Introduction to Clinical Physiology

Zoltán Papp
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Department of Cardiology
Division of Clinical Physiology

Clinical Physiology

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Lectures of Clinical Physiology are available on the internet:

https://aok.unideb.hu/en/clinfiz

Clinical Physiology

Lectures

Semester II: 14 lectures

Circulation (9 lectures)
Respiratory system (2 lectures)
Nutrition (1 lecture)
Nervous system (2 lectures)

(9th week: self control)
(14th week: self control)

Clinical Physiology

Seminars

Seminars are compulsory!

Semester II (week 1-14):

Electrocardiography
(10th week: self control)

Respiratory functions
Echocardiography
Cardiac catheterisation

Clinical Physiology

Exam at the end of semester II

“A” exam: written
“B” exam: written
“C” exam: oral

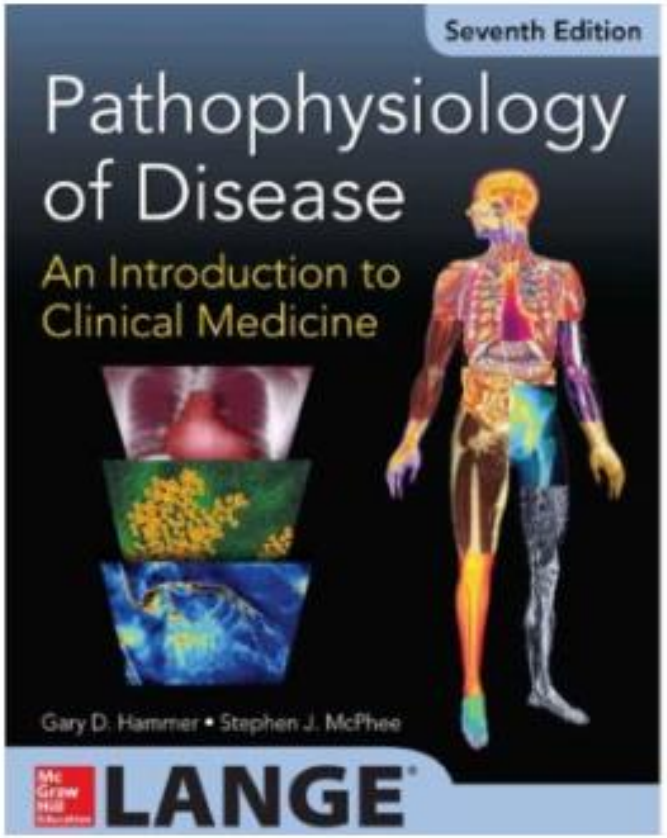
Clinical Physiology

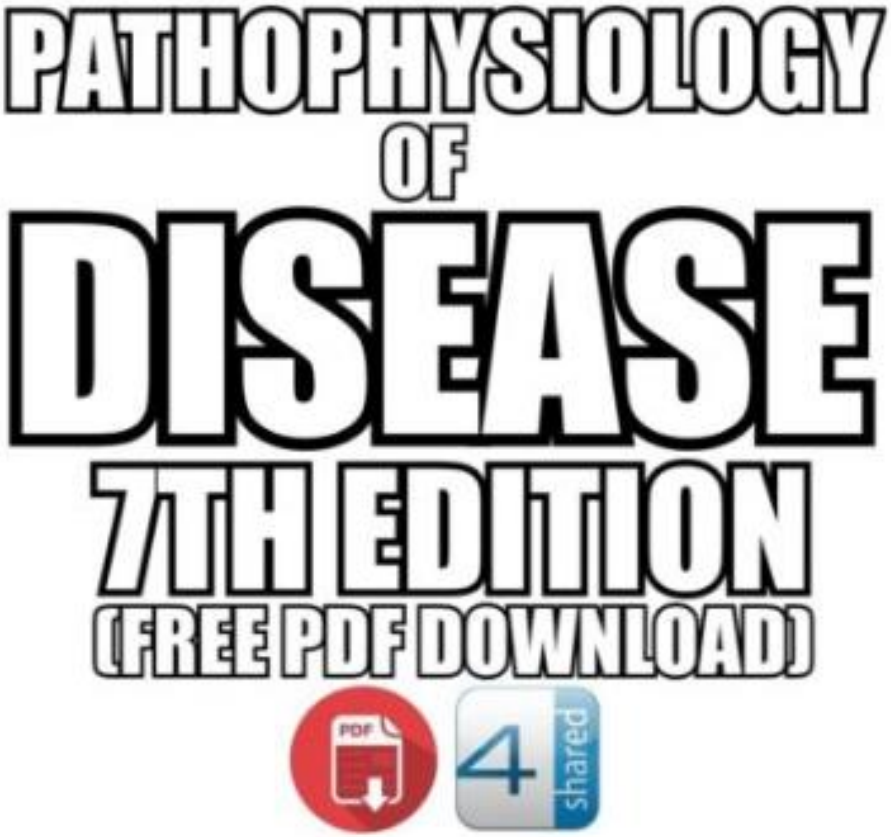
2nd self control results in 2025:

	average:	fail:
English program gen. med.:	2,33	25 %
Hungarian program gen. Med.:	2,49	21 %

Clinical Physiology

Recommended textbooks





Clinical Physiology

ECG BASICS

Recommended text for the seminars:

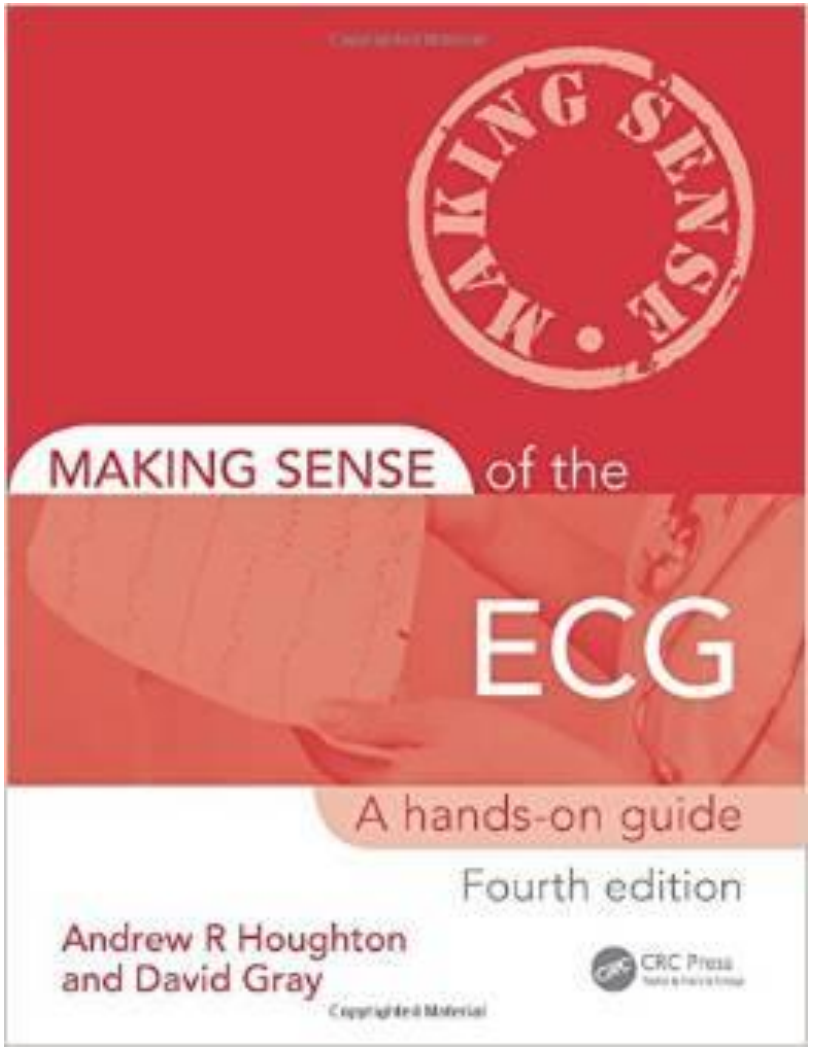
Written by:
László Balogh M.D.

