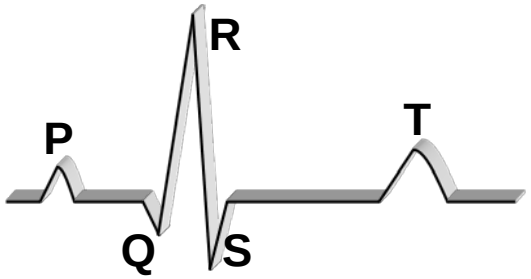
**Disclosures**

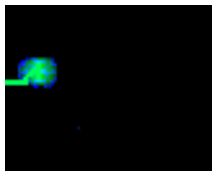


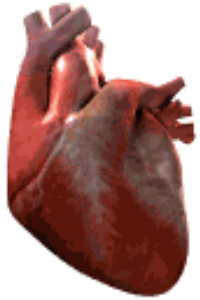
**Cellular & Molecular Arrhythmia Research Program**

**University of Wisconsin-Madison**

# *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**
  - **Arrhythmia mechanisms**
- **Cellular Mechanisms of Drug Action**
  - **Effects on ion channels**
  - **Effects on protein trafficking**
- **Tissue Consequences**
  - **Torsades de Pointes (TdS)**
- **Summary – need for improved comprehensive assays**

# Background: Definitions

## Cellular/tissue Mechanisms of Cardiac Arrhythmias

- **Triggered activity**
  - **Early afterdepolarizations (EADs): Trigger for Torsades de Pointes**
  - **Delayed afterdepolarizations (DADs): $Ca^{2+}$ overload syndromes**
- **Reentry (most common serious arrhythmia mechanism)**
  - **Monomorphic (fixed circuit): The more common reentrant mechanism**
  - **Polymorphic (varying circuit): LQTS related Torsades de Pointes**
- **Abnormal (accelerated) automaticity**
- **Parasystole (competing foci, rare)**

# Proarrhythmia and Non-antiarrhythmic Drugs

## LQTS 1st characterized >50 years 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)**

## Non-antiarrhythmic drugs

- **Antihistamines were the first non-cardiovascular agents clearly linked to drug-induced QT interval prolongation and TdS.**
  - **Craft TM. Torsade-de-pointes after astemizole overdose.** *Br Med J. 1986. 292:660.*
  - **Monahan BP et al. Torsades de pointes occurring in association with terfenadine use.** *JAMA. 1990. 264:2788-2790.*
  - **Zimmermann M et al. Torsades de Pointes after treatment with terfenadine and ketoconazole. First report of drug-drug interaction.** *Eur Heart J. 1992. 13:1002-1003.*
- **FDA became concerned in 1991 about non-sedating antihistamines (terfenadine and astemizole).**

