

ABC dell' ECG:
Elettrocardiografia pratica
La sindrome del QT lungo

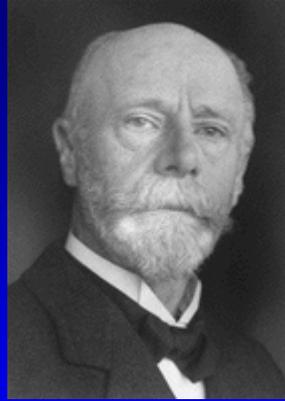
dr Giovanni Morani

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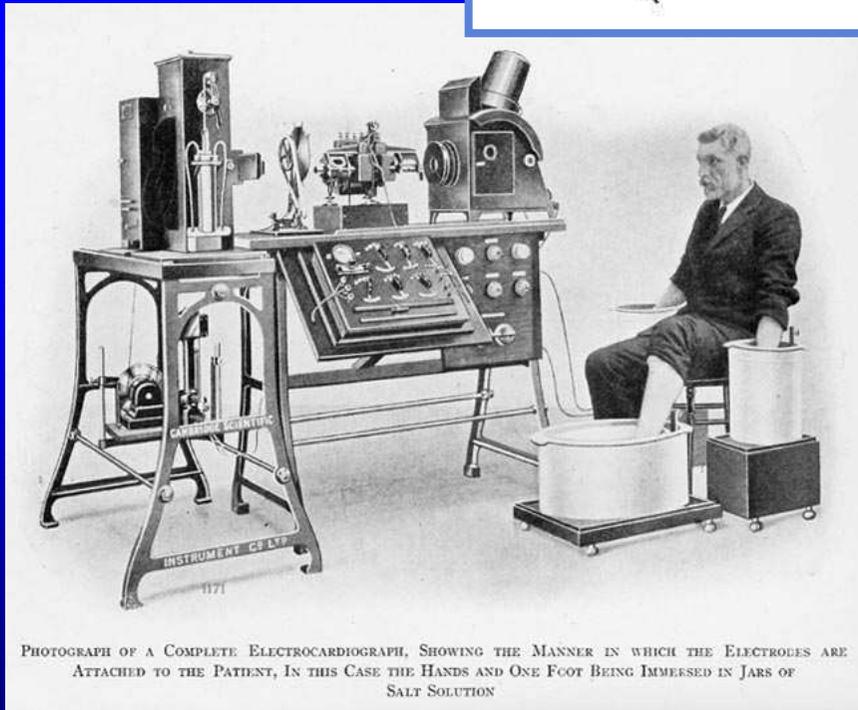
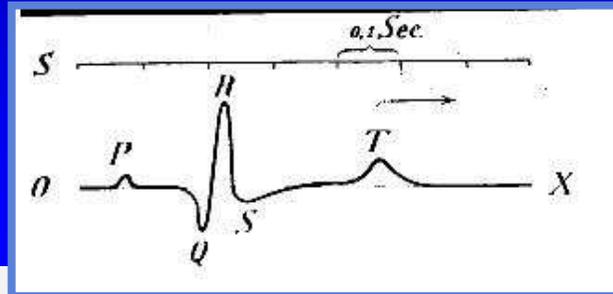
Direttore Prof Corrado Vassanelli

ECG Electrocardiogram

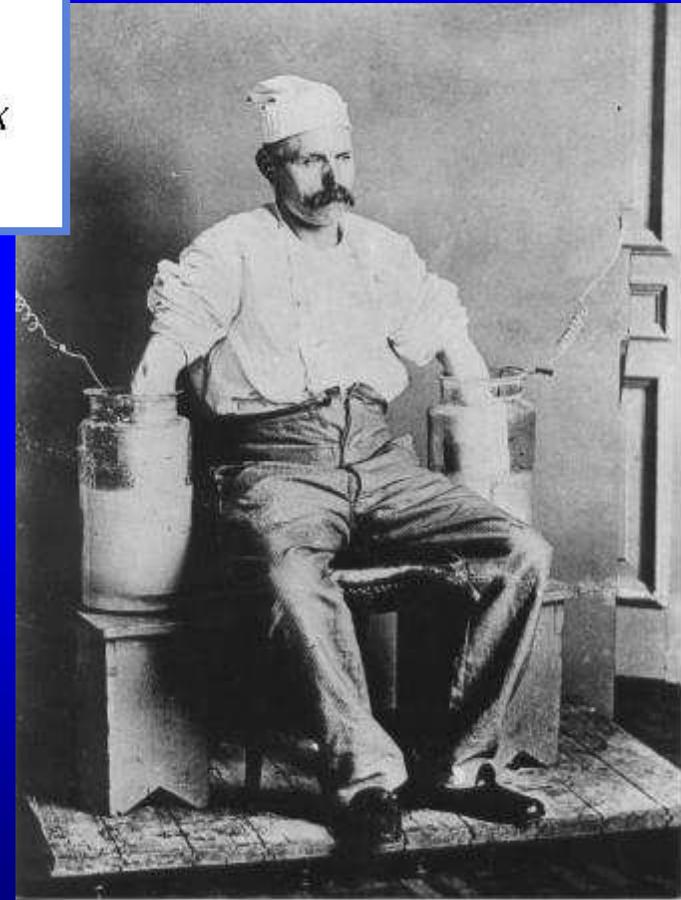
EKG Elektrokardiogram



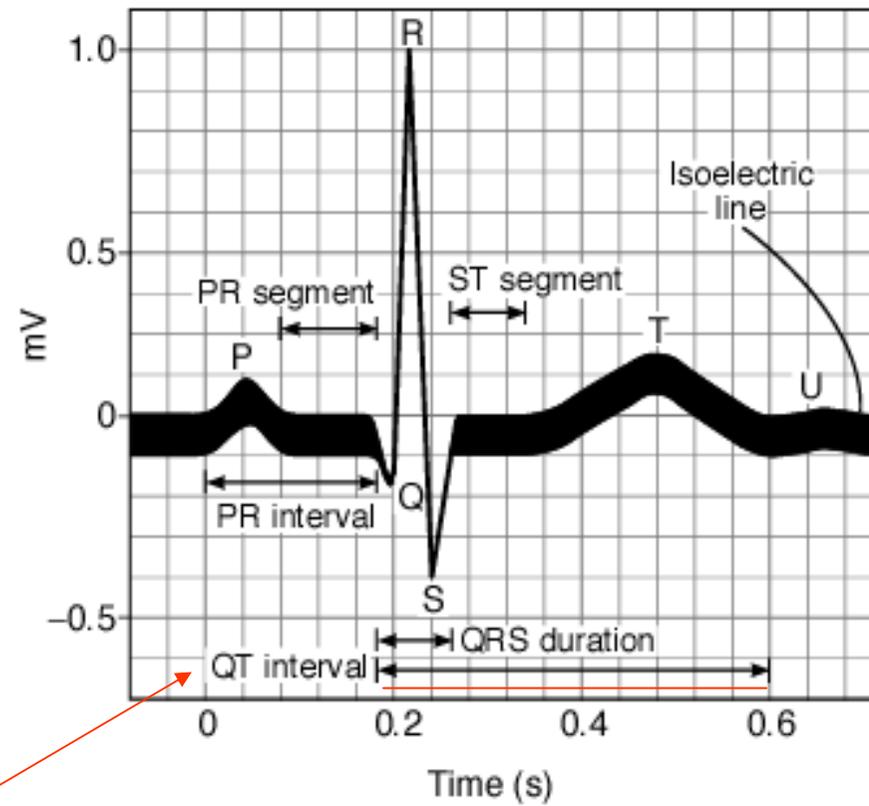
Willem Einthoven



PHOTOGRAPH OF A COMPLETE ELECTROCARDIOGRAPH, SHOWING THE MANNER IN WHICH THE ELECTRODES ARE ATTACHED TO THE PATIENT, IN THIS CASE THE HANDS AND ONE FOOT BEING IMMERSSED IN JARS OF SALT SOLUTION



L'ECG



Il QT lungo e' un disordine clinico di
origine genetica

Caratterizzato da

QT lungo

Aritmie pericolose per la vita (TdP)

2 forme ereditarie

Autosomica dominante (Romano-Ward)
stato di eterozigote , piu' comune

Autosomica Recessiva (Jervell and Lange-
Nielsen) , stato di omozigote , piu' rara

Origine genetica della LQTS

- Mutazione Geni che codificano per Canali ionici (K,Na,Ca)
- Causano alterata funzione del Canale ionico K , Na , Ca con *gain* o *loss* of function → alterazione dei flussi transmembrana
Alterazione del Potenziale d'azione → prolungamento del plateau (e del QT)

Canalopatie

Esiste una correlazione stretta tra mutazione del Gene che codifica per Canale Ionico e Sindrome aritmica (genotipo-fenotipo)

LQTS

SQTS

Brugada

CPVT

ARVD

Lenegre disease

SSS familiare

Fa familiare

Canalopatie

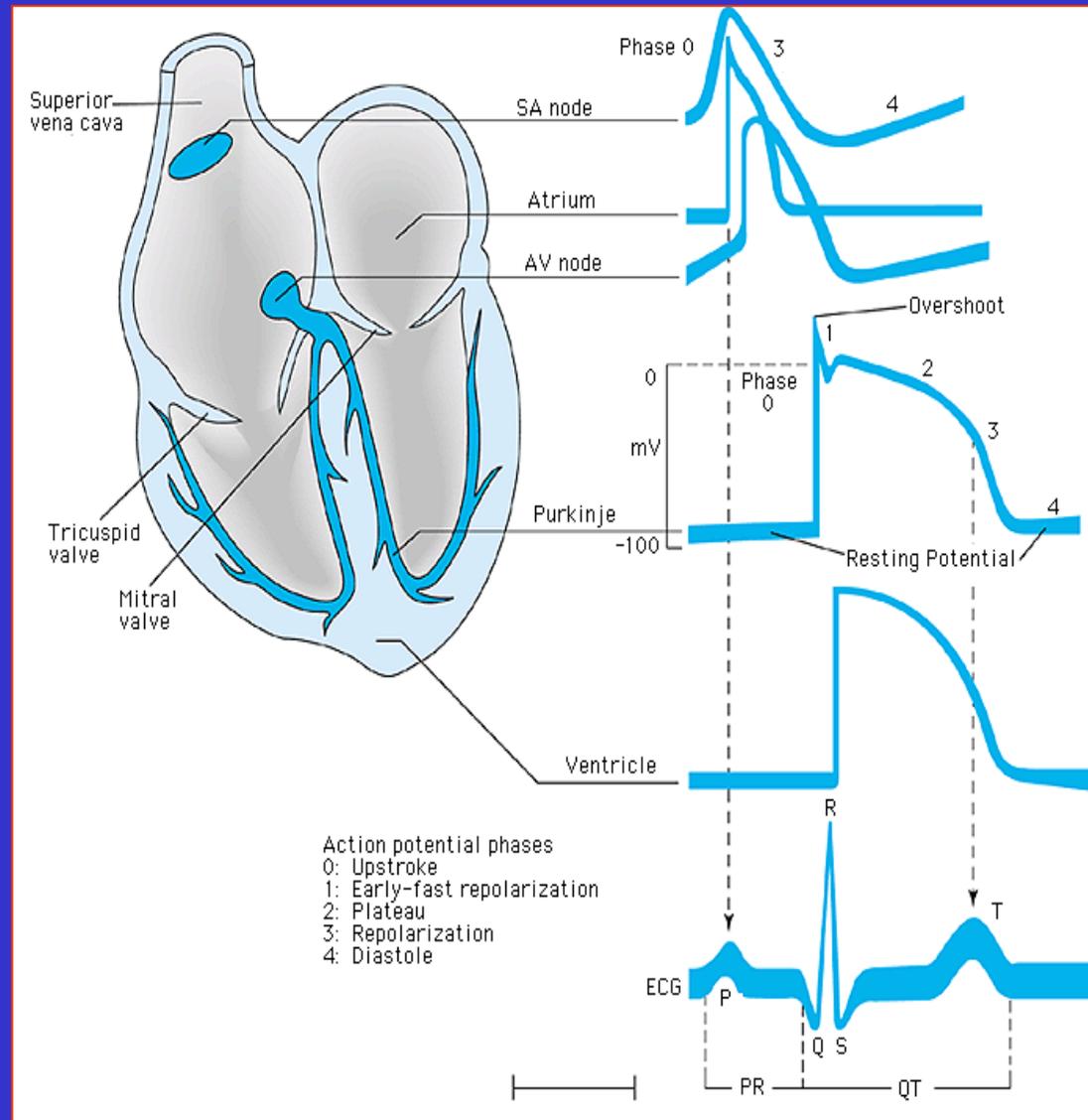
- Correlazione tra
mutazione *GENE* →

alterata funzione CANALE ionico →

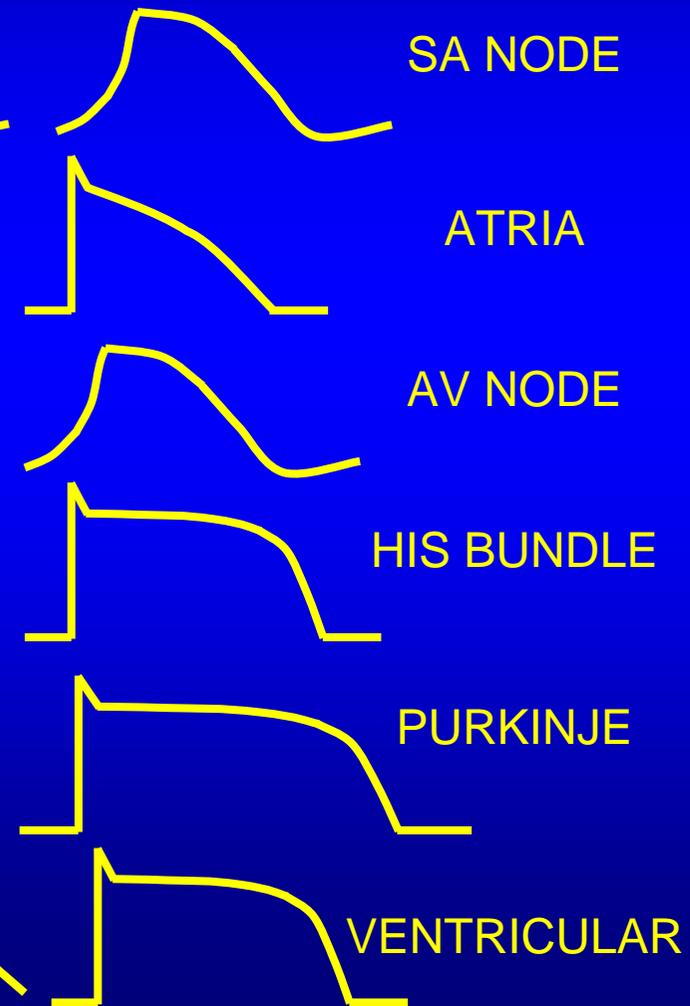
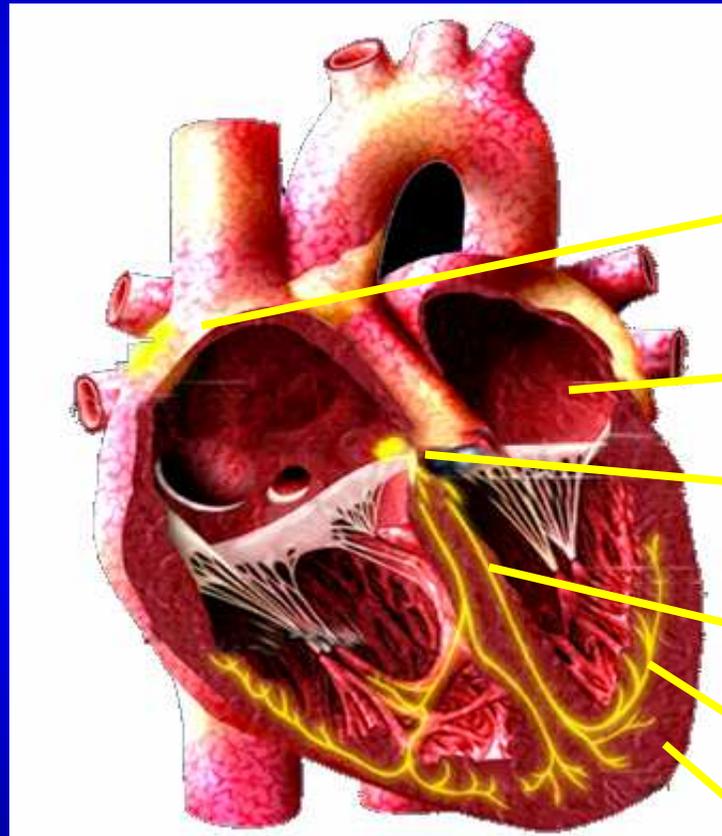
alterazione POTENZIALE D'AZIONE →