University of Debrecen Clinical Center
Institute of Cardiology and Cardiac Surgery

https://aok.unideb.hu/en/educational-materials-clinical-physiology-medical-program

Making Sense of the ECG (4th edition, 2014)

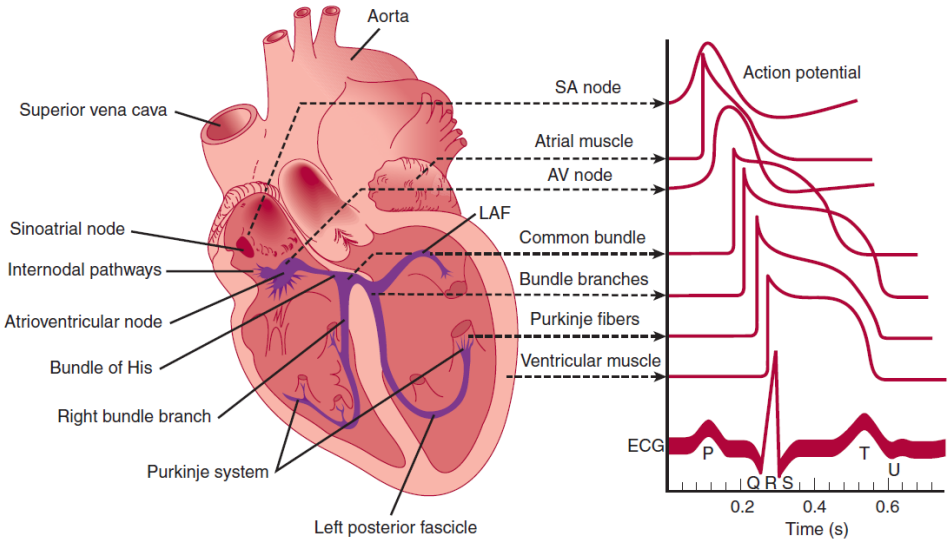
Date of publication: 2014
Publisher: CRC Press
ISBN-13: 978-1444181821
ISBN-10: 1444181823

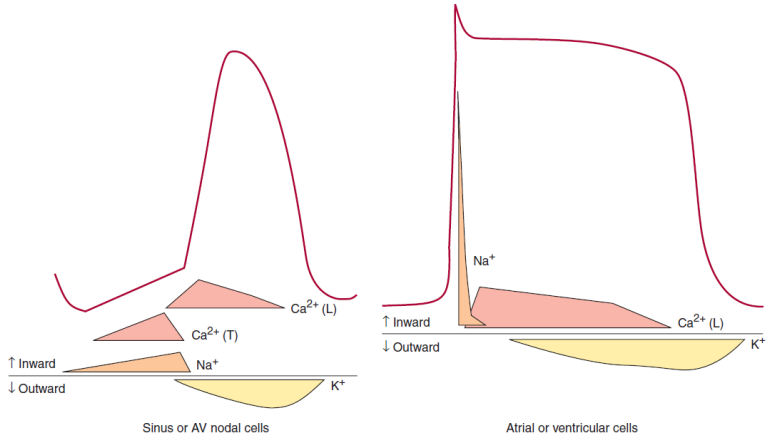


Cellular and molecular factors of pathologic cardiac excitability

Dr. Zoltán Papp
UD Faculty of Medicine
Department of Cardiology
Division of Clinical Physiology

Physiological background

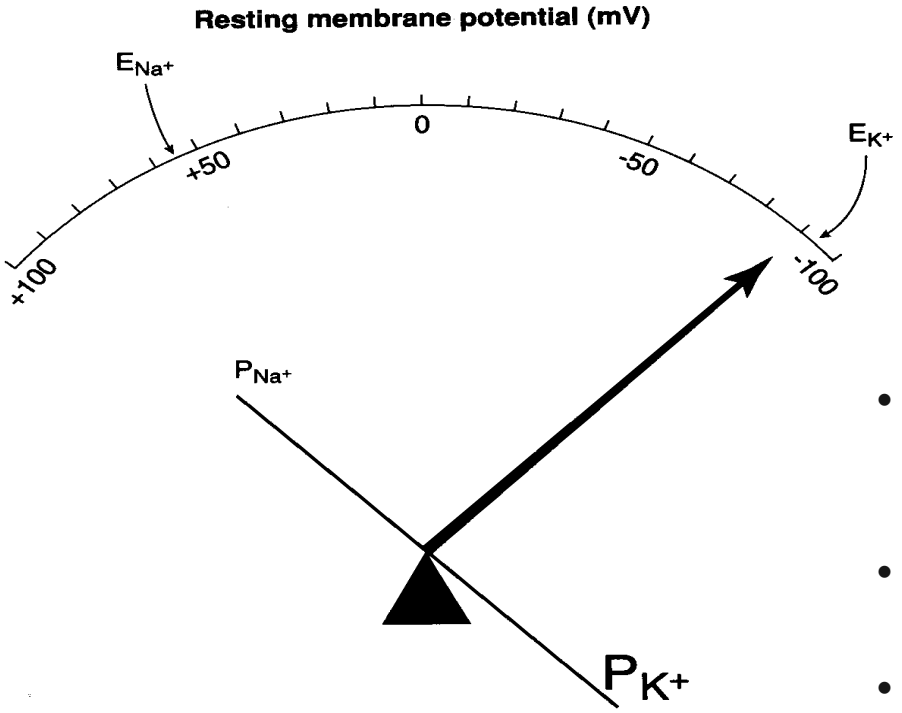




Membrane potential depends on ionic gradients and permeability.

K^+ balance and membrane potential

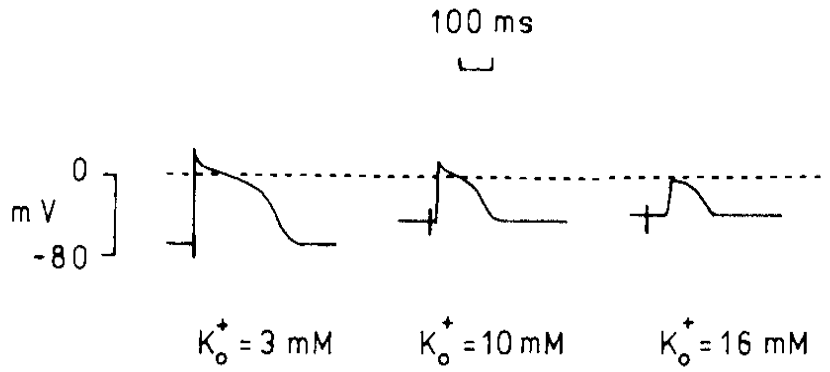
$$E_m = -\frac{RT}{ZF} \ln \frac{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{Cl}[Cl^-]_e}{P_K[K^+]_e + P_{Na}[Na^+]_e + P_{Cl}[Cl^-]_i}$$

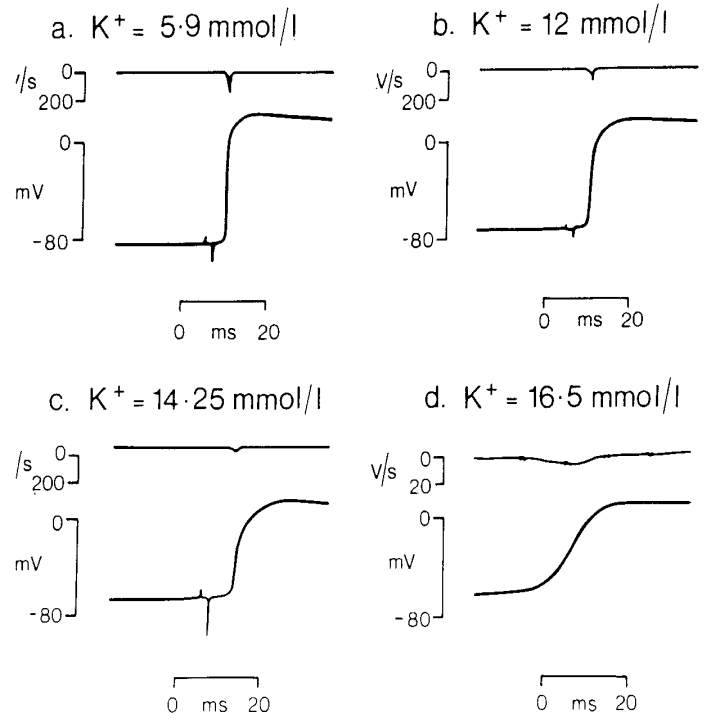


- resting potential ≈ -90 mV
  in ventricular cardiomyocytes
- primarily determined by K^+ gradient
- changed by alterations in $[K^+]_e$