# Acquired (*and Congenital*) LQTS: Many Models and Mechanisms

| **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** |

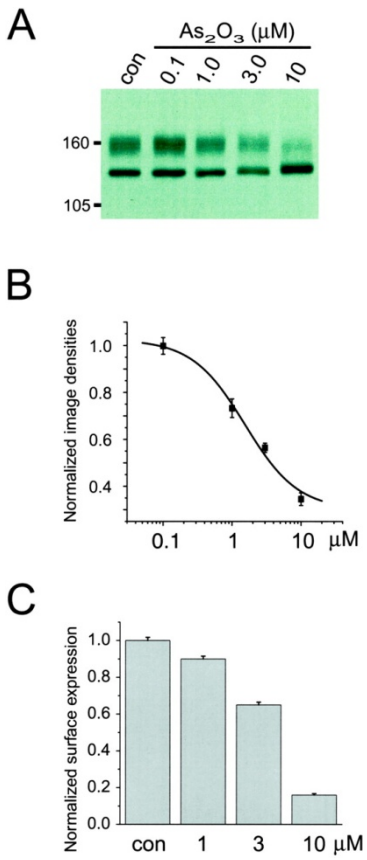
**Conclusions:**

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

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

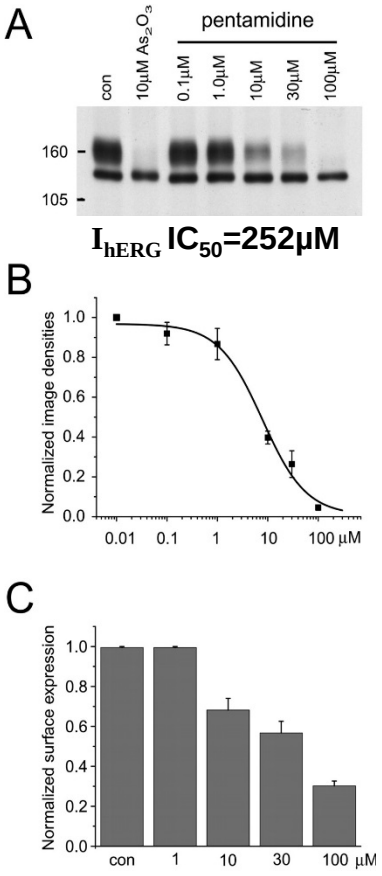
## Drug-induced disruption of WT hERG channel protein trafficking