ARITMIA

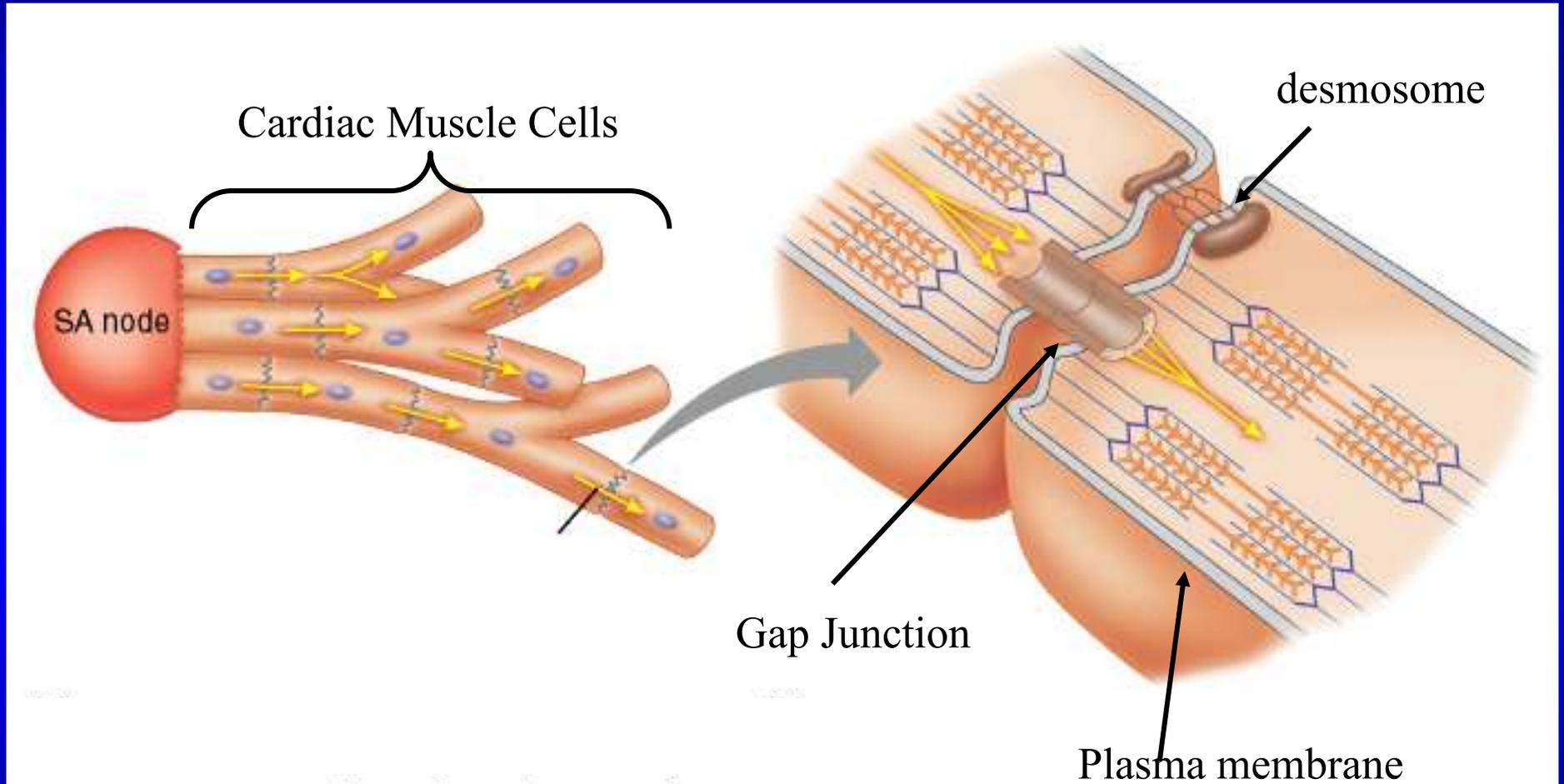
Dal potenziale d'azione all'ECG



Potenziale di Azione Cardiaco

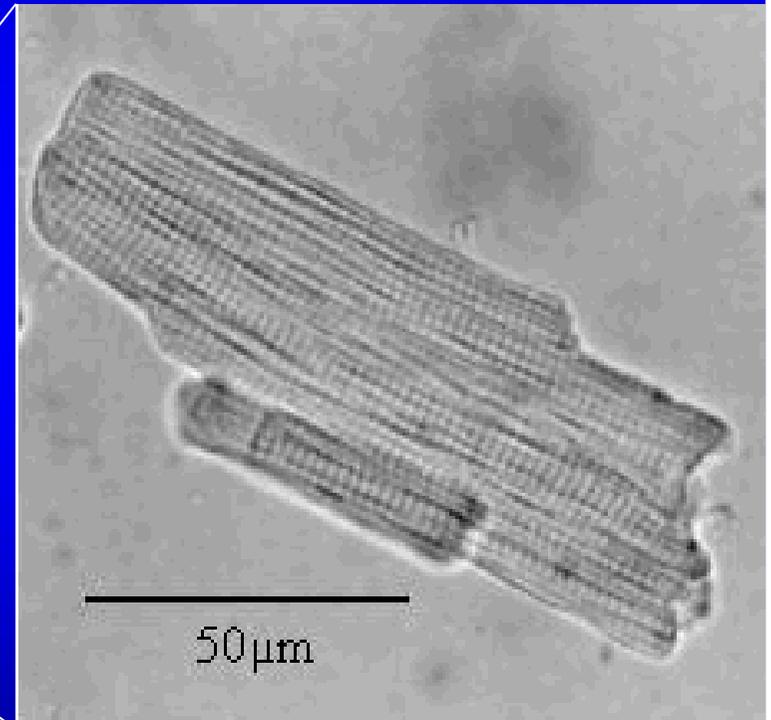
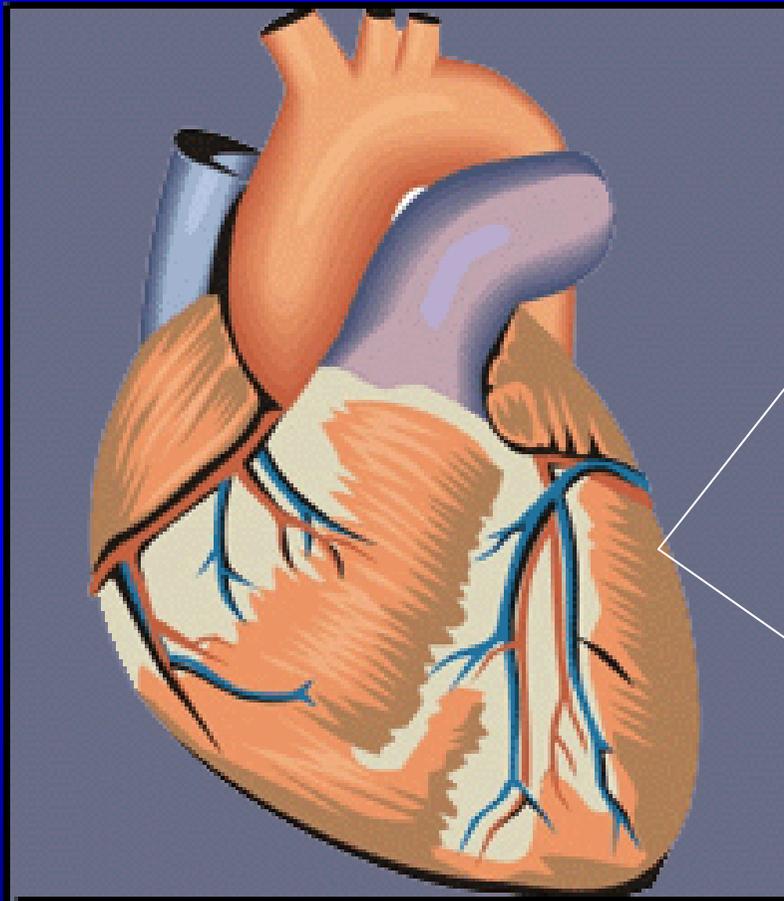