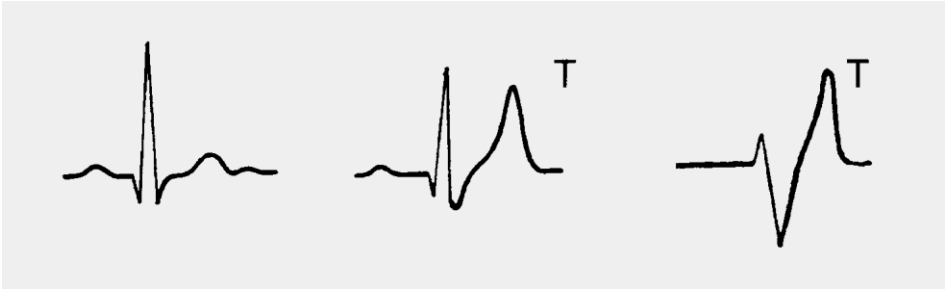
Hyperkalaemia and cardiac excitability

Depolarized resting potential → inactivates Na^+ channels → ↓ excitability





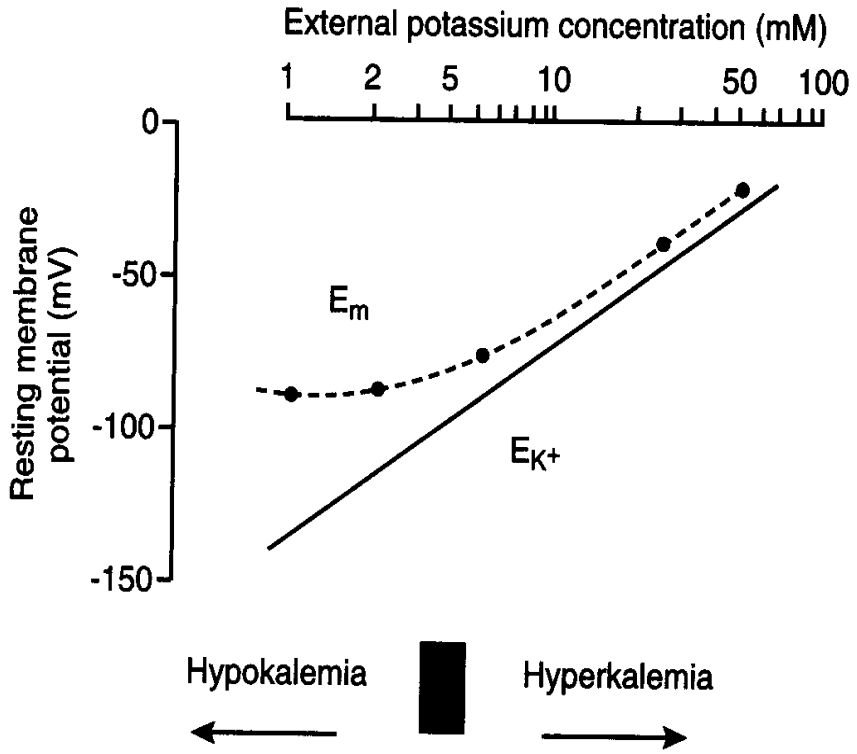
ECG alterations



Normal level: 3.5 to 5.2 mmol/L

$[K^+]_e$ > 7.5 mM: cardiac arrest!

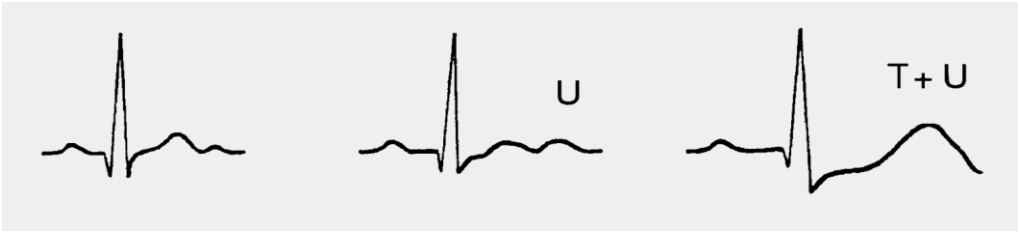
Hypokalaemia and cardiac excitability



$[K^+]_e$ < 2.7 mM:

paradox effect on E_m
prolonged repolarization
unstable resting potential
ectopic activity↑
ventricular ES
ventricular tachycardia
ventricular fibrillation