### I. $As_2O_3$




Ficker et al, *Molec Pharm*. 2004

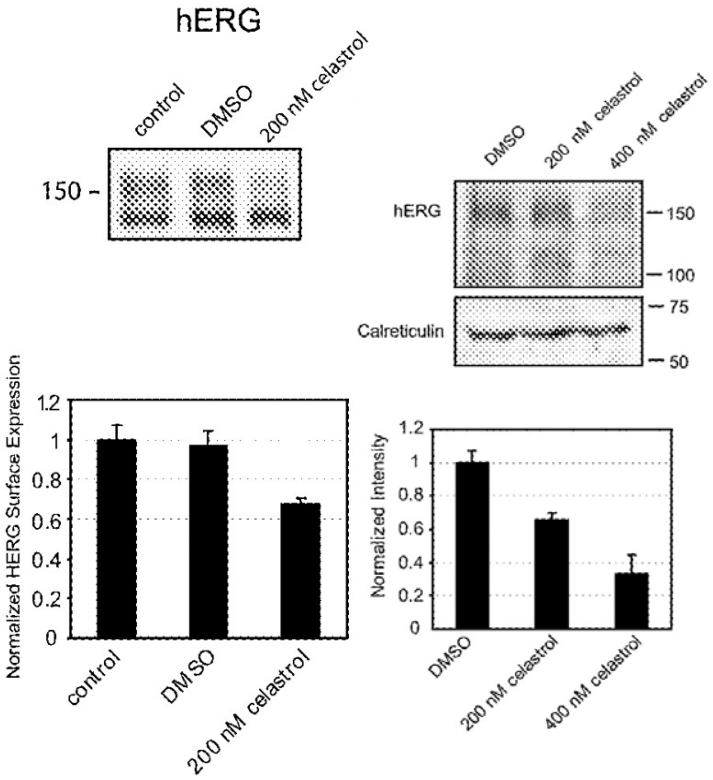
### II. Pentamidine




$I_{hERG}$ $IC_{50}$=252μM

Kuryshev et al, *Molec Pharm*. 2005

### III. Celastrol




Yang et al, *JBC.* 2006

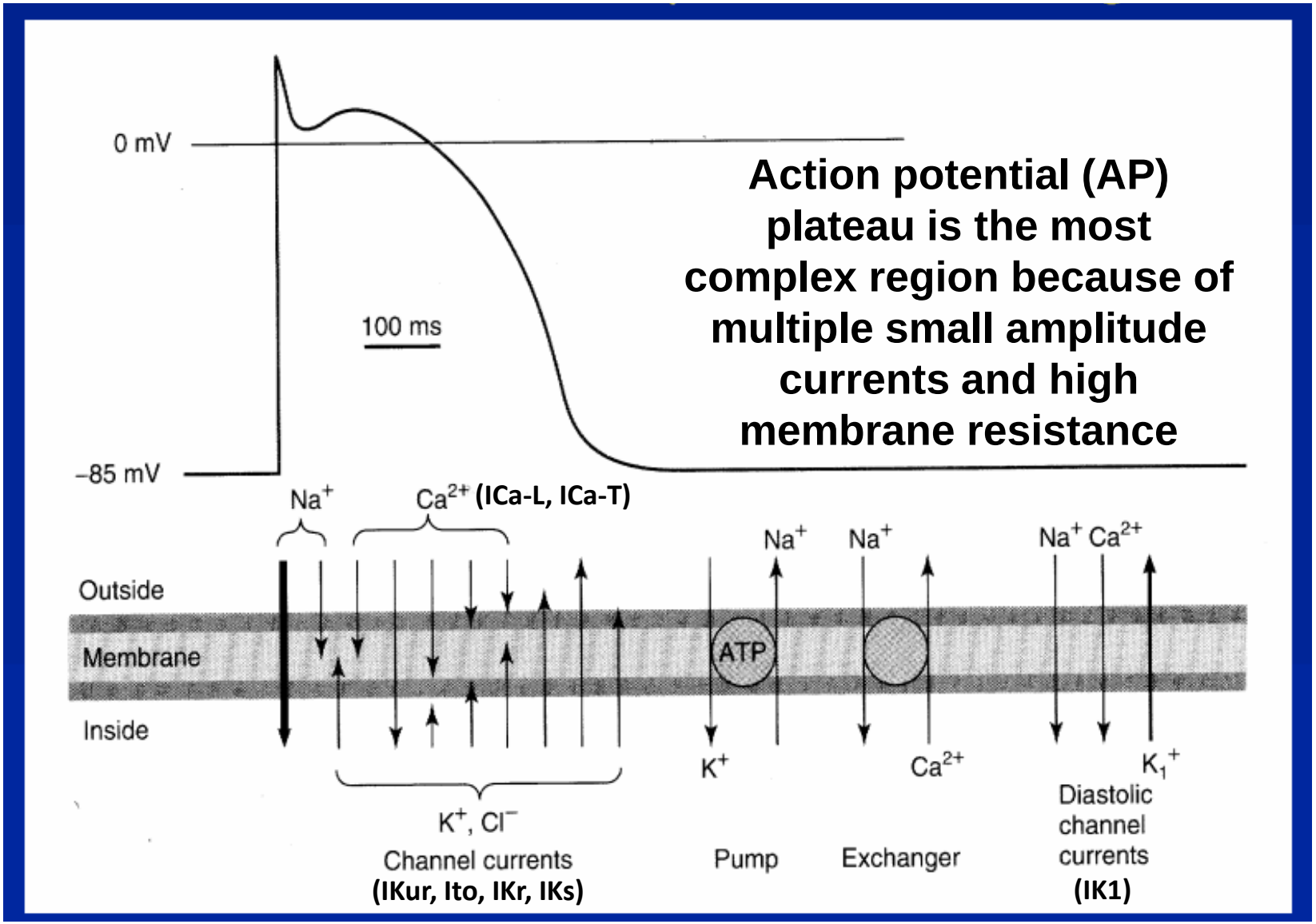
# Direct vs Indirect hERG Effects: Complex Drug Interactions to Reduce $I_{Kr}$

| 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**

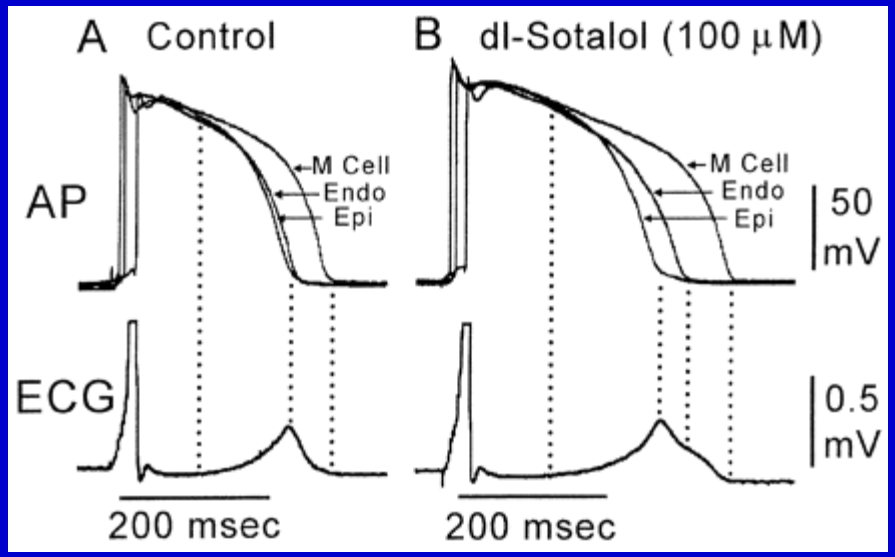
# Cardiac Myocyte Ionic and Exchanger Currents