Cardiac Muscle Cells are Electrically Connected via Gap Junctions

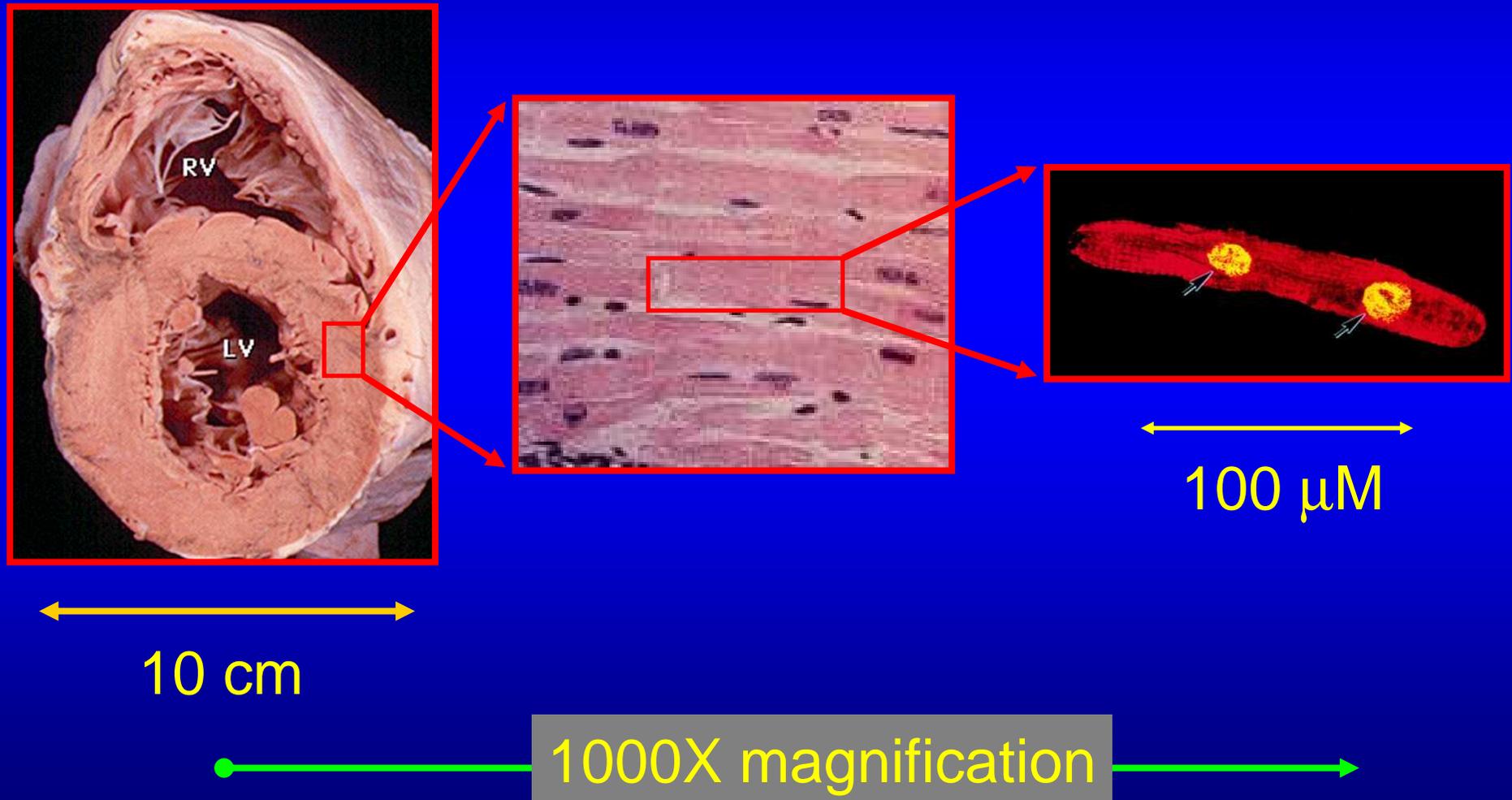


desmosome – resist stretching
gap junction – passage of current

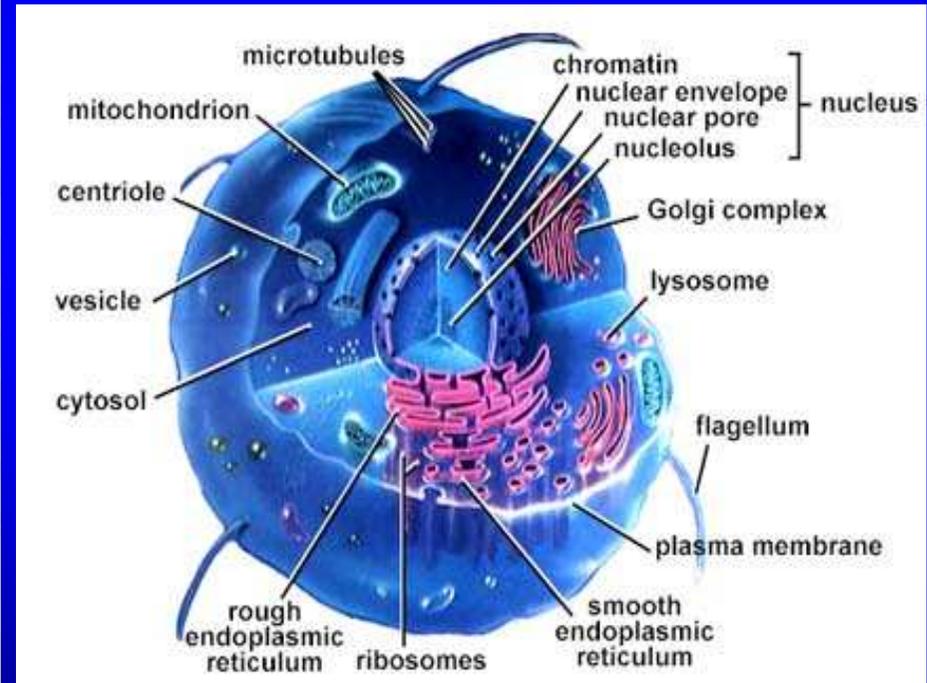
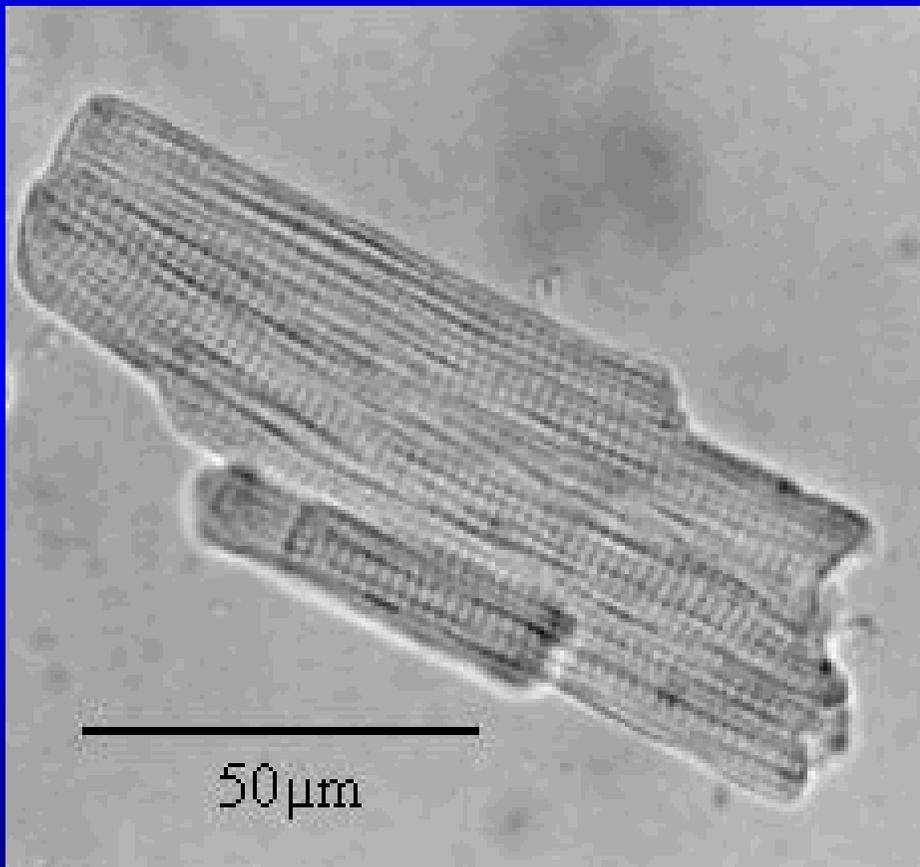
Il miocardio e' composto da cellule



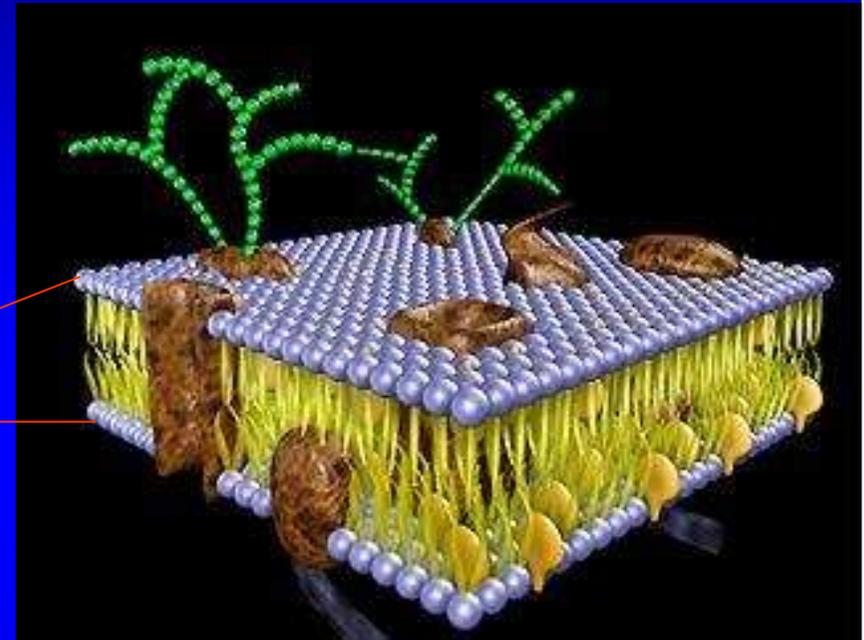
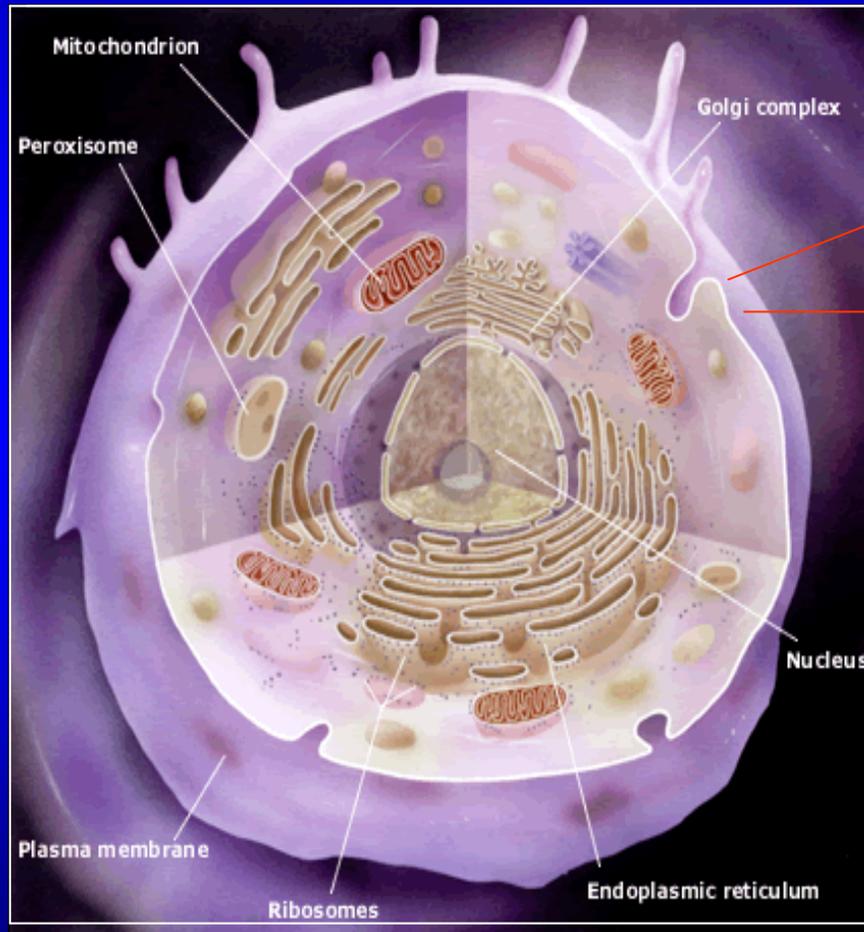
Il muscolo cardiaco ed il miocita



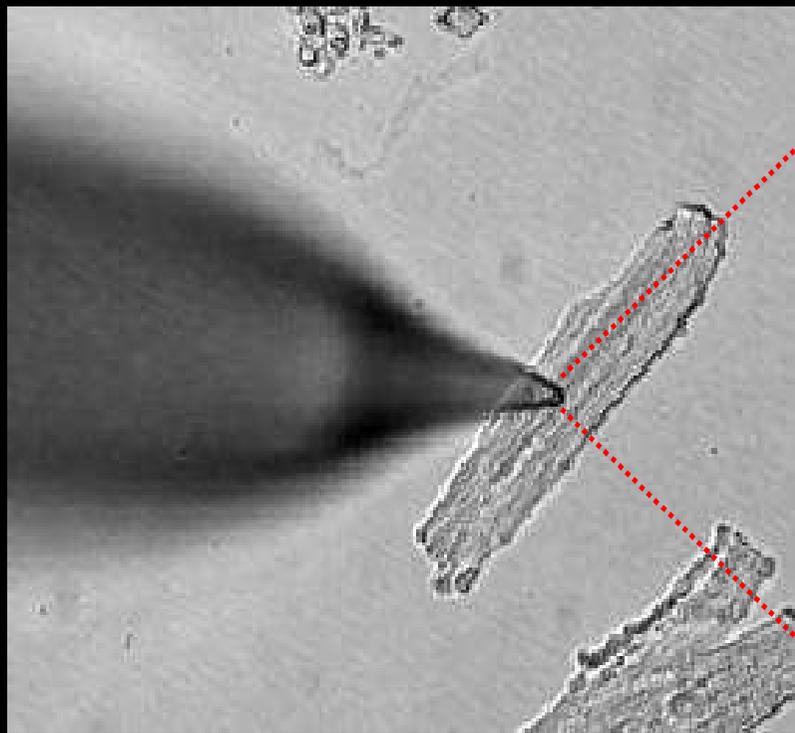
Struttura del miocita

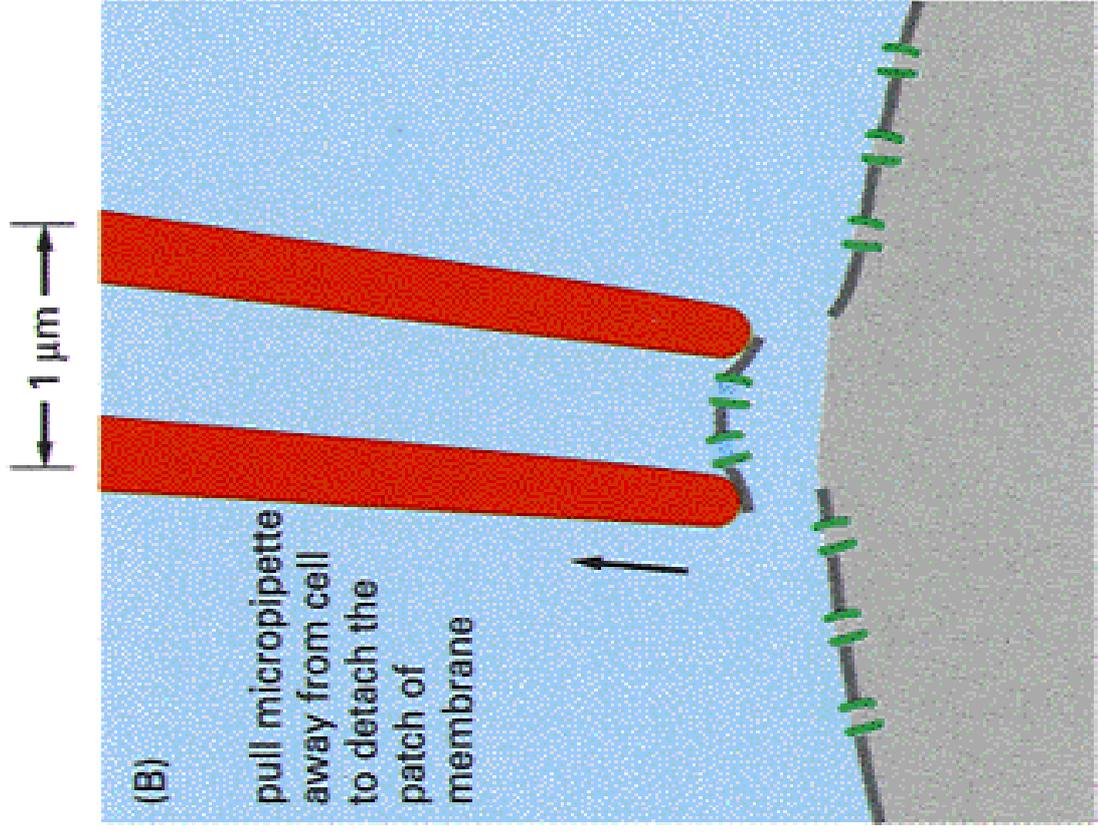
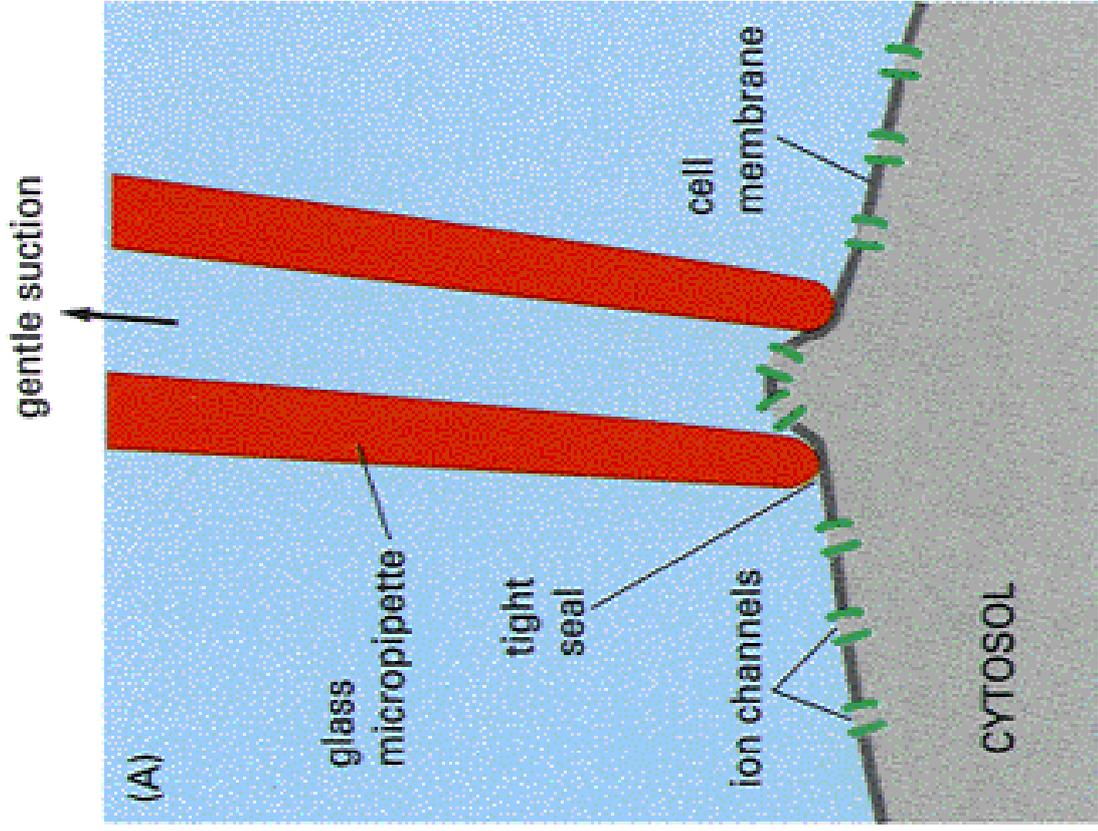