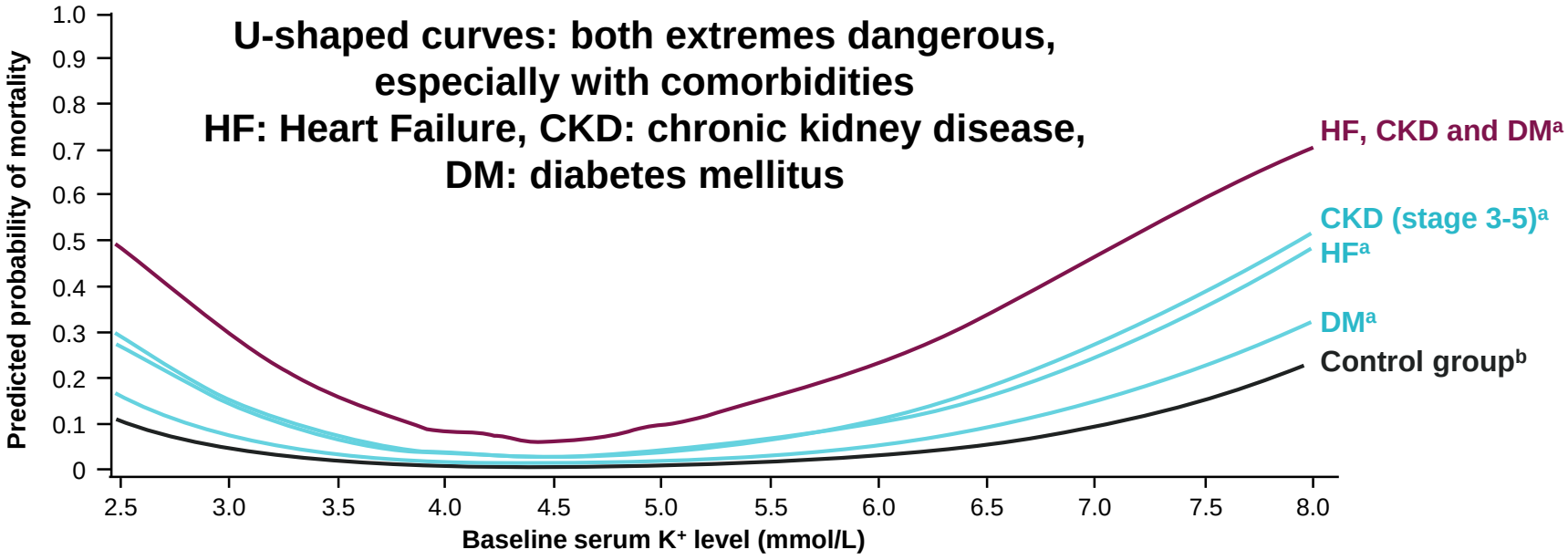
ECG alterations



Hypo- and hyperkalemia associated mortality is higher with comorbidities

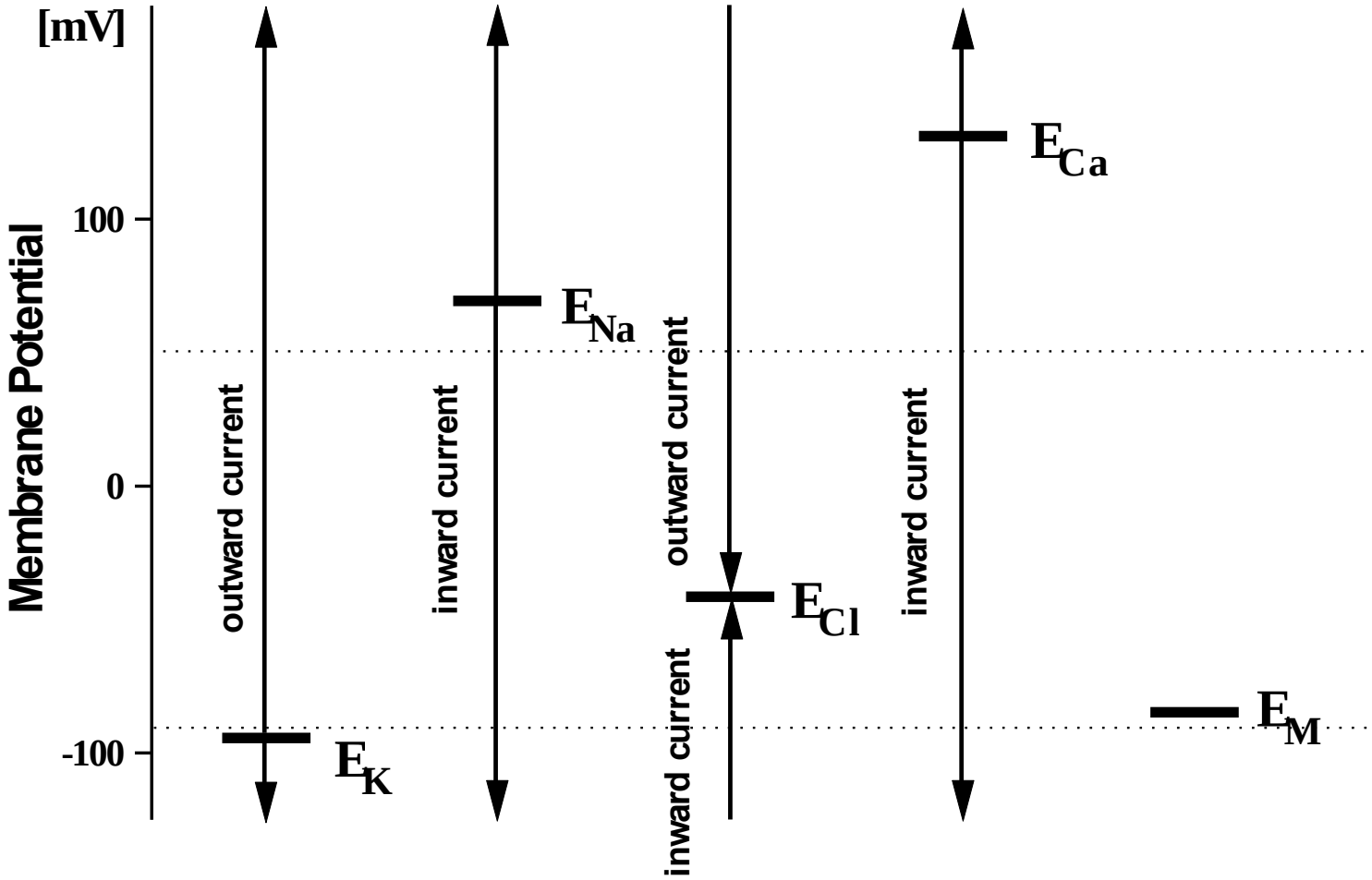
Analysis of electronic medical record data from multiple US integrated health delivery networks of 911,698 patients with ≥2 potassium measurements between 2007 and 2012

Relationship between serum K^+ value and mortality over an 18-month period

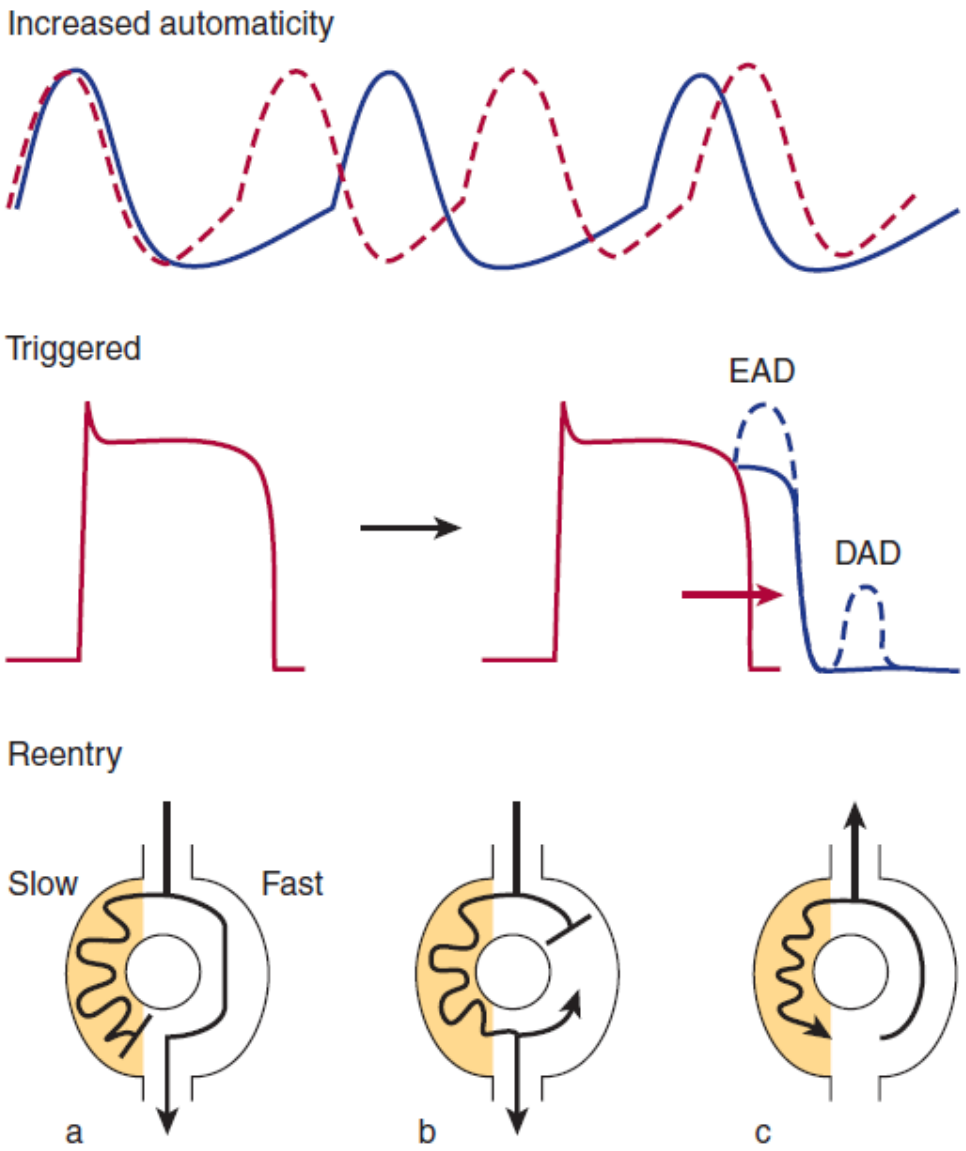


[a]Signficant vs. control group; [b]Control group comprised of individuals without known HF, CKD, DM, CVD, or HTN.
CKD = chronic kidney disease; CVD = cardiovascular disease; DM = diabetes mellitus; HF = heart failure; HTN = hypertension; US = United States.
Collins AJ et al. *Am J Nephrol.* 2017;46:213–221.