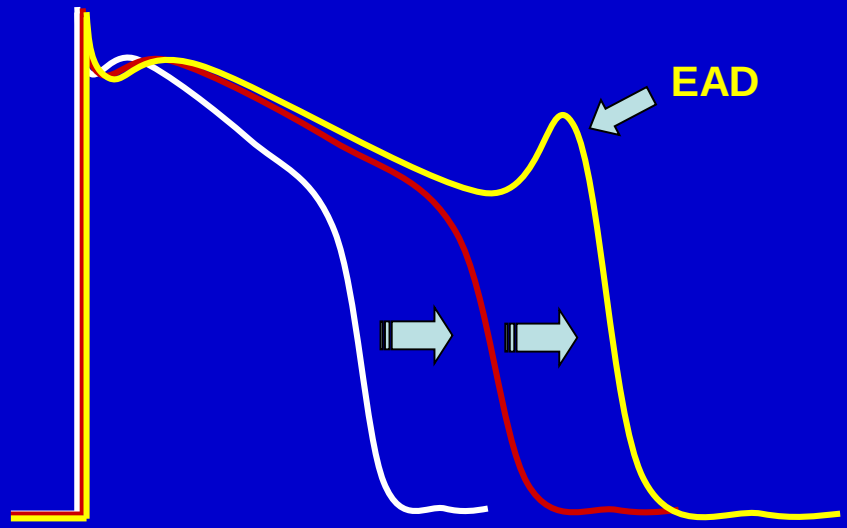



**Many drugs interact with $I_{Kr}$ but other channels/currents are also important**

# Action Potential Prolongation (AP)

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

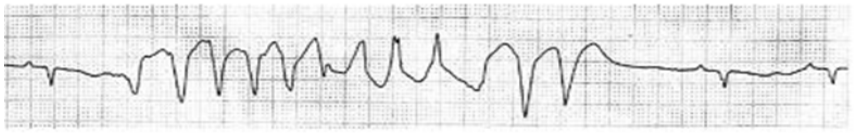


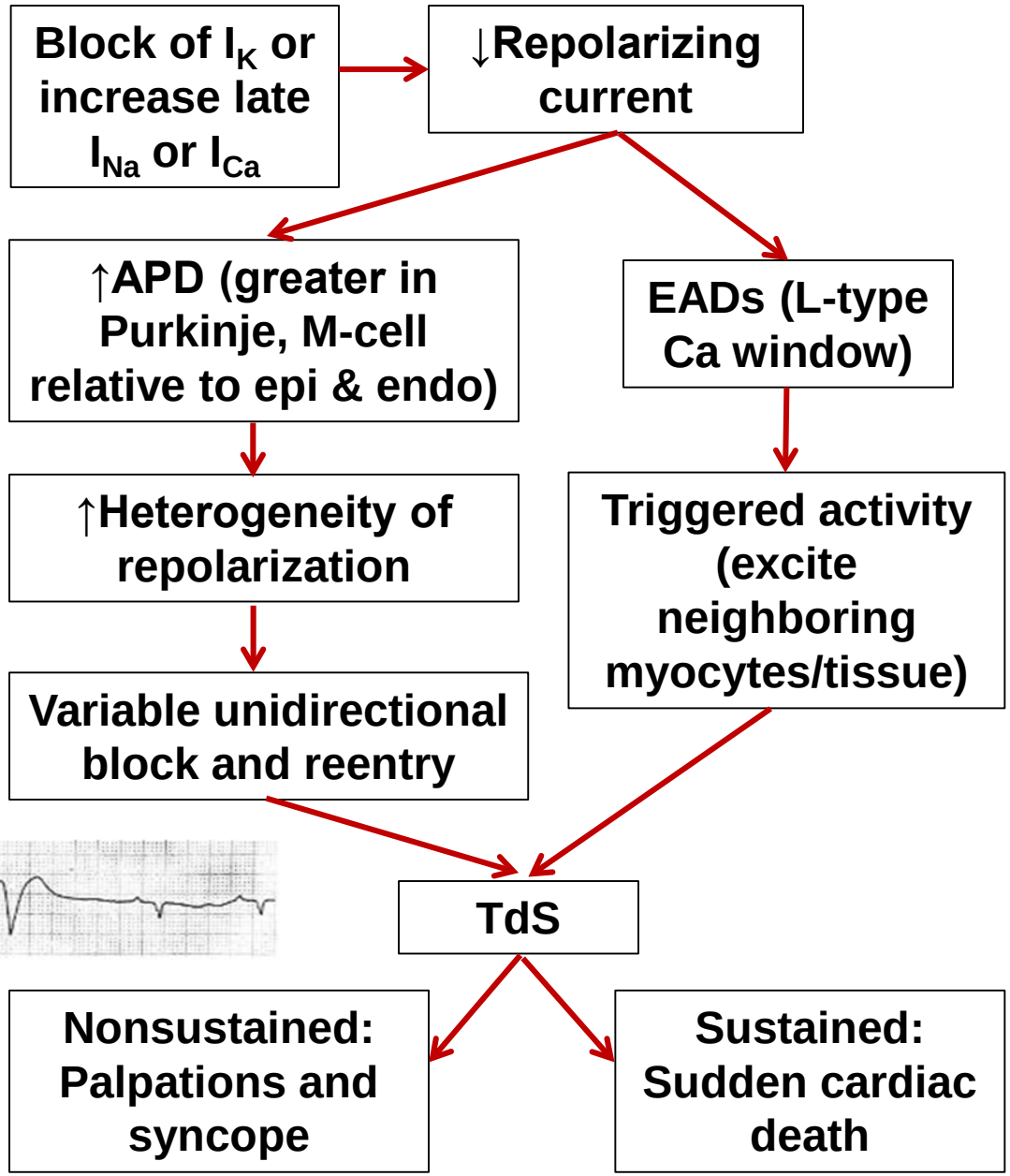