I miociti hanno una membrana

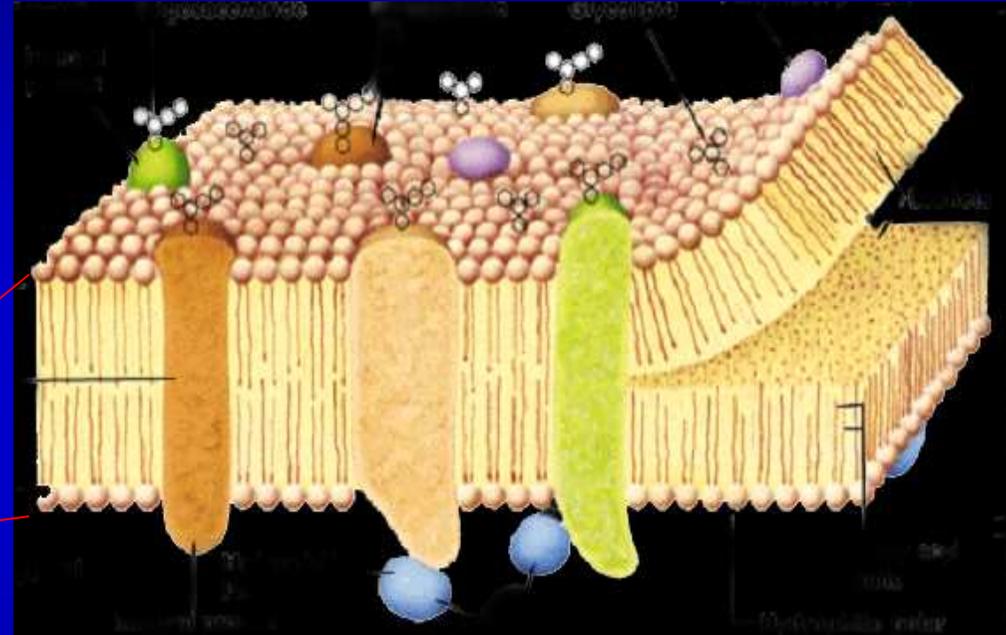
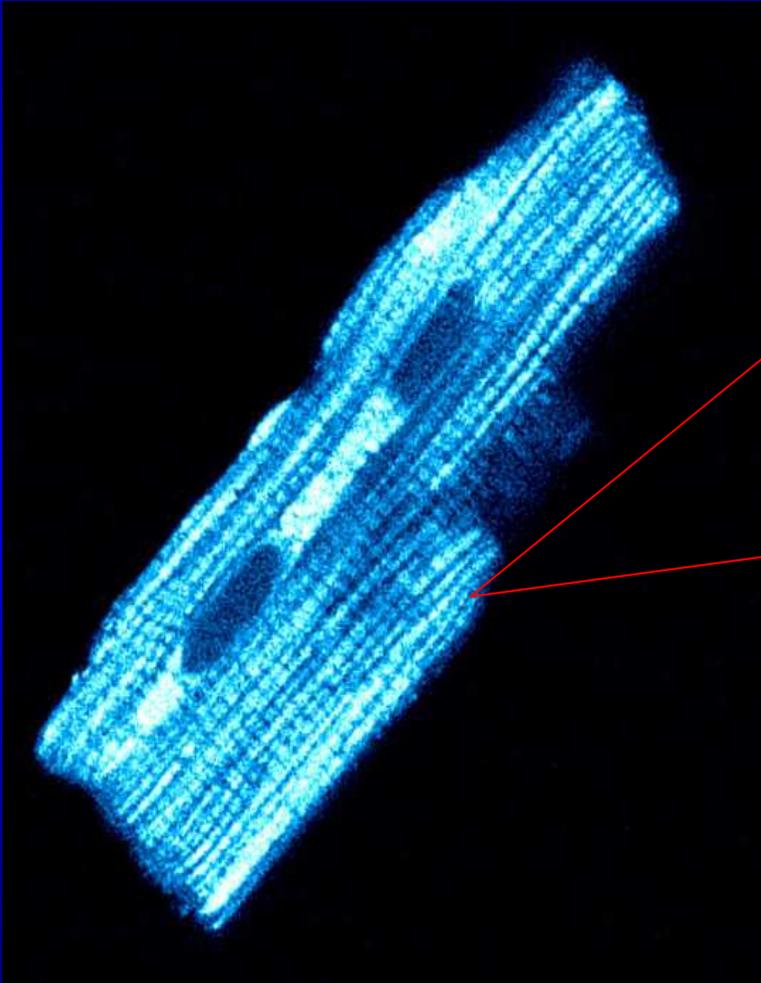


Patch Clamping

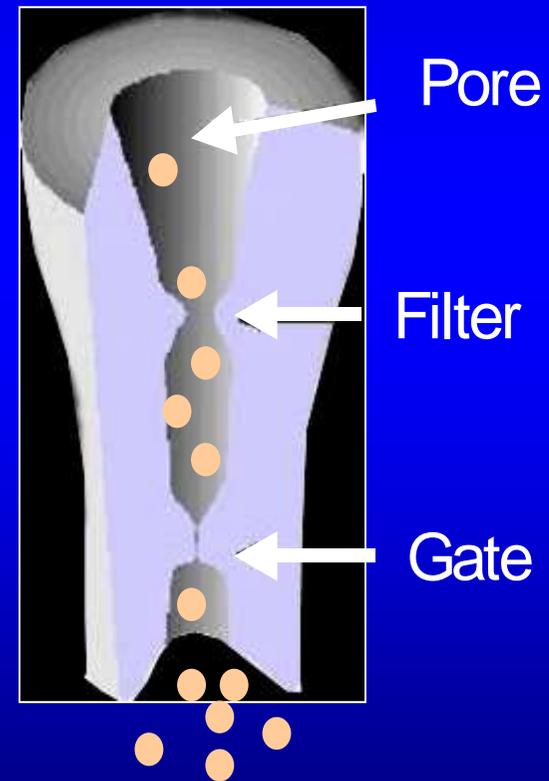
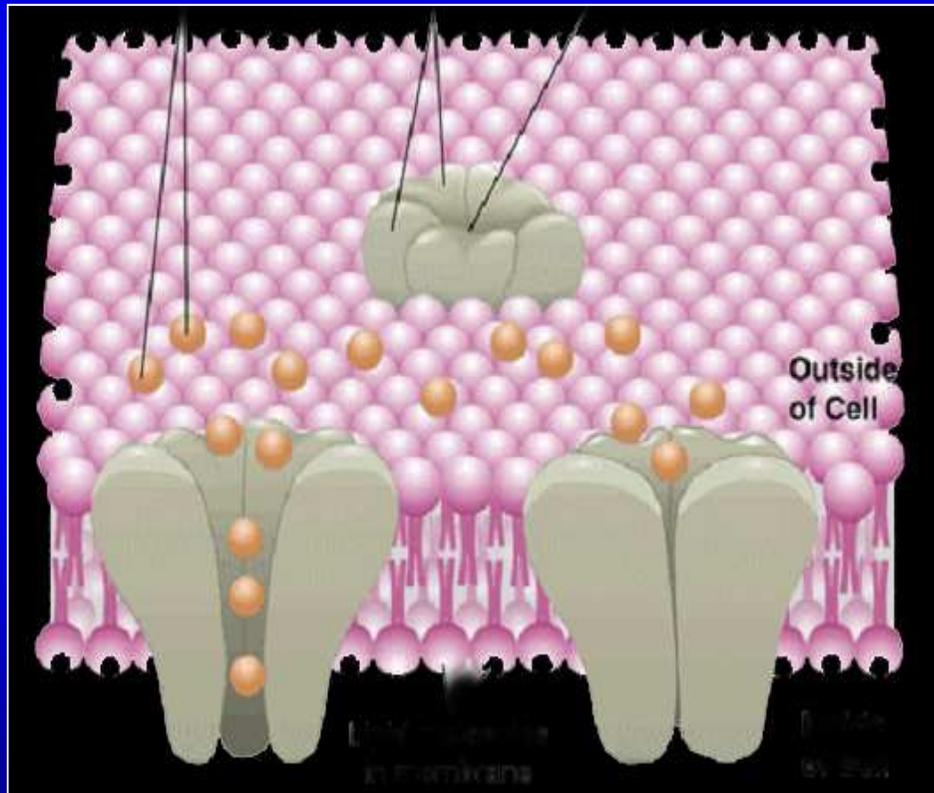


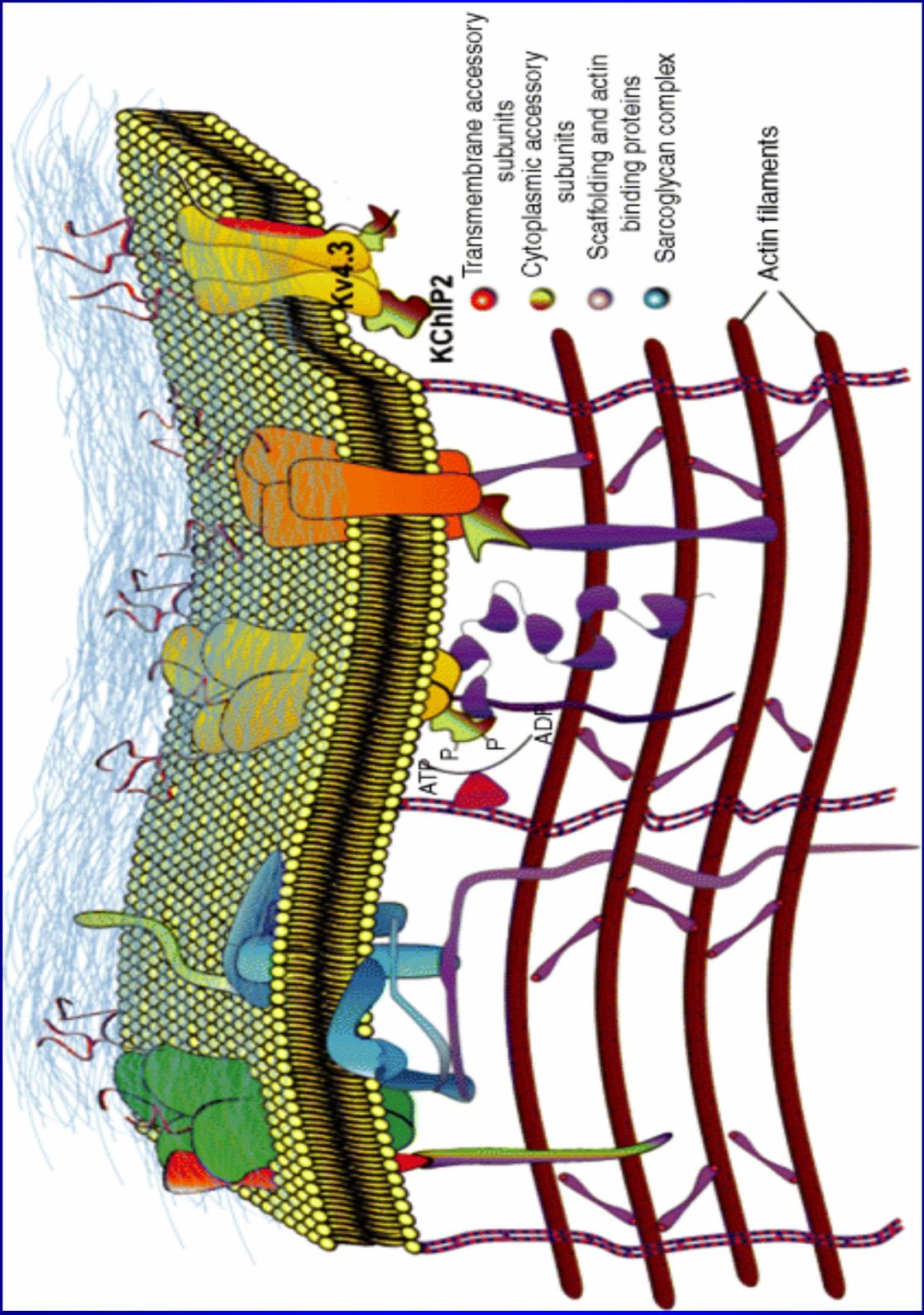


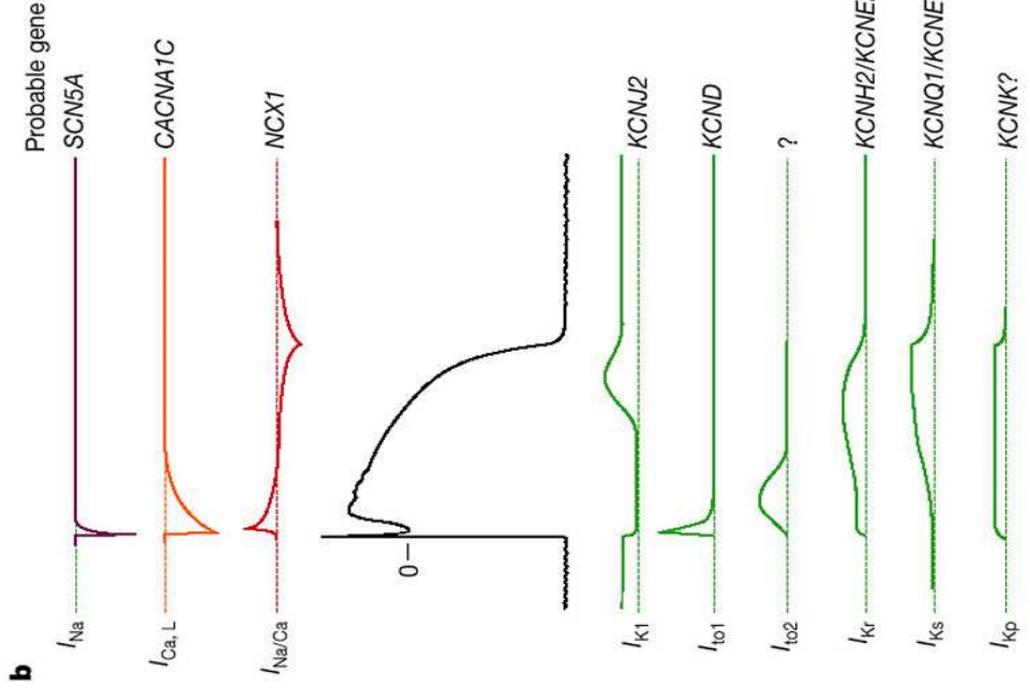
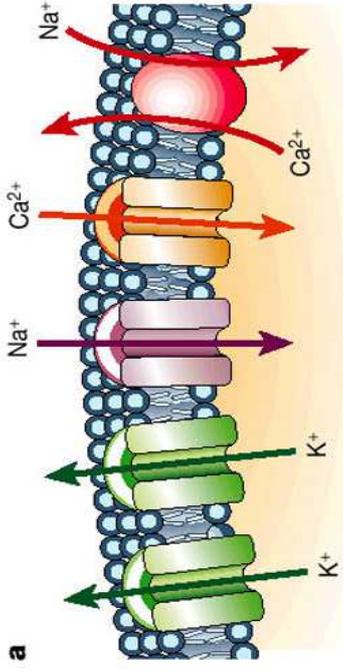
Struttura della membrana