Ionic currents and membrane potential changes

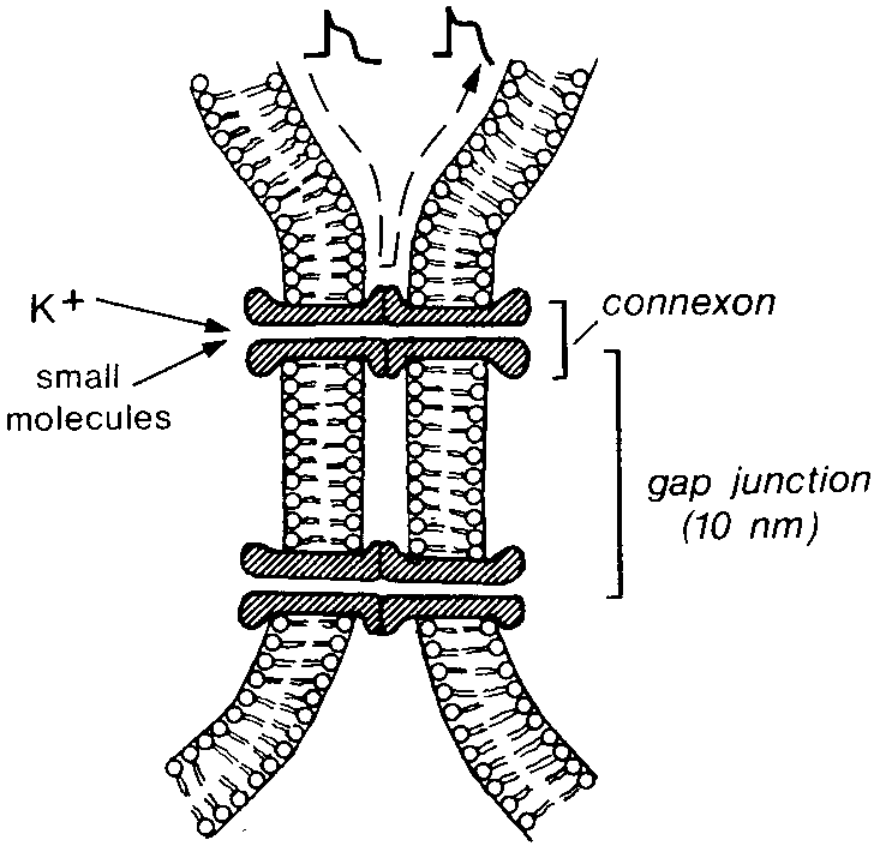


Basic arrhythmogenic mechanisms

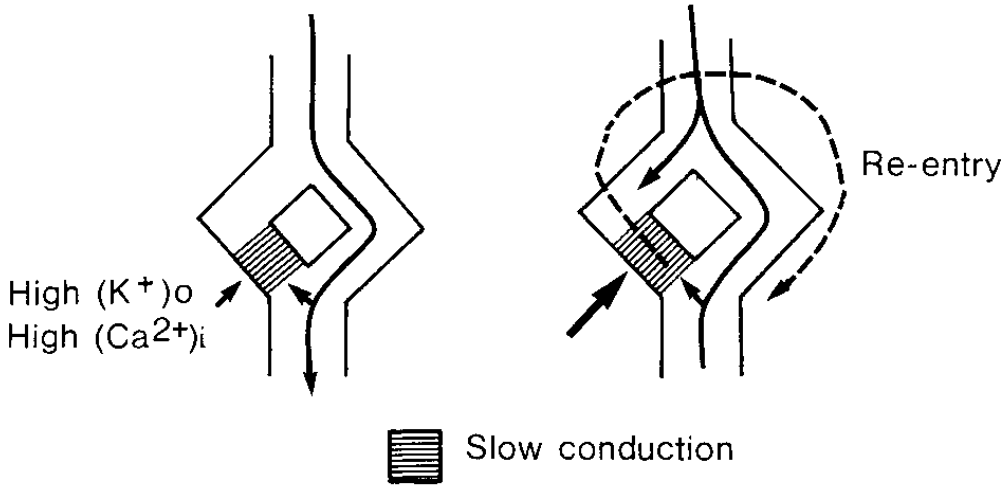


Cardiac gap junctions

- **Connexins allow electrical coupling**
- **Disrupted in ischemia/fibrosis → conduction blocks**

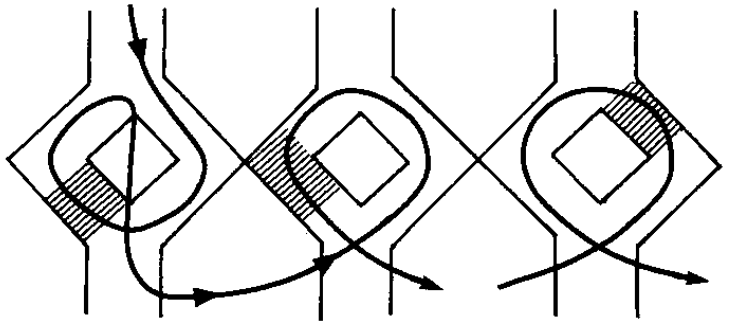


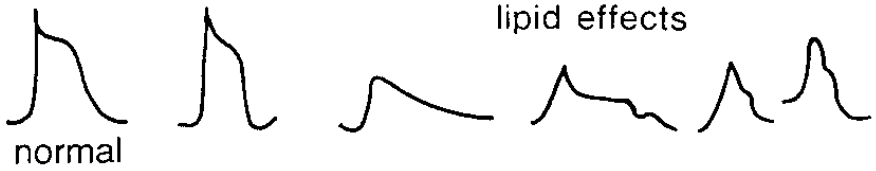
Re-entry



Requirements:

- **unidirectional block**
- **slow conduction**
- **dispersion of refractory periods**



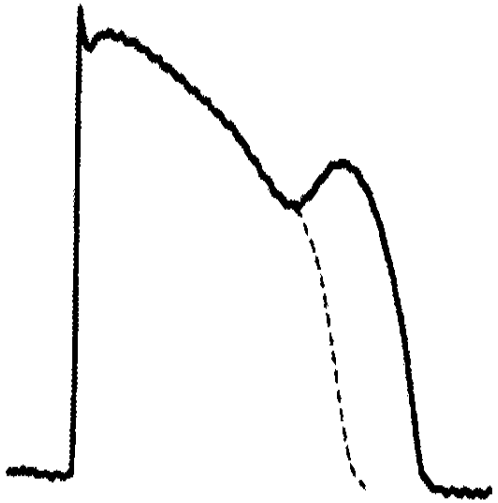


Afterdepolarizations (triggered activity)

Delayed AfterDepolarization (DAD)

$[Ca^{2+}]_{cyt}$ - dependent inward current (I_{Ti})

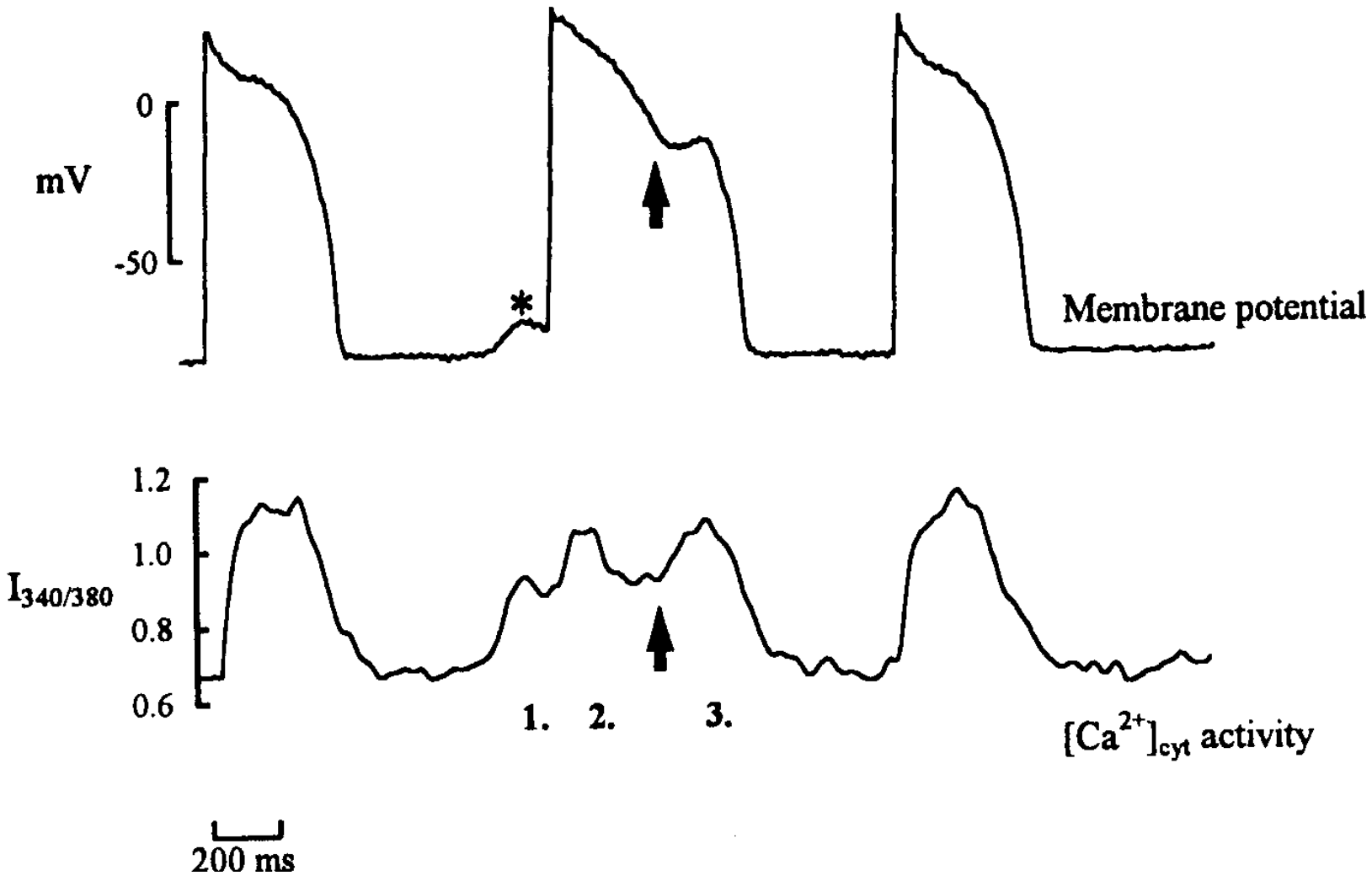
Early AfterDepolarization (EAD)