EAD mechanism: Recovery and reopening of L-$Ca^{2+}$ channels at the AP plateau "window" voltage range. January and Riddle. *Circ Res*, 1989.

# Mechanism of Torsades de Pointes (TdS)

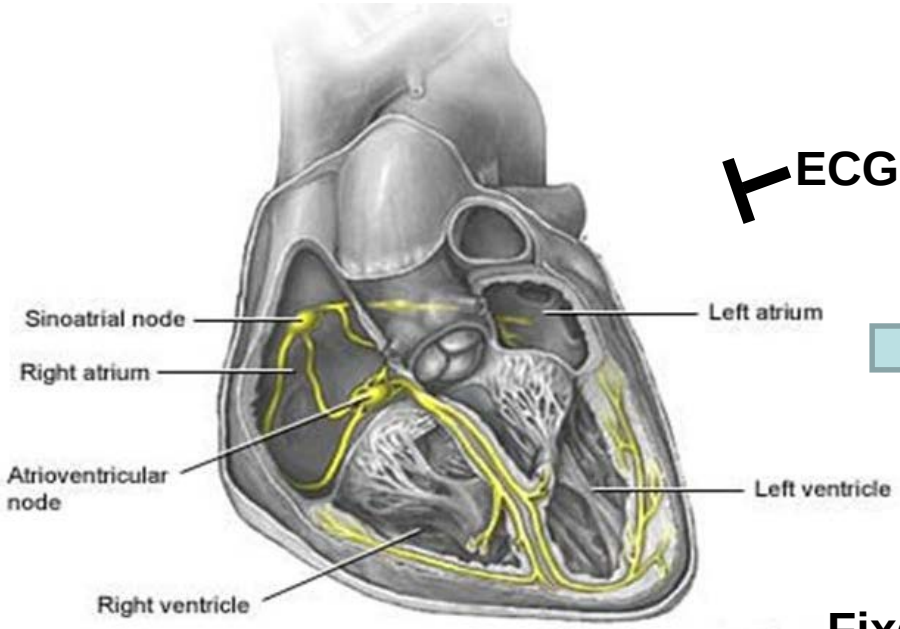
**EADs excite polymorphic (transmural) reentry in the ventricles**