Canali di membrana



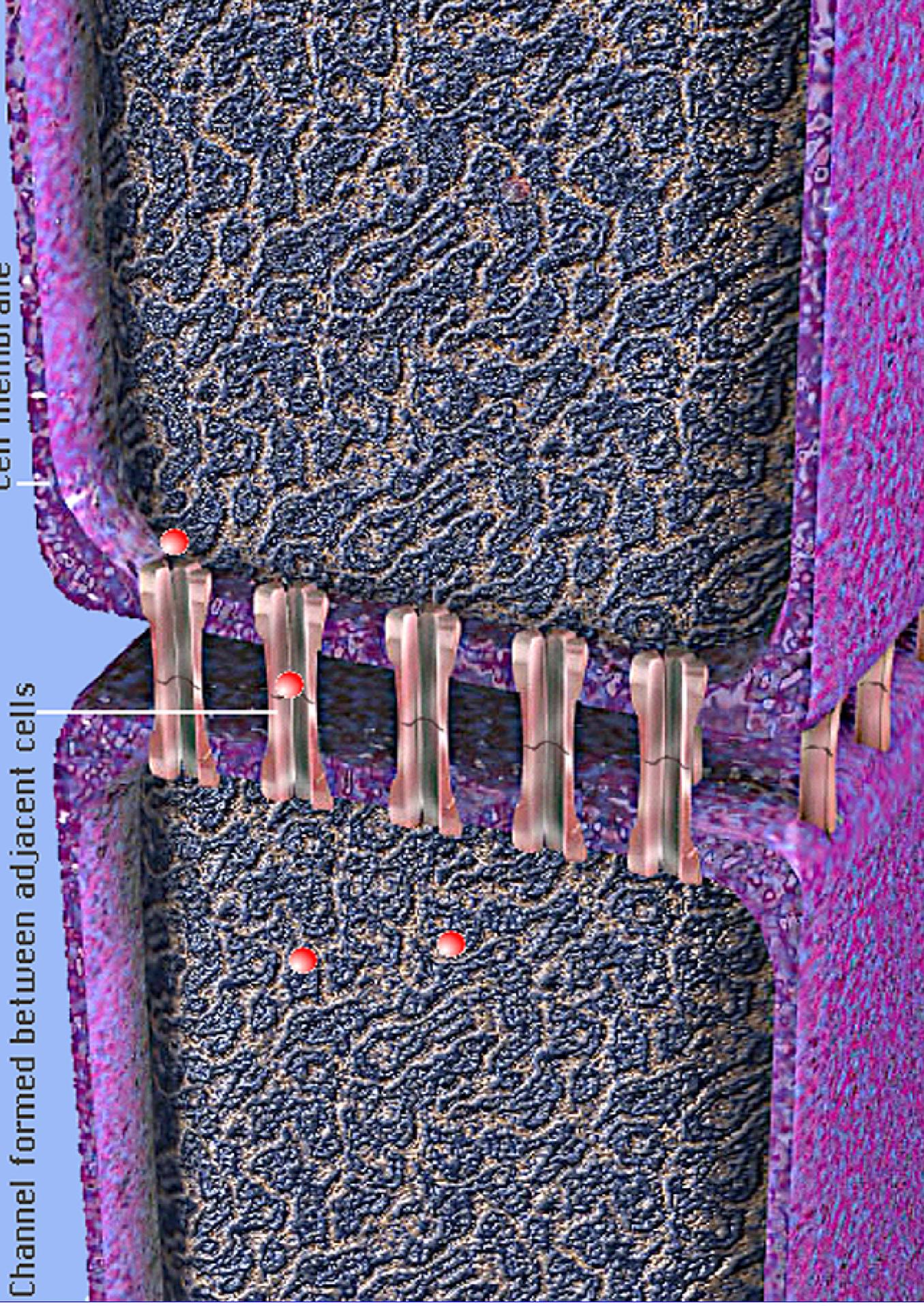




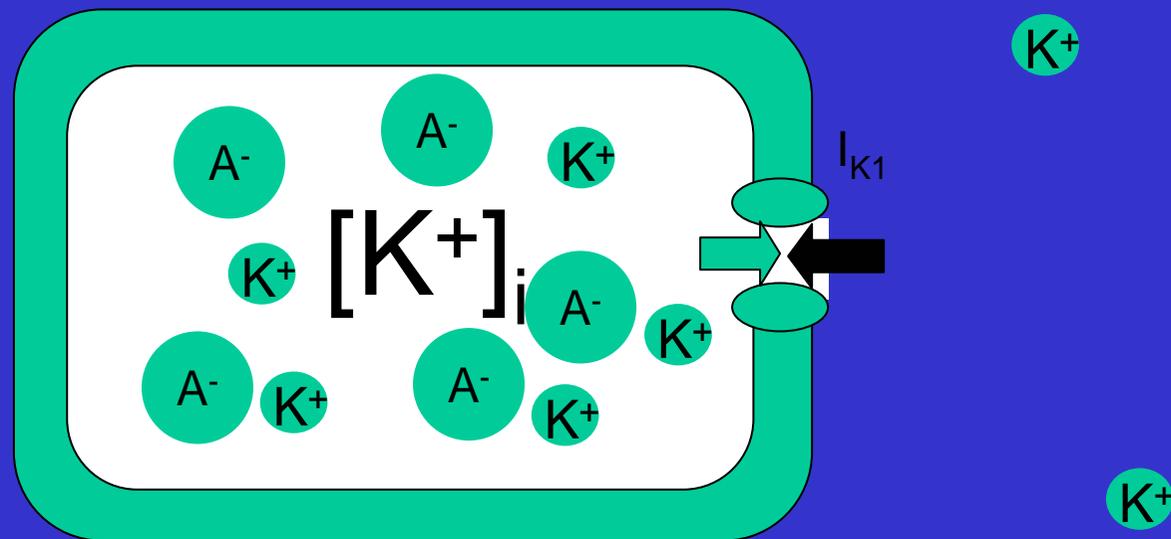
GAP JUNCTIONS

Channel formed between adjacent cells

Cell membrane



Basi ioniche del potenziale di membrana a riposo



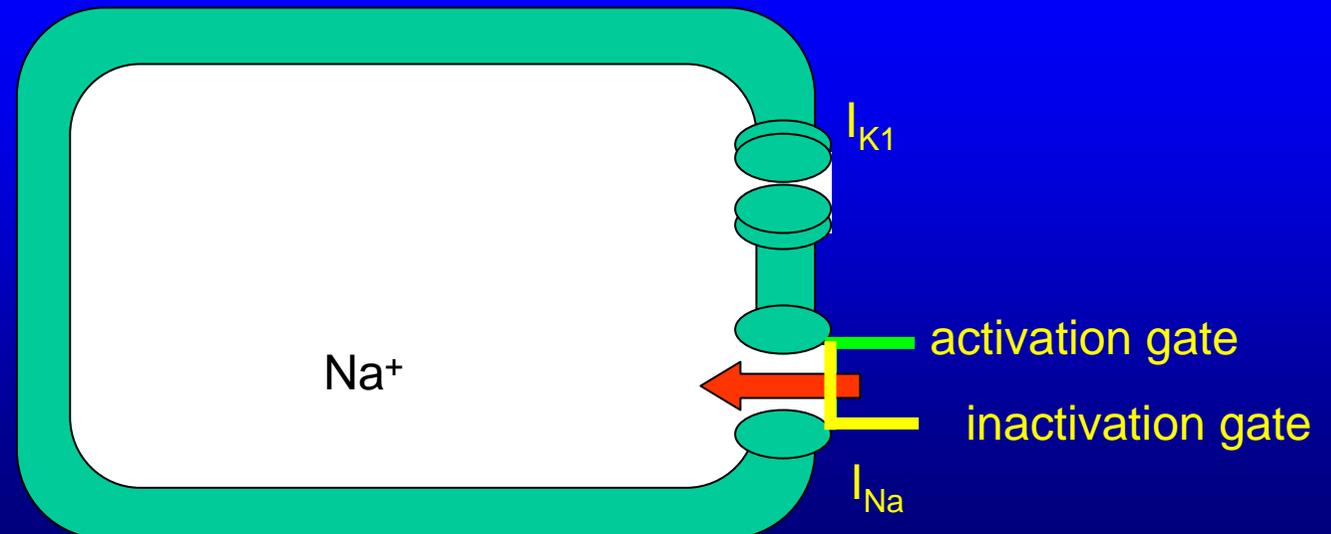
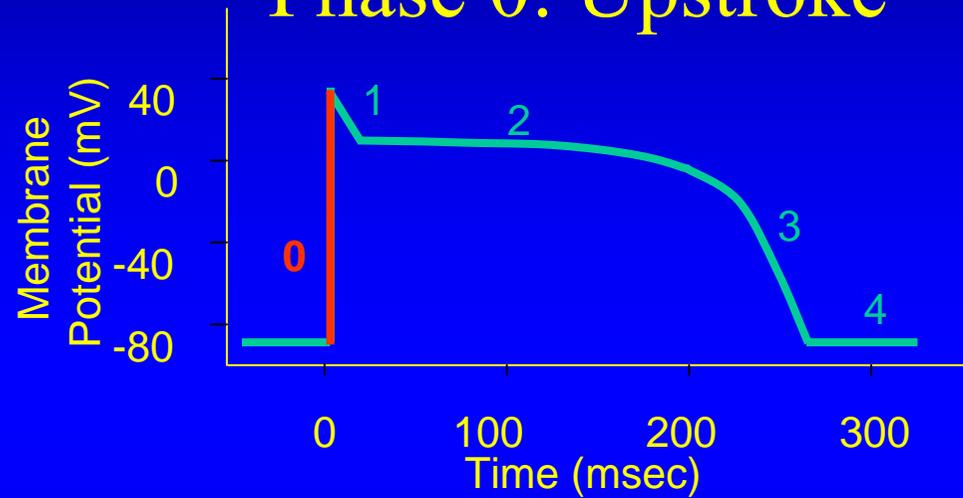
$[K^+]_o$

Chemical
Electrostatic

Nernst Equation
$$E_K = 61.5 \log \left(\frac{[K^+]_i}{[K^+]_o} \right)$$

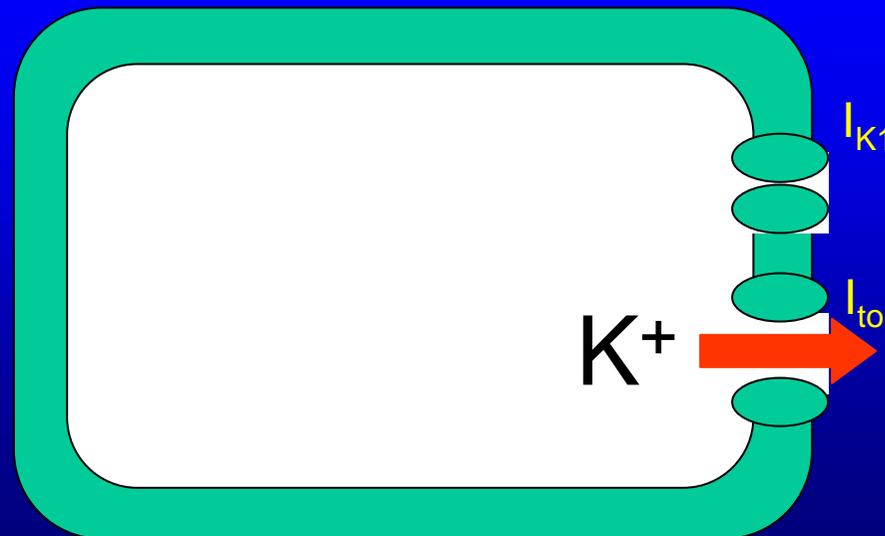
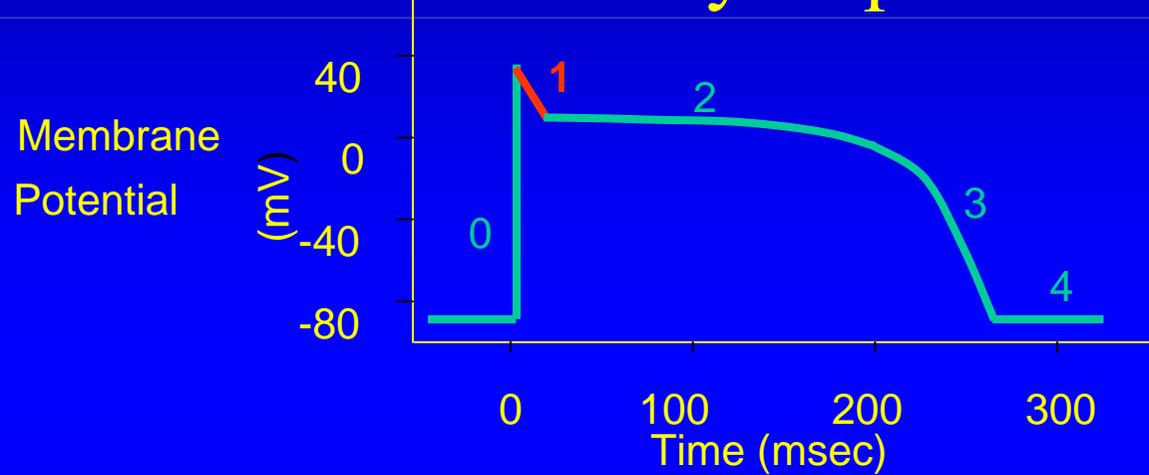
Fast Response Action Potential