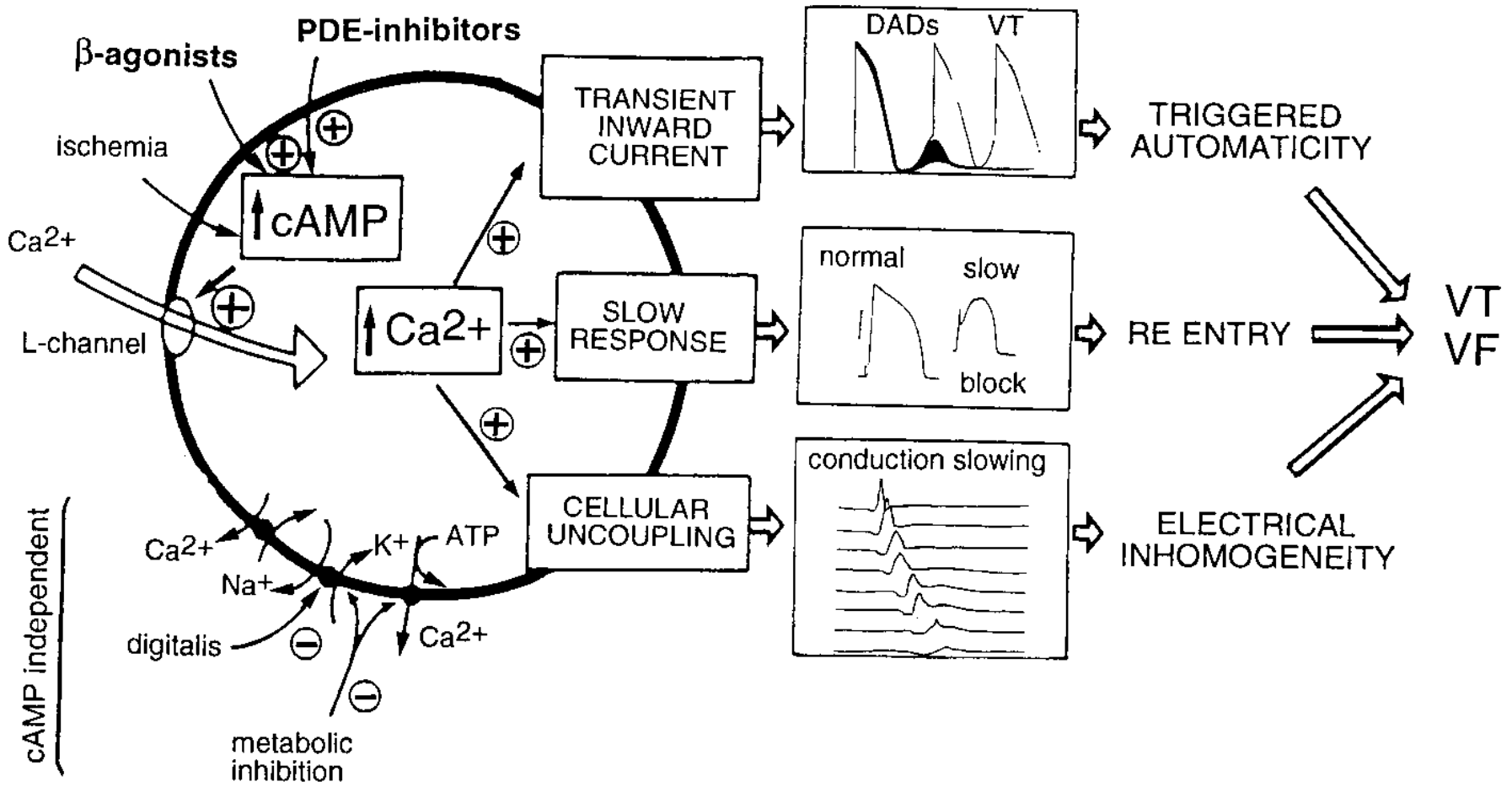
conditioning phase | EAD upstroke

$[Ca^{2+}]_{cyt}$ - dependent inward current | I_{Na} and/or I_{CaL}

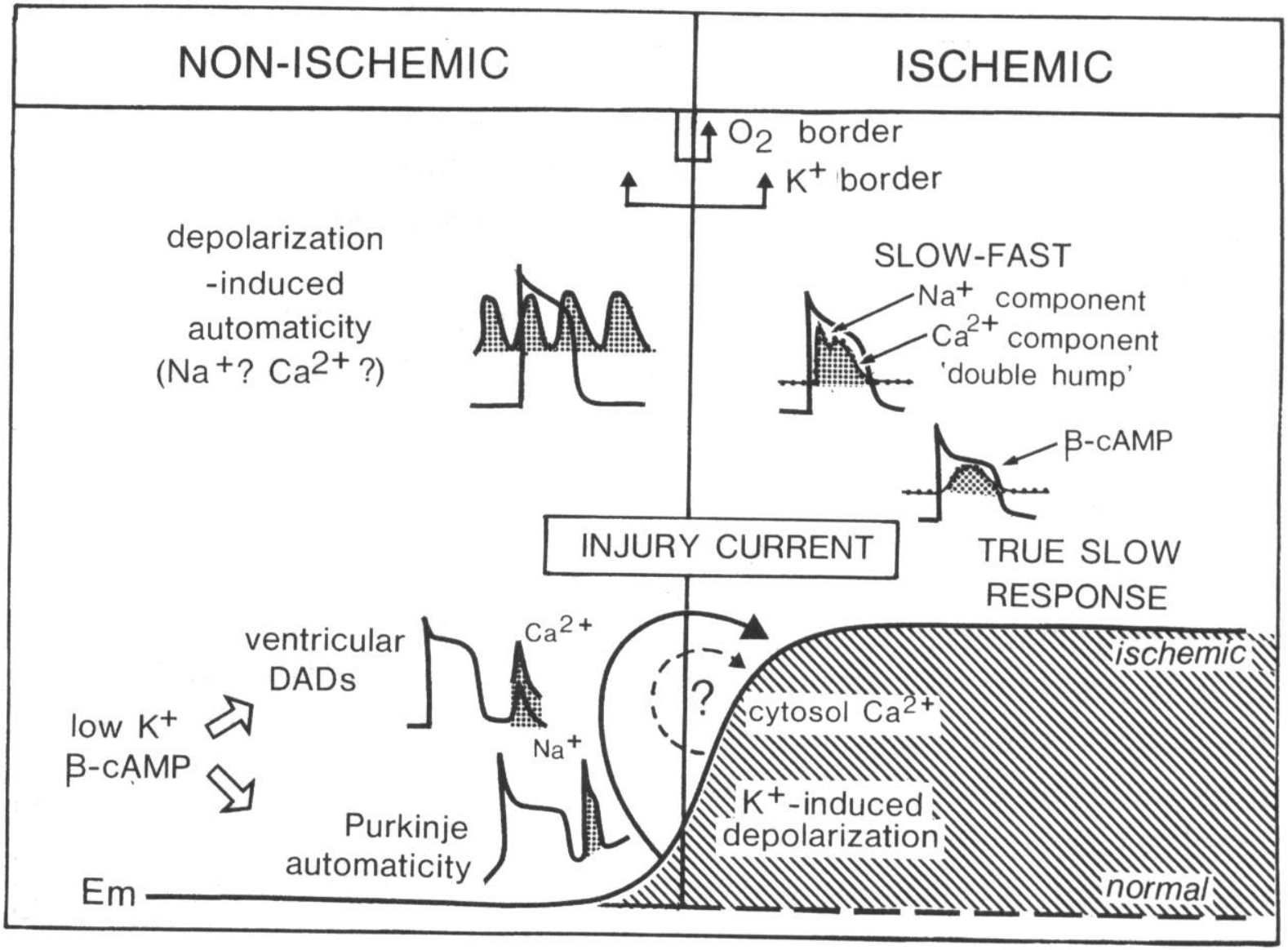
Afterdepolarizations are triggered by spontaneous Ca^{2+} release from the SR