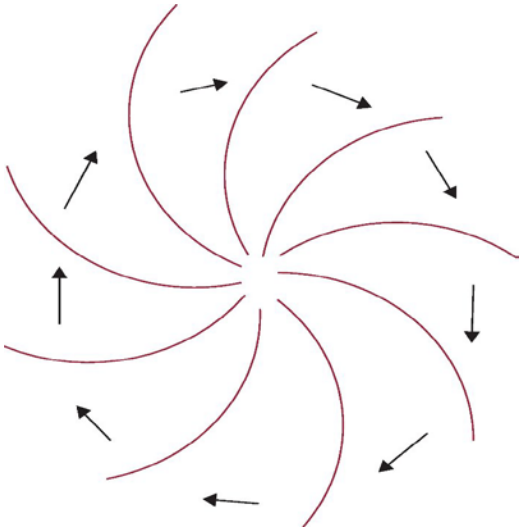

Modified from Yap and Camm. *Heart,* 2003

# TdS




ECG

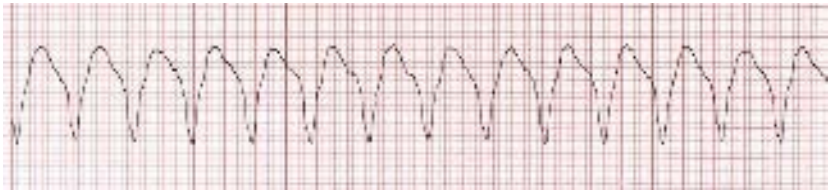
Arrhythmia Rotor



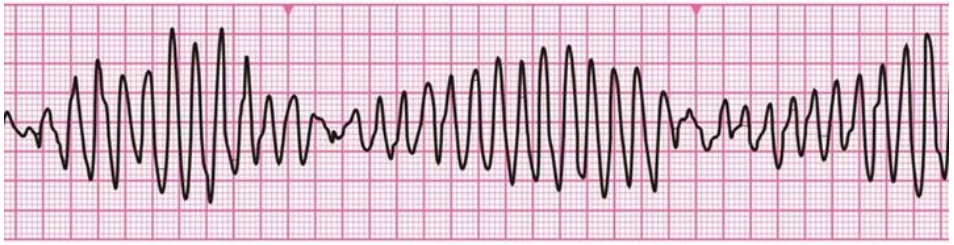
Fixed position

Not Fixed

Monomorphic VT



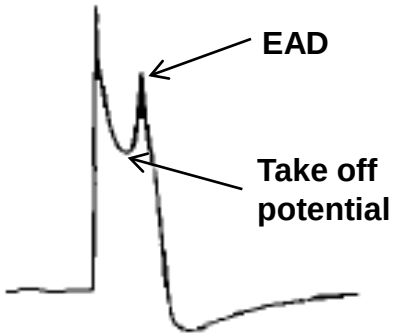
Polymorphic VT/TdS



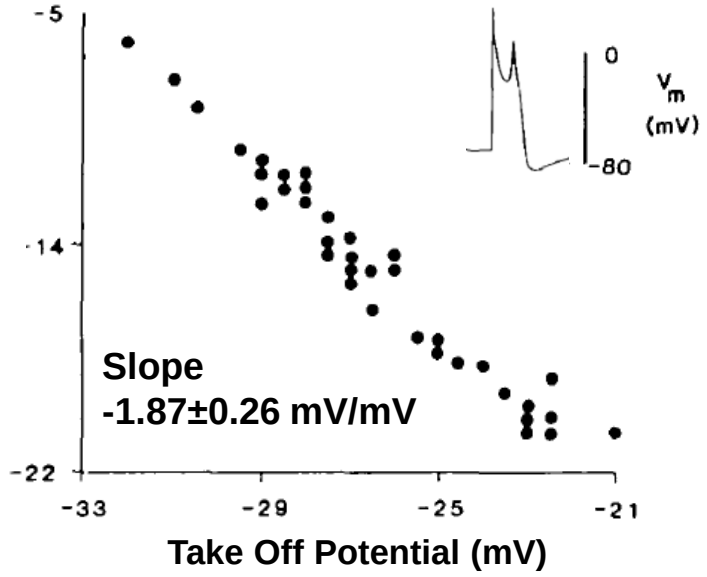
# iPS-CMs: EAD Mechanism the Same

## EAD amplitude varies inversely with its take off potential

**Adult Canine Purkinje Fiber APs**

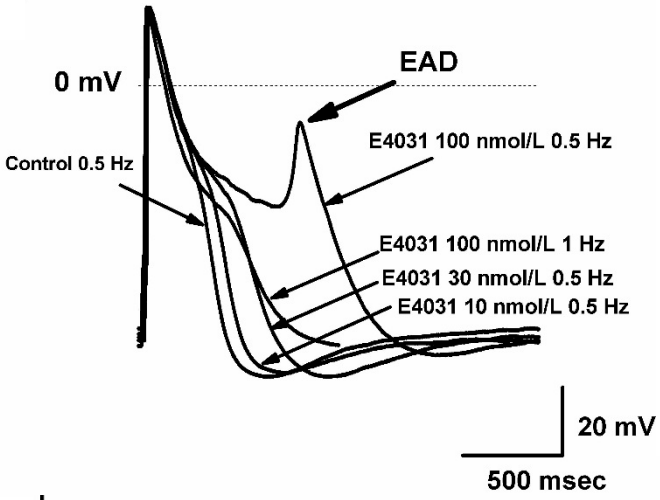


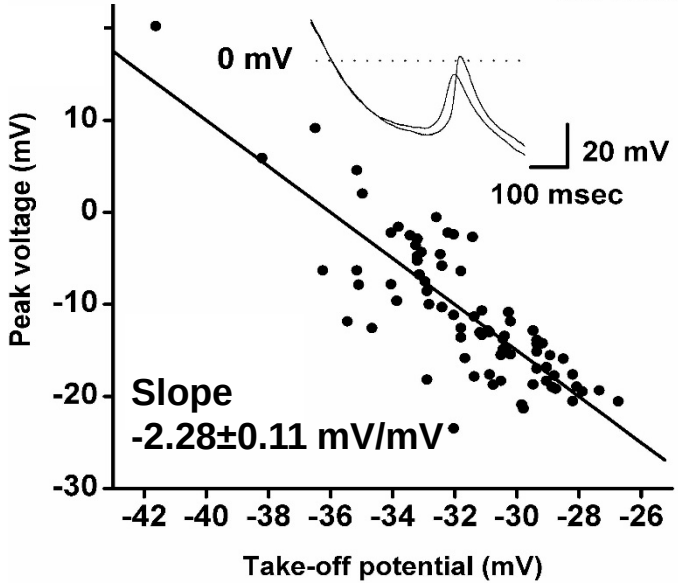

Bay k 8644




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