Phase 0: Upstroke



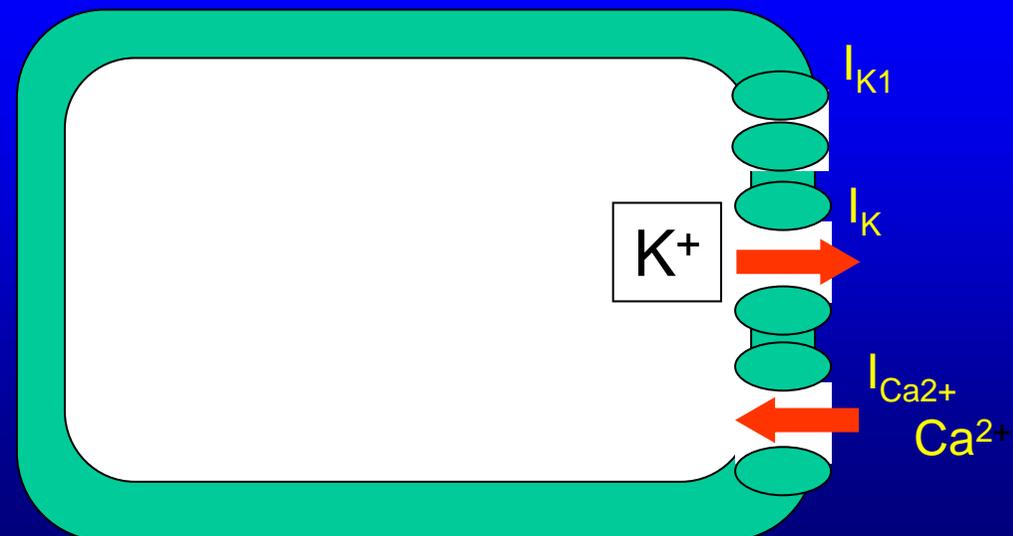
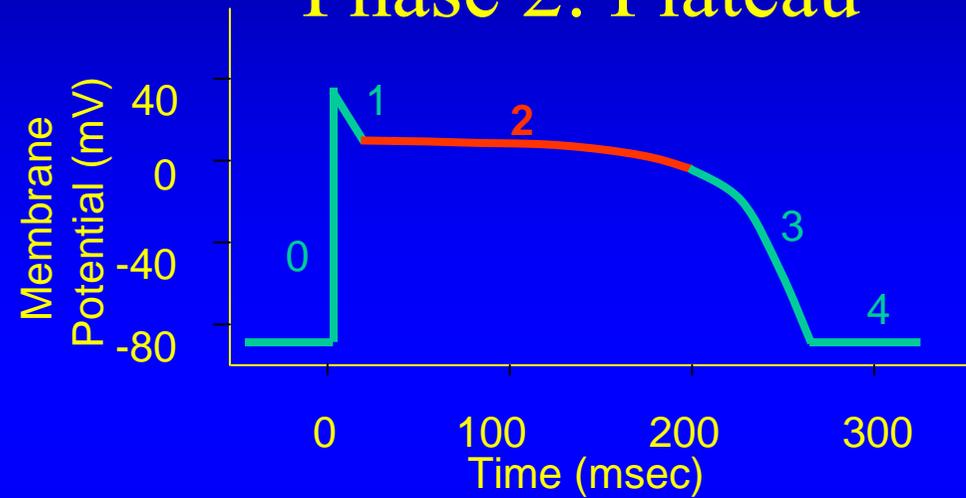
Fast Response Action Potential

Phase 1: Early Repolarization



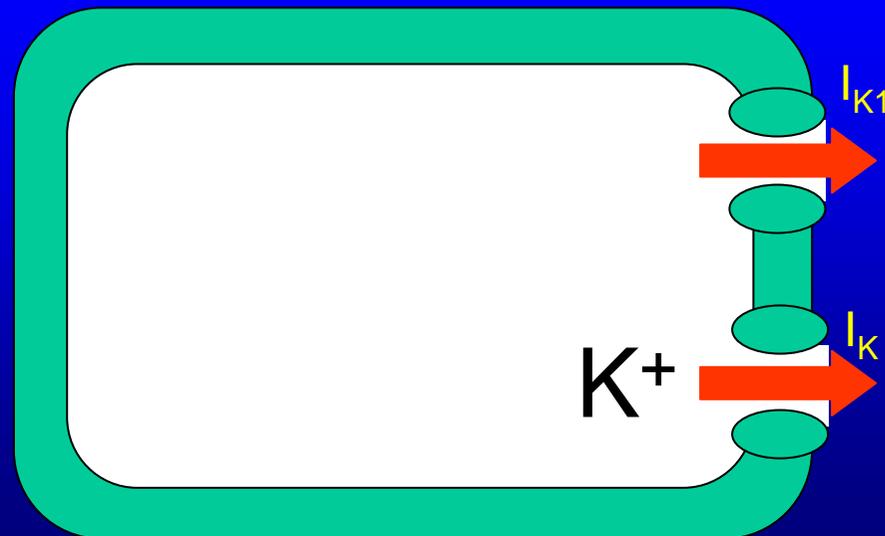
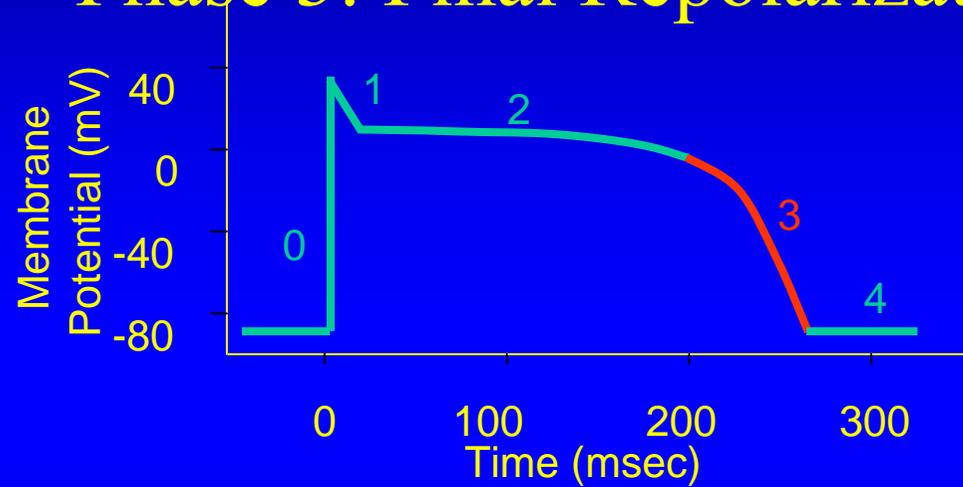
Fast Response Action Potential

Phase 2: Plateau



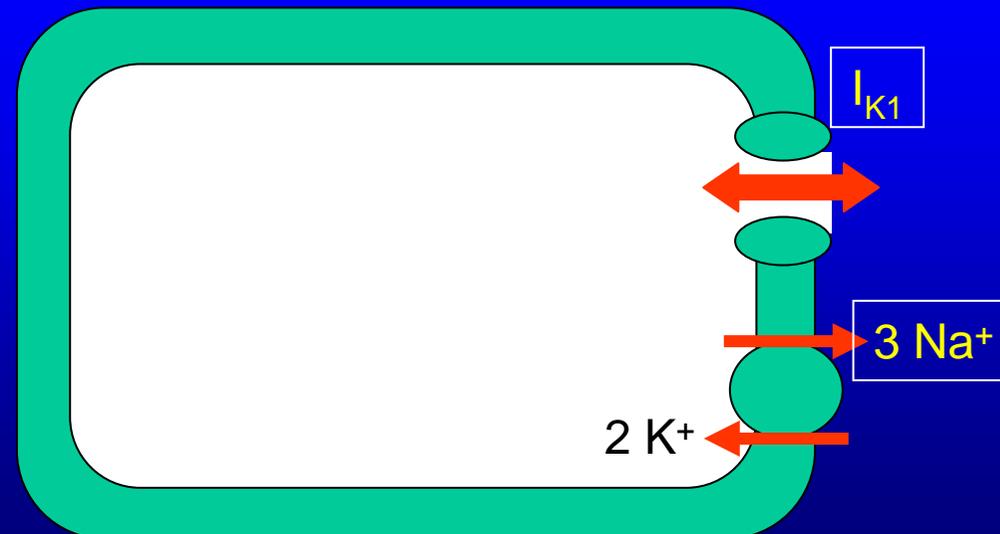
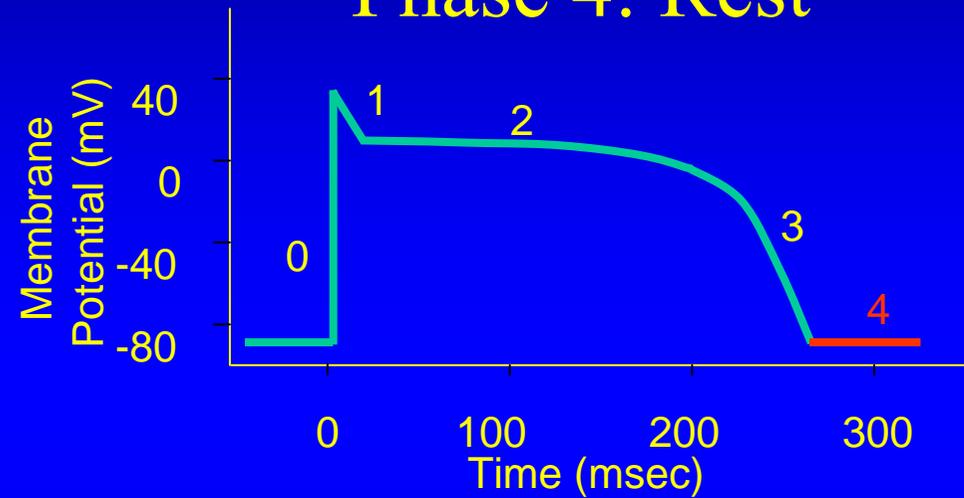
Fast Response Action Potential