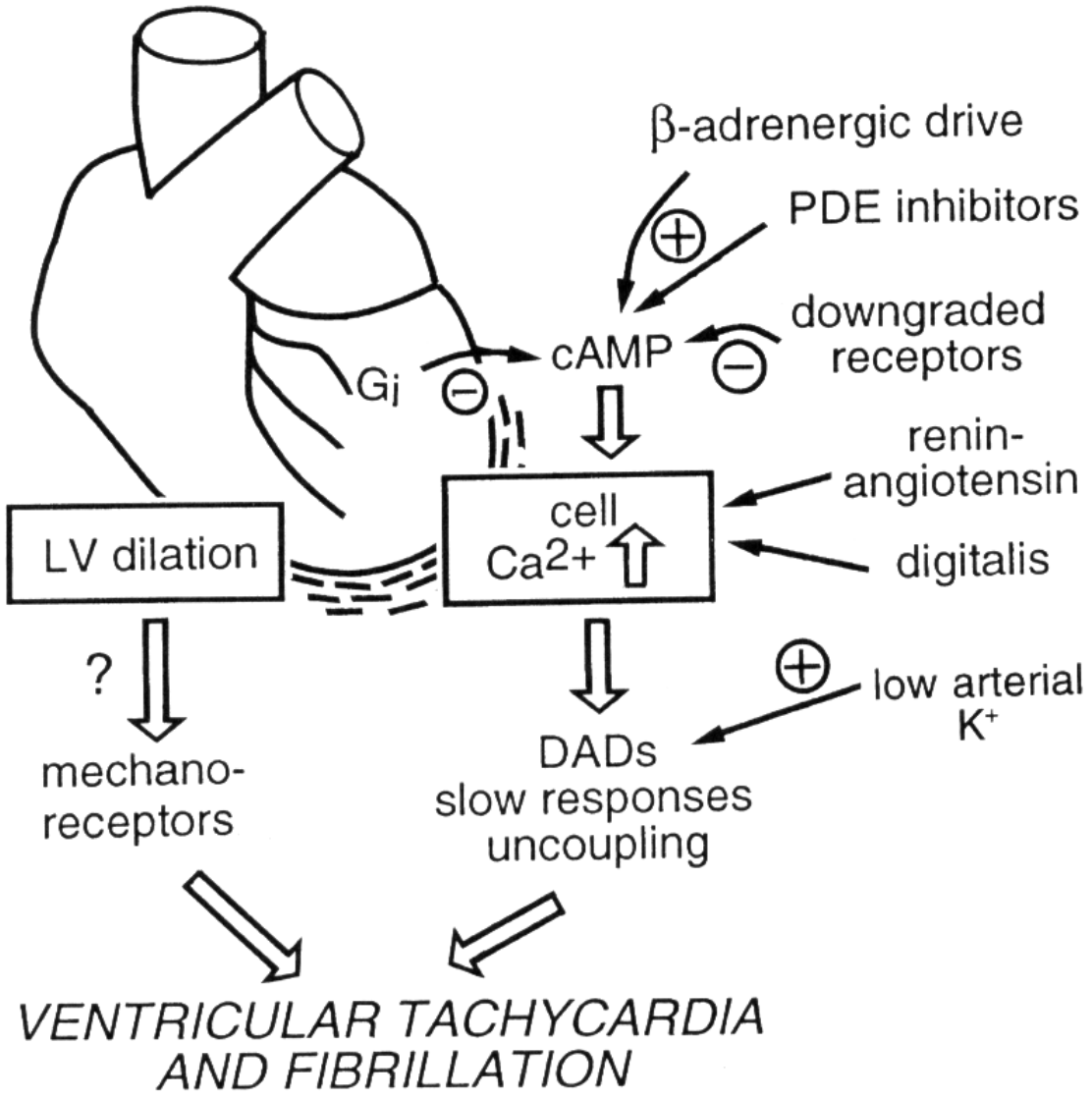
$[Ca^{2+}]_i$ –dependent arrhythmogenic mechanisms



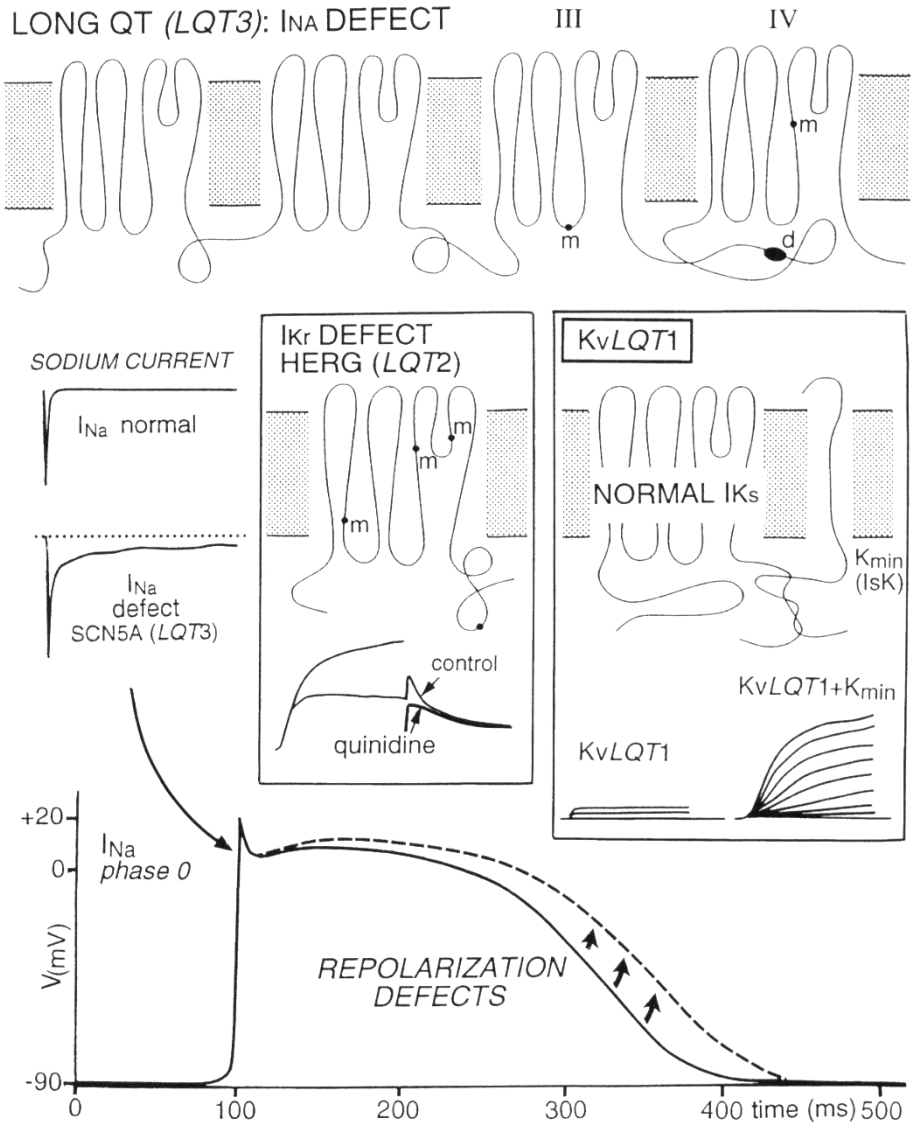
Myocardial infarction and arrhythmias



Chronic heart failure and arrhythmias



Inherited long QT syndromes



The beginning of evidence-based medicine

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mortality and Morbidity in Patients Receiving Encainide, Flecainide, or Placebo — The Cardiac Arrhythmia Suppression Trial