**iPS CM APs**

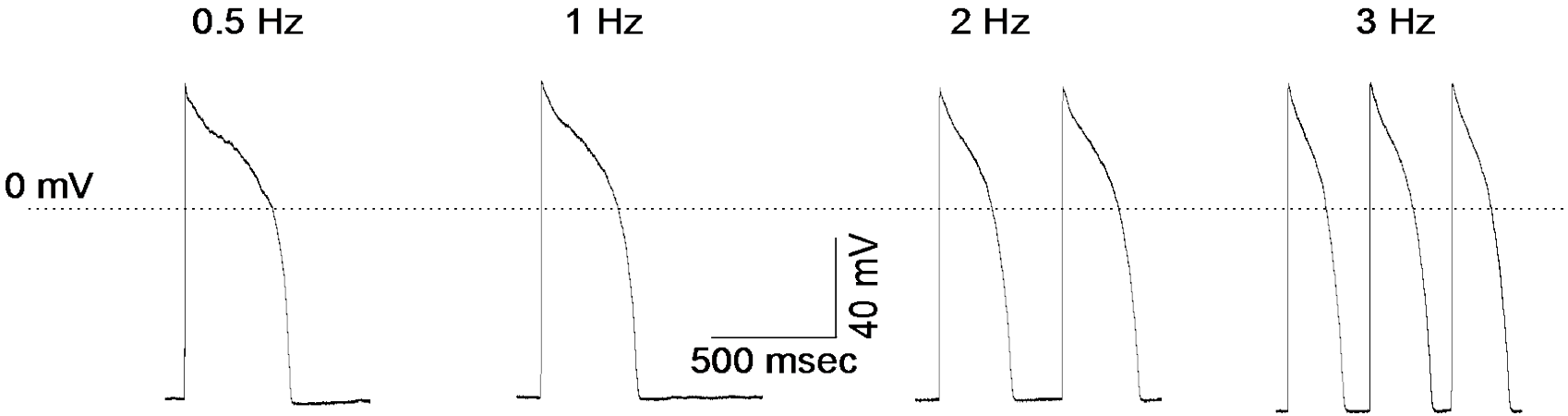


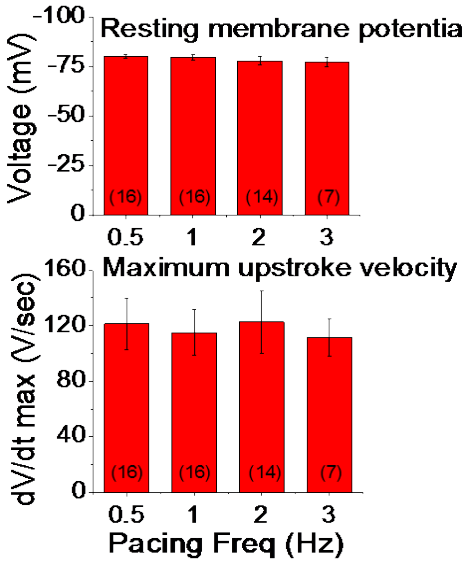

Ma et al, *AJP:H&C*, 301:H2006+, 2011

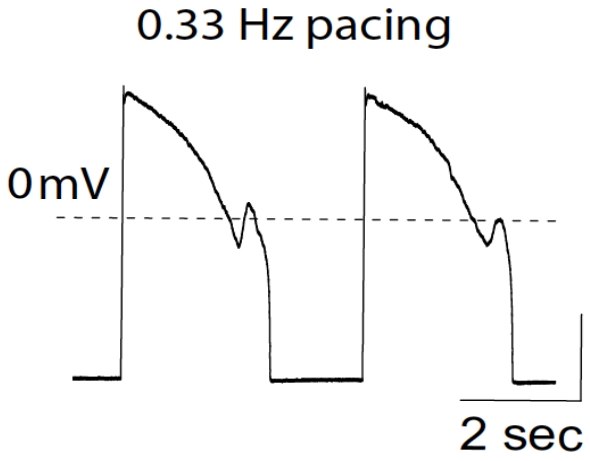
# Improved iPS-CM Models: Enhancing $I_{K1}$

## Mature ventricular action potentials and rate-dependence




## Normal RP and dV/dt

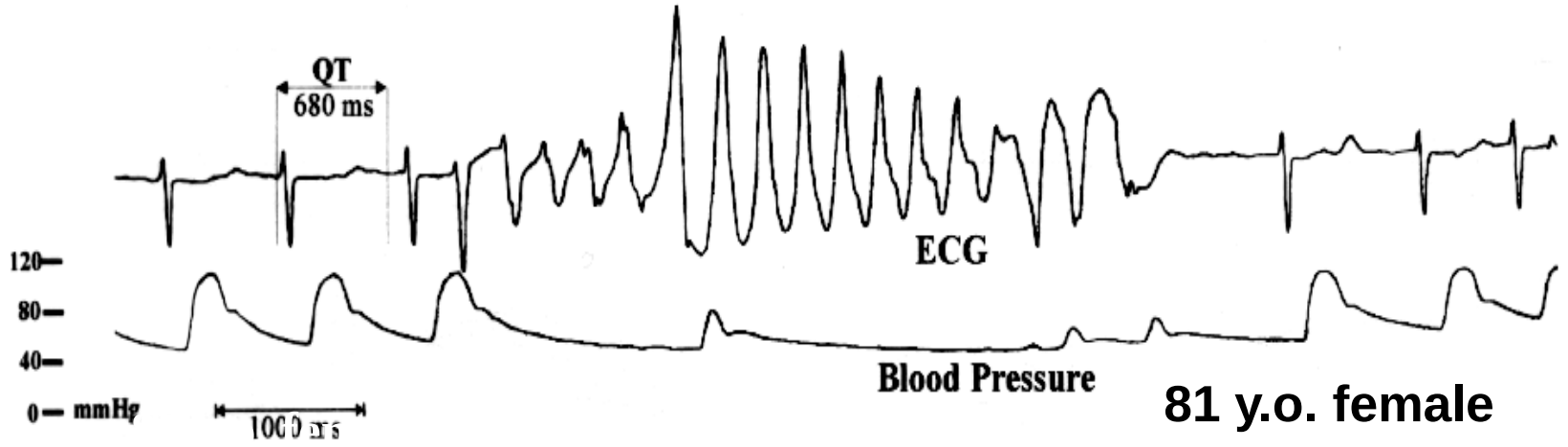



**$I_{K1}$ enhanced iPS-CMs expressing LQT9 Cav3 F97C mutant with EADs.** Vaidyanathan R et al. *AJP: Heart Circ Physiol.* 2016. 310:H1611-21.

# Long QT Syndrome (LQTS): A Long Journey

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




**81 y.o. female**

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

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

# Why CiPA?

- **No single cause of action potential prolongation or cardio-toxicity**
- **Multiple cell types (triggered activity in ventricular cells, Purkinje cells, etc)**
- **Multiple ventricular types with differing properties (epicardial, mid-myocardial, endocardial cells)**
- **Heterogeneity varies within the ventricles (refractoriness, conduction velocity, innervation, etc)**
- **Heterogeneity in drug effects and drug responses (channel block, channel selectivity, protein trafficking)**
- **Differences in genetic background**