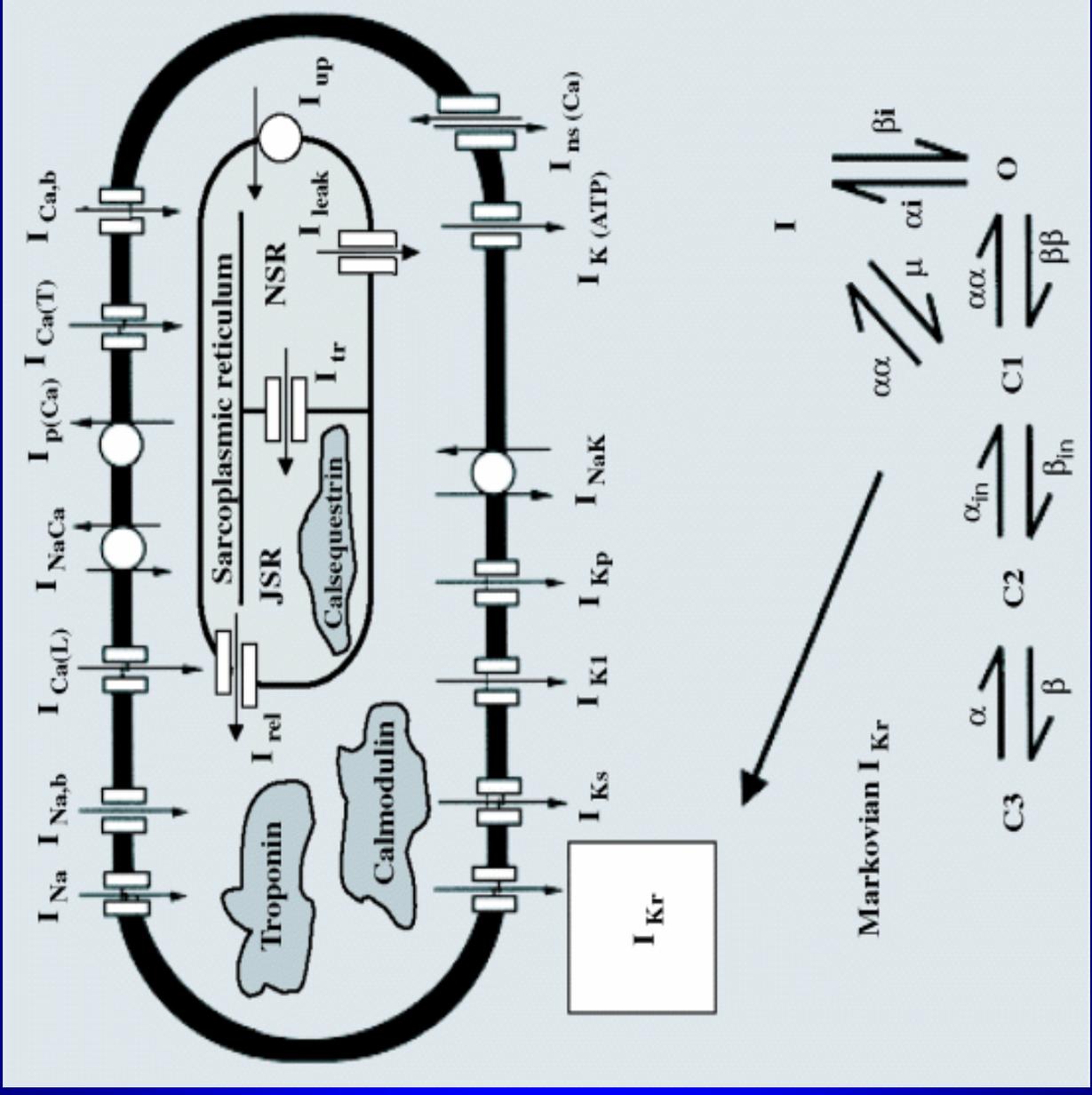
Phase 3: Final Repolarization

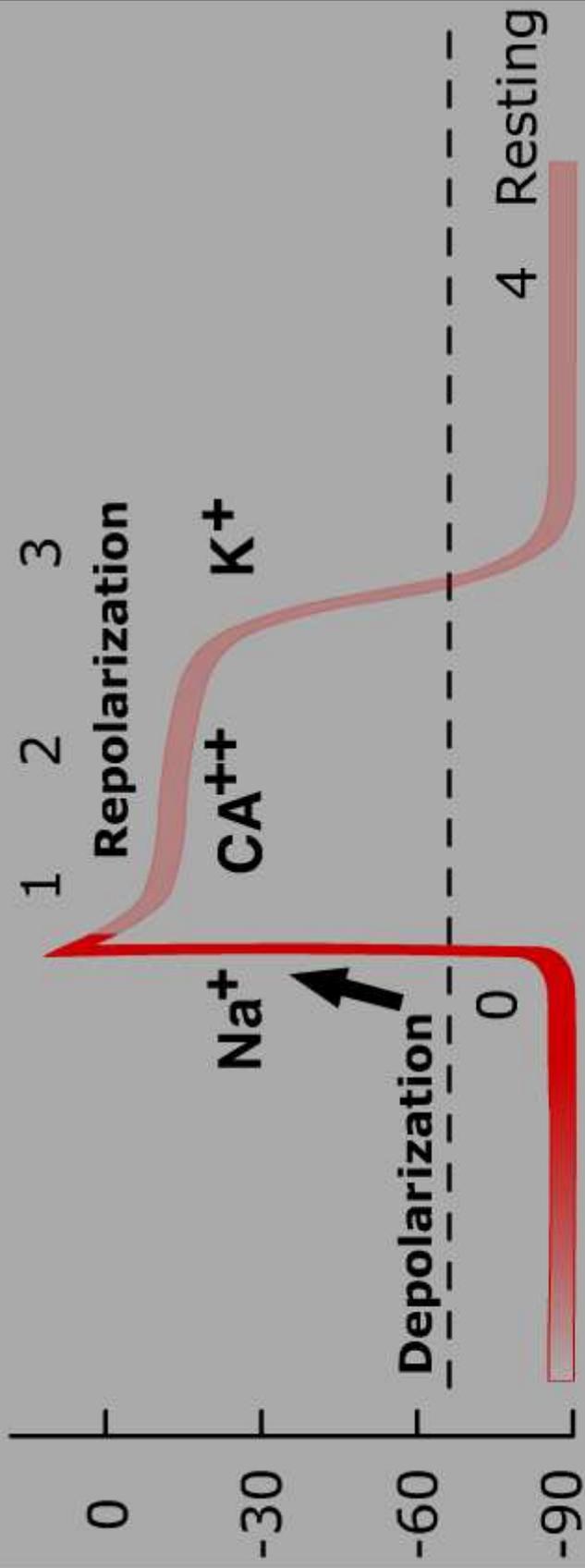


Fast Response Action Potential

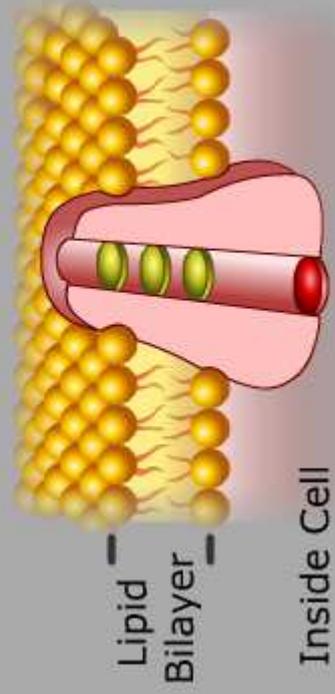
Phase 4: Rest





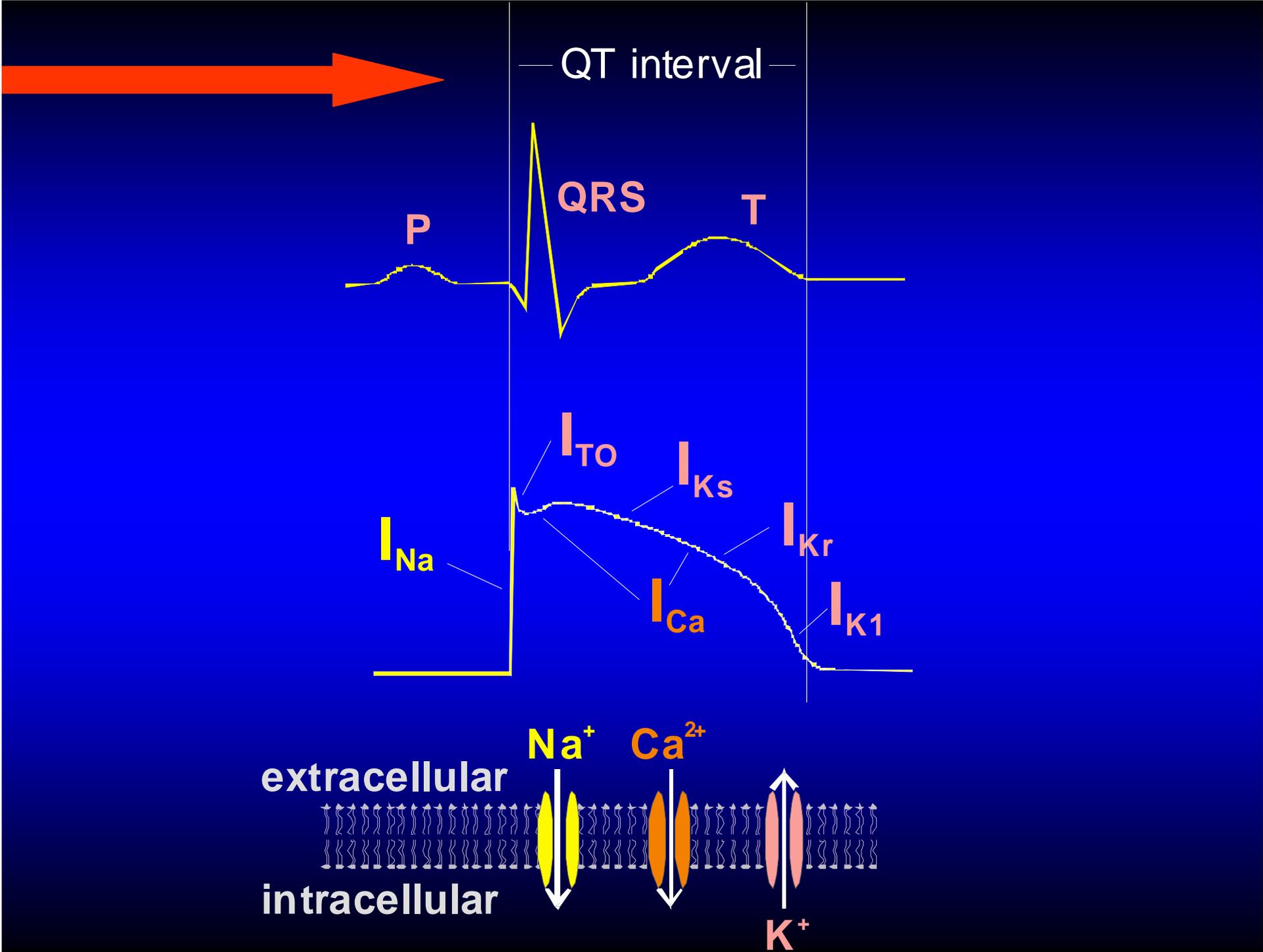


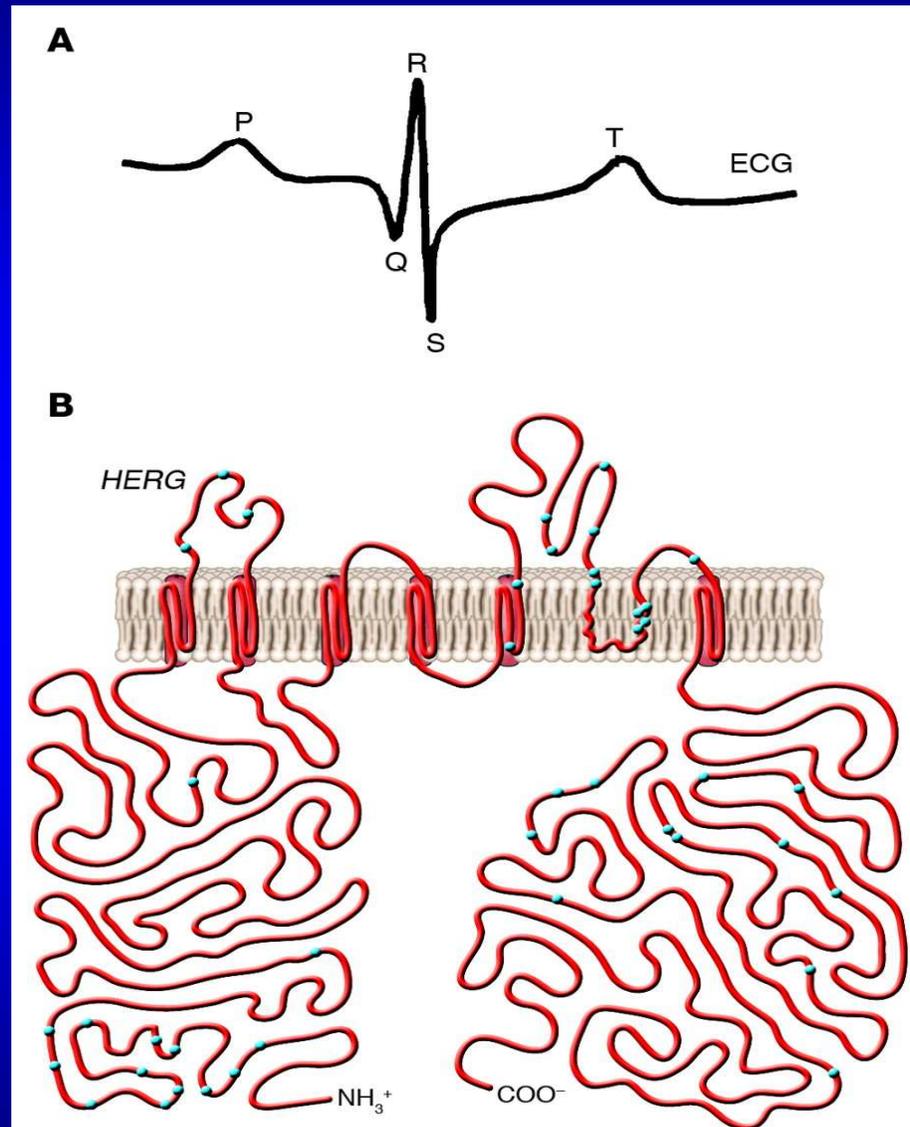
Outside Cell Sodium Channel

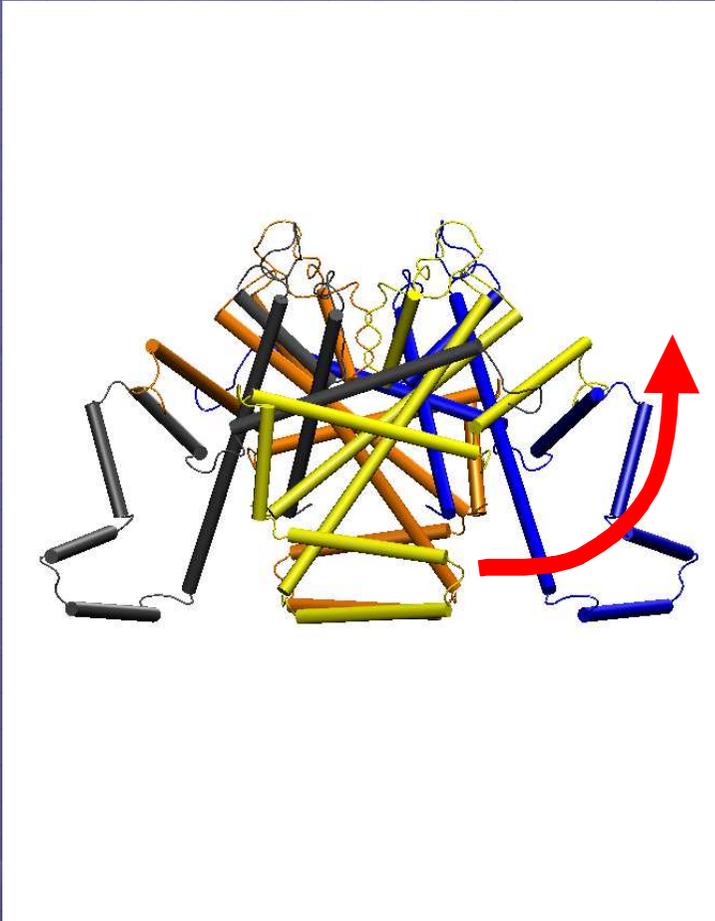


Lipid Bilayer
Inside Cell

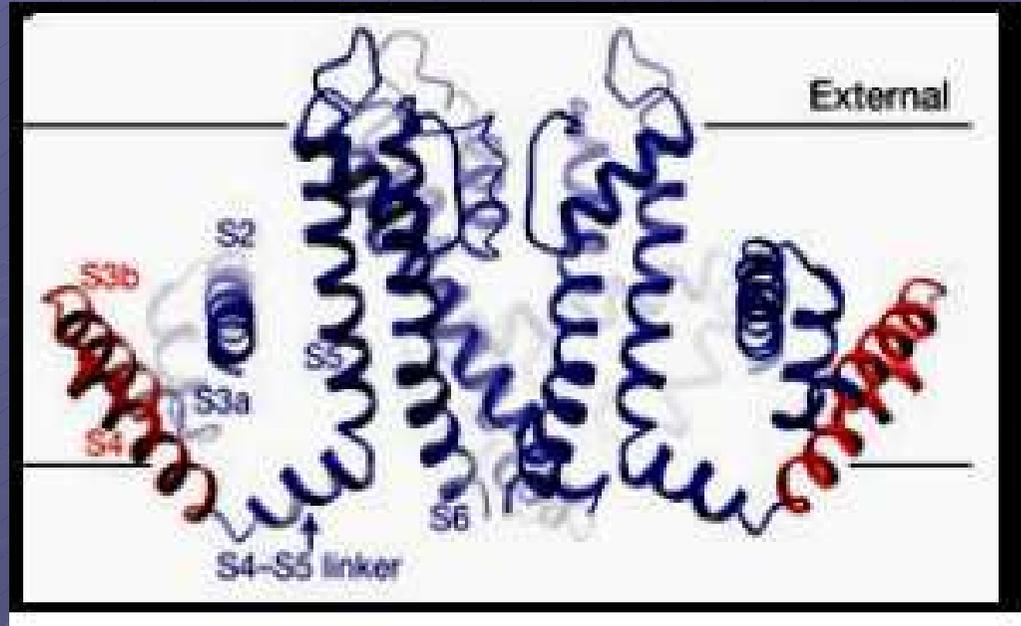
Na^+



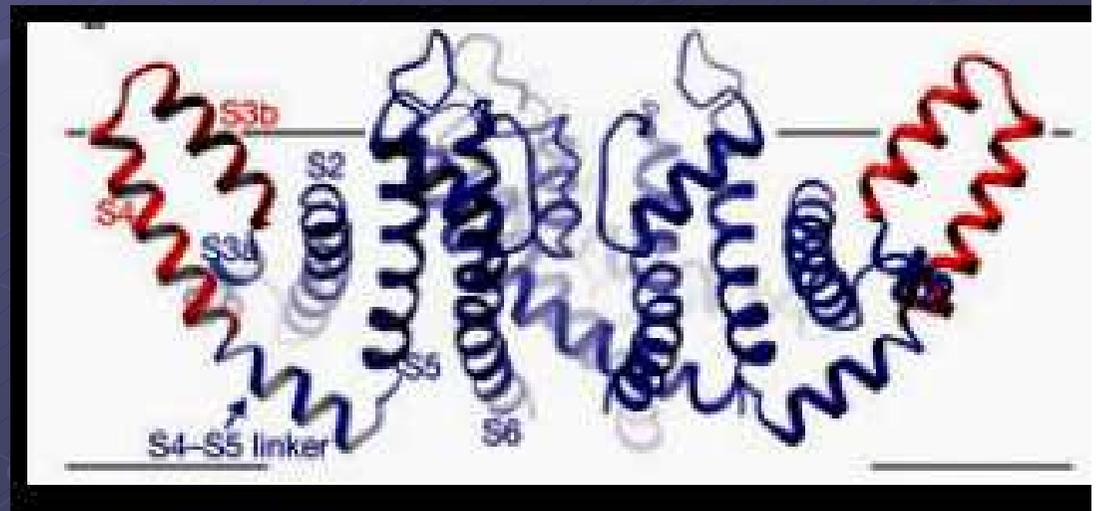


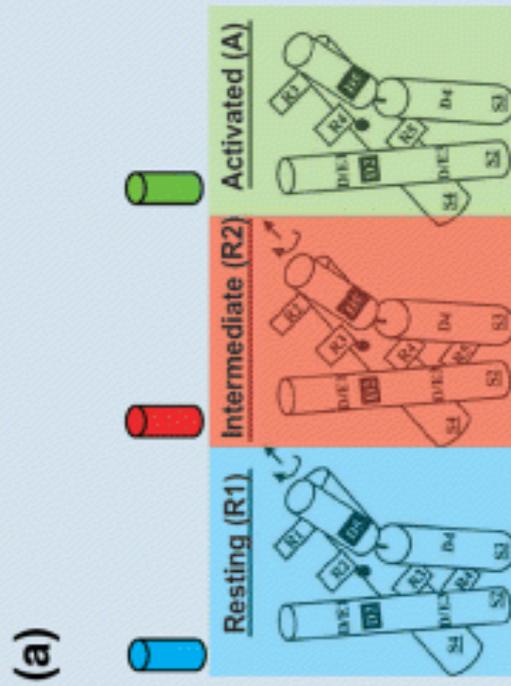