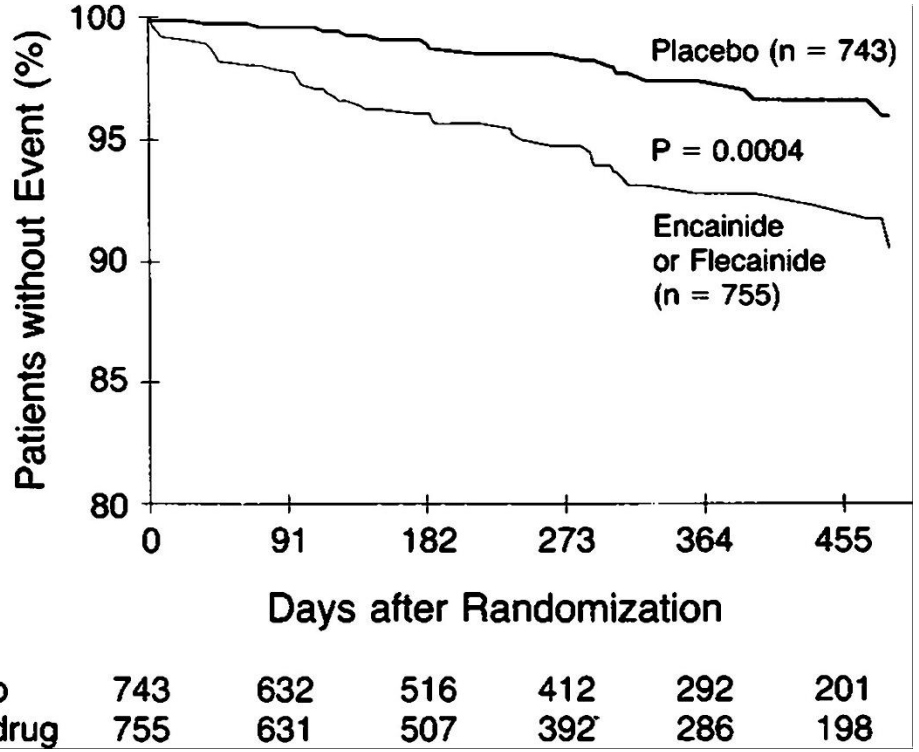
Authors: Debra S. Echt, M.D., Philip R. Liebson, M.D., L. Brent Mitchell, M.D., Robert W. Peters, M.D., Dulce Obias-Manno, R.N., Allan H. Barker, M.D., Daniel Arensberg, M.D., +5, and the CAST Investigators * Author Info & Affiliations

Published March 21, 1991 | N Engl J Med 1991;324:781-788 | DOI: 10.1056/NEJM199103213241201
VOL. 324 NO. 12

- **Hypothesis: Suppressing PVCs post-MI should improve survival**
- **Result: Increased mortality with Na^+ channel blockers**
- **Lesson: Good idea ≠ good outcome; need RCTs**

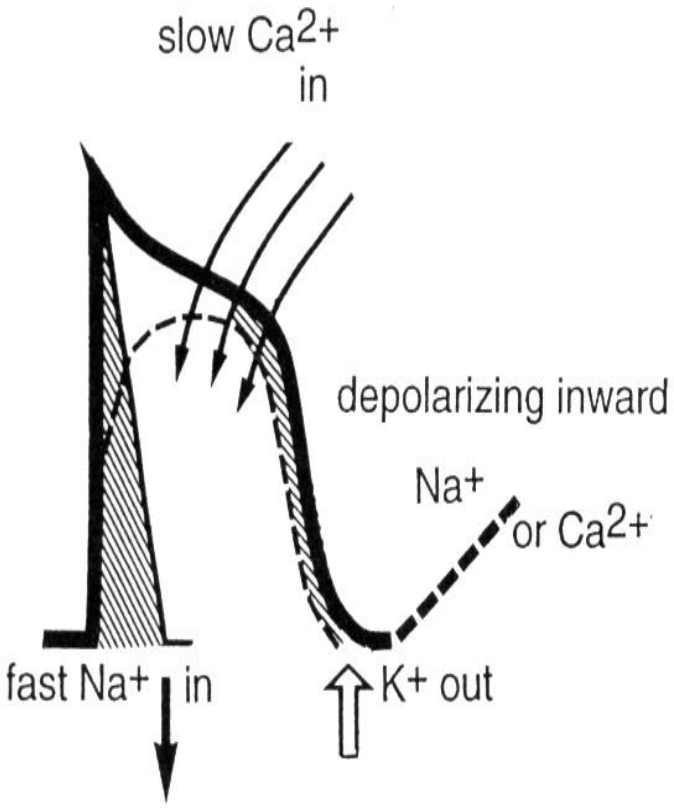
CAST = Cardiac Arrhythmia Suppression Trial

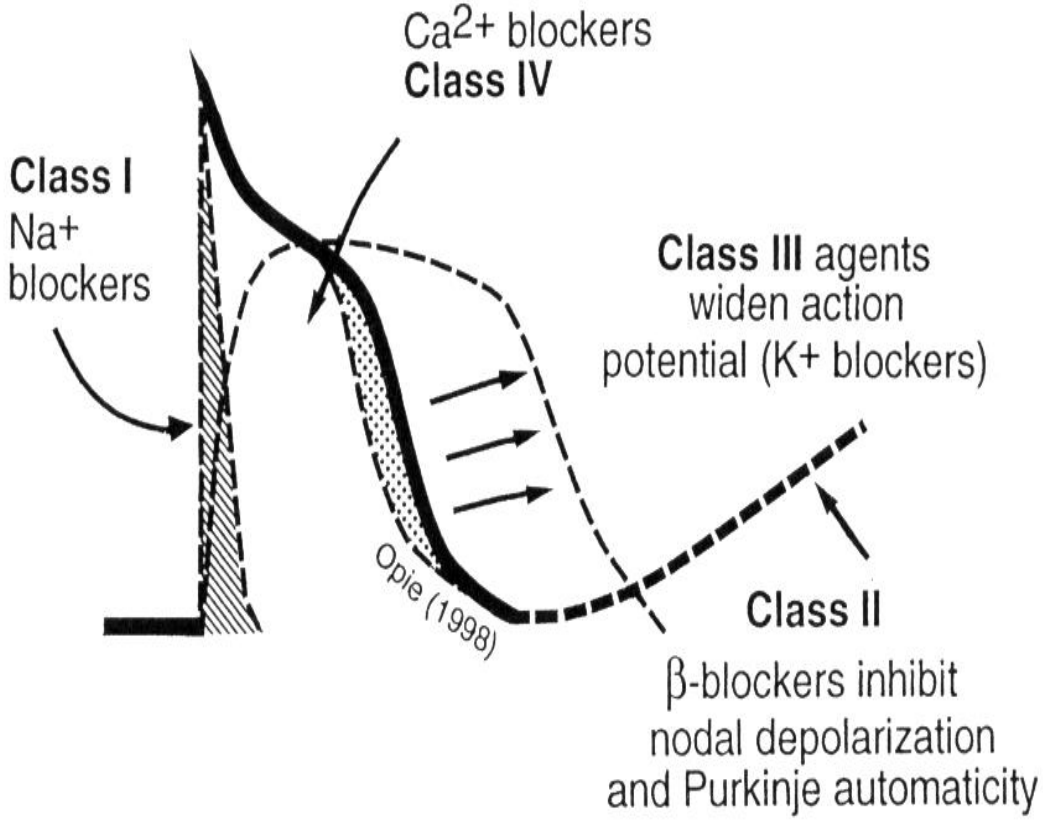
RCT = randomized clinical trial



Placebo	743	632	516	412	292	201
Active drug	755	631	507	392	286	198

Antiarrhyhtmic drugs





Take-home messages

- K^+ balance is critical for cardiac excitability
- Three main arrhythmogenic mechanisms:
  re-entry, pathologic automaticity, triggered activity
- Clinical implications require evidence-based approach