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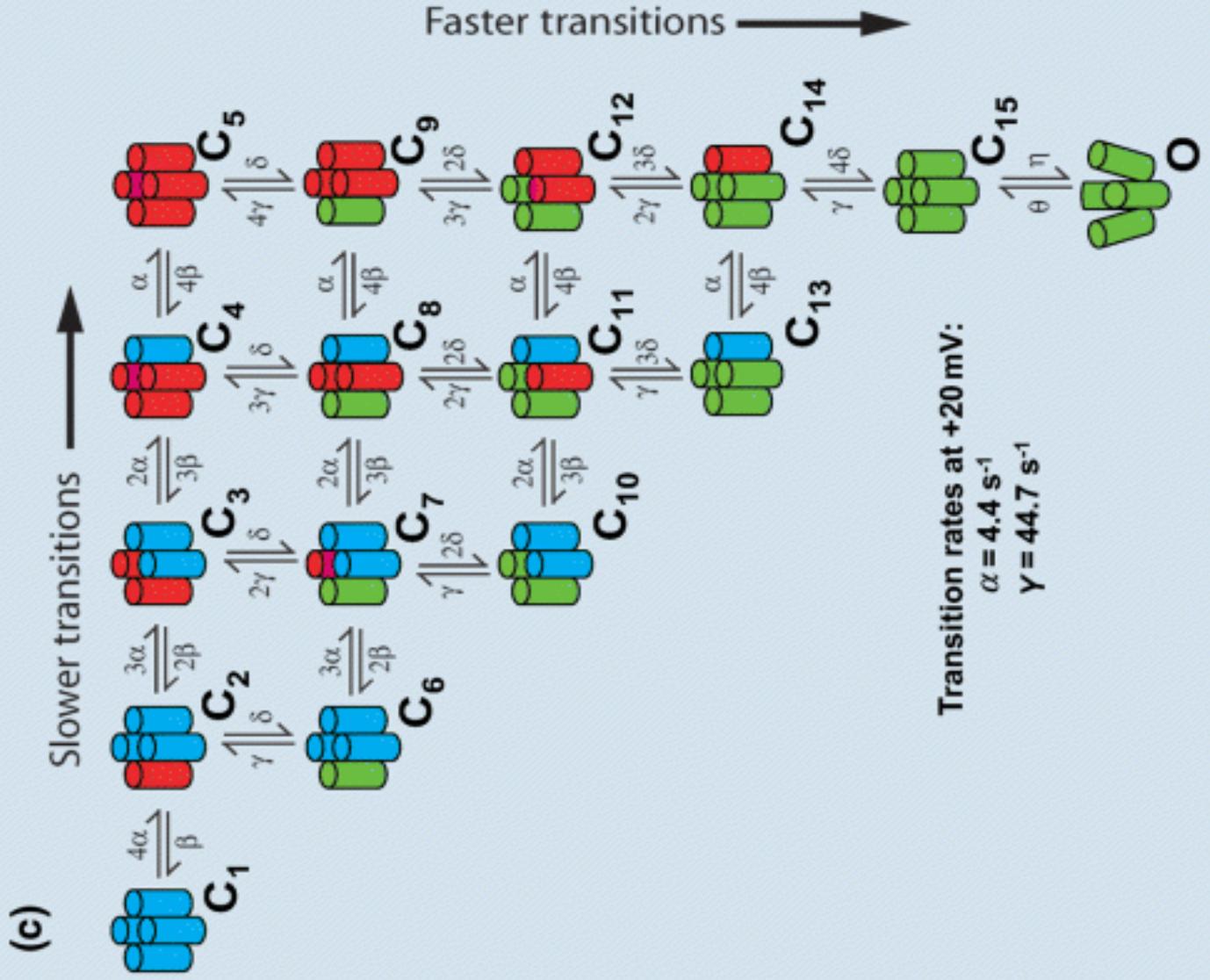
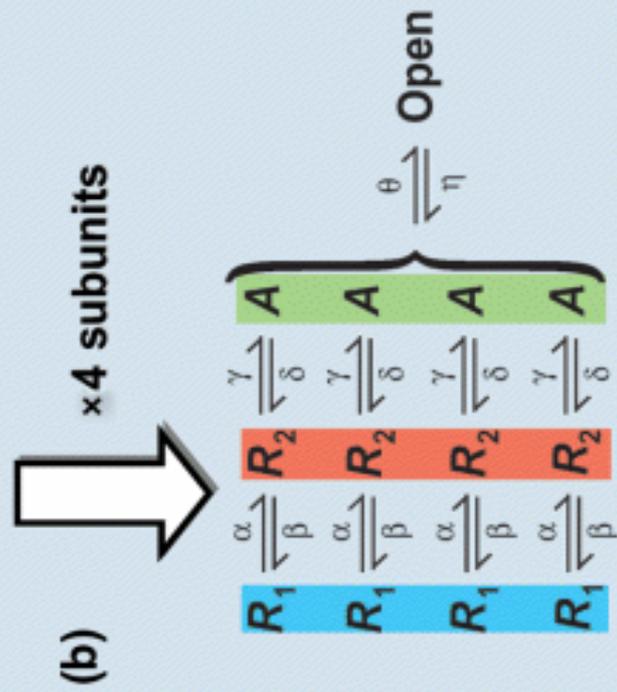


OPEN

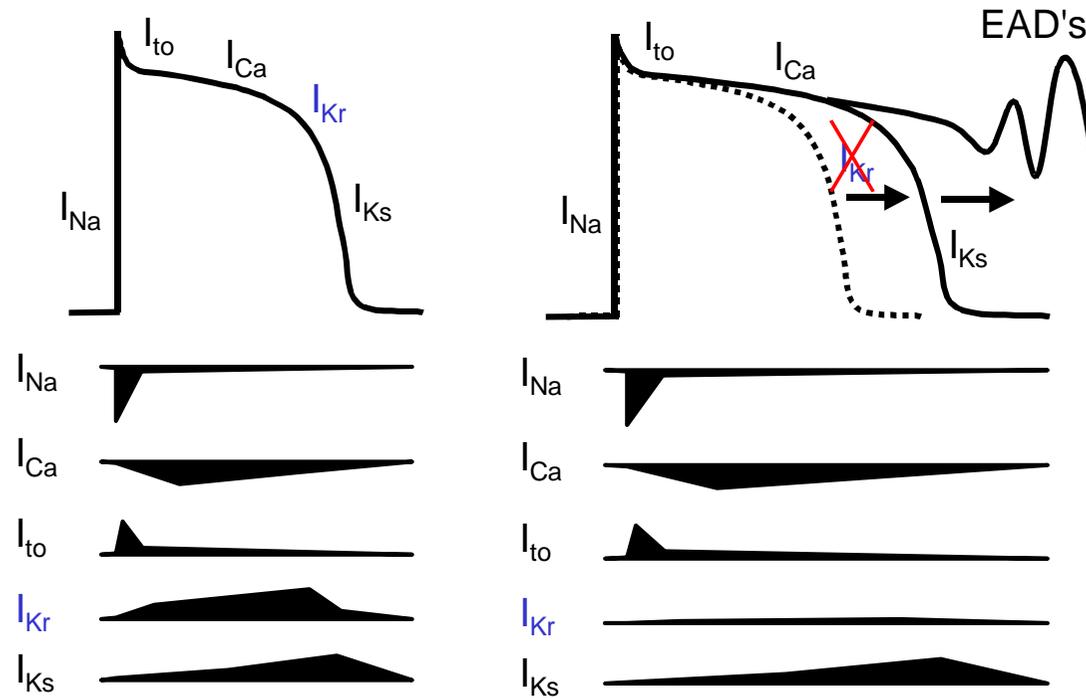




Silverman et al., PNAS 2003



Decremento I_{Kr} prolunga il Potenziale d'azione

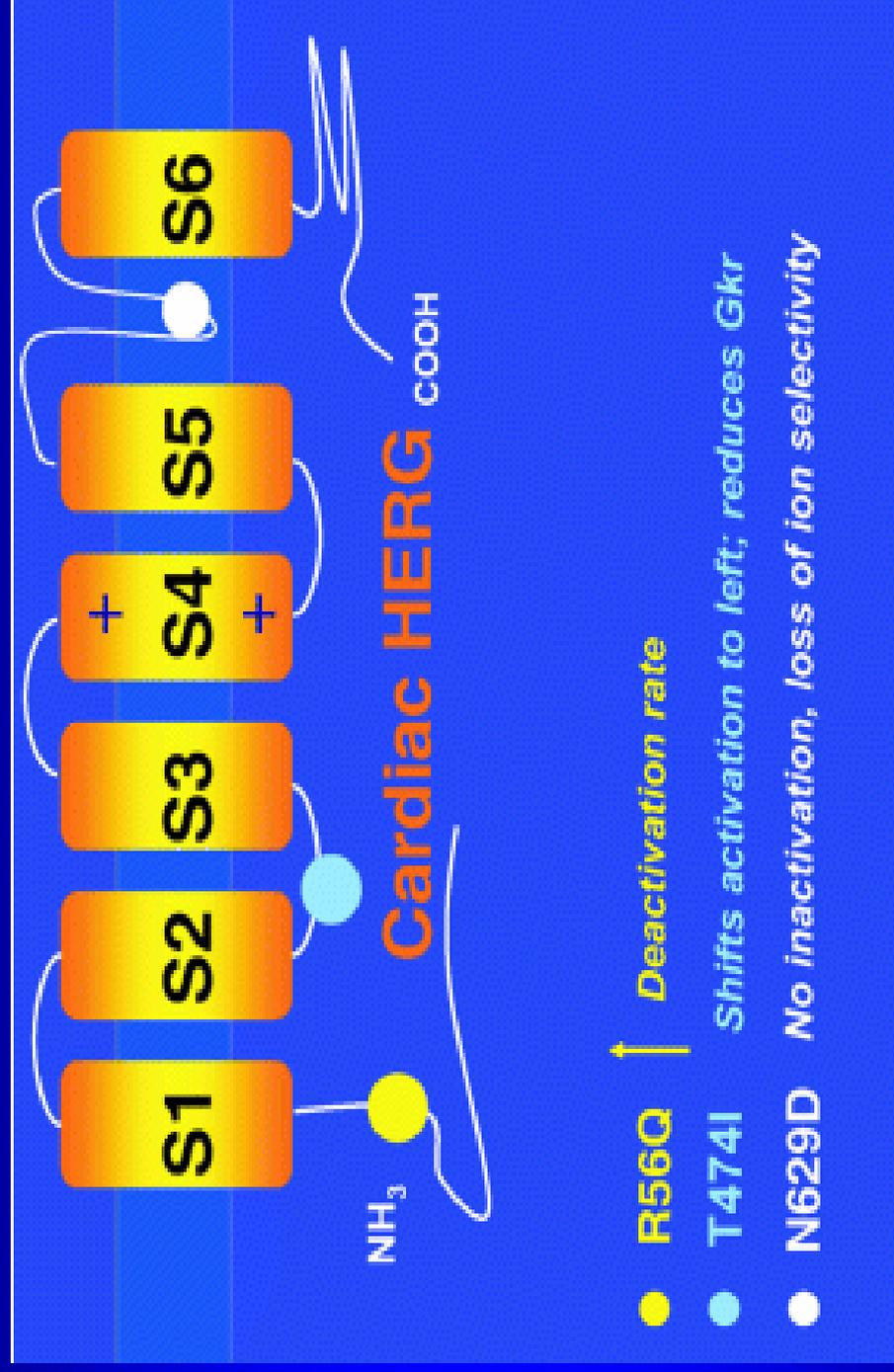


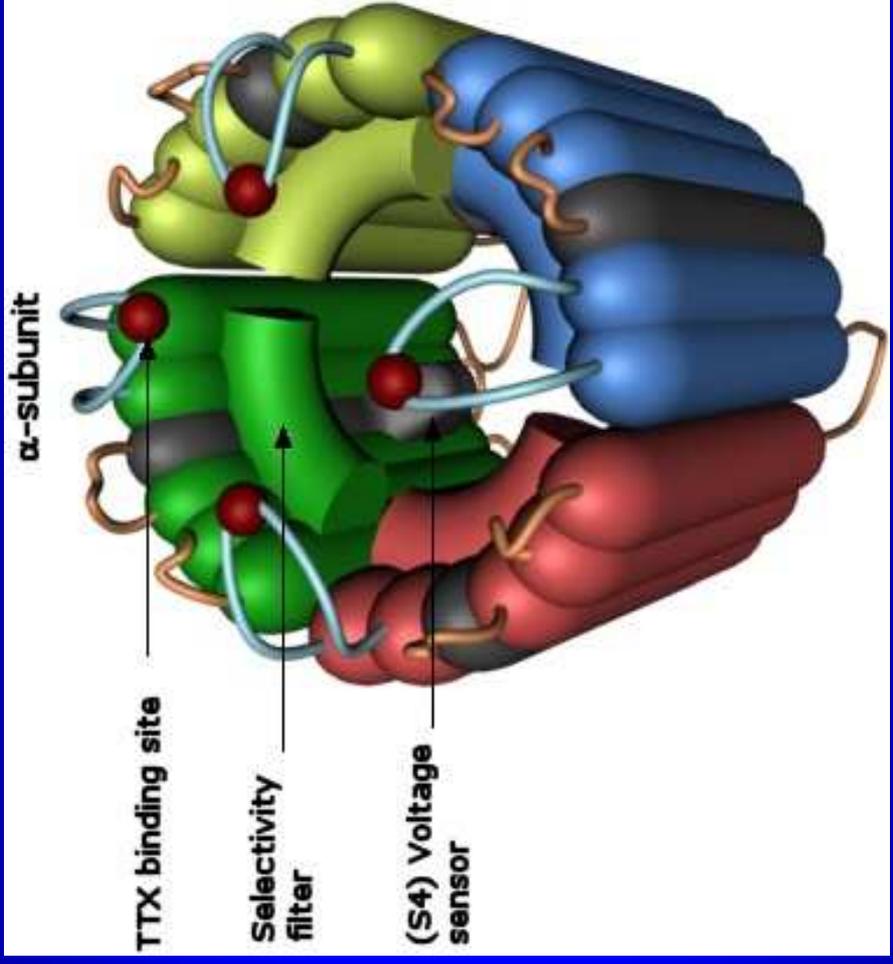
LQTS

- Alterazione su base genetica dei Flussi ionici in particolare I_{ks} I_{kr} Na e Ca determinano un allungamento della ripolarizzazione e quindi del QT, predisponendo a post-depolarizzazioni e rientri
- Oltre 300 mutazioni in 8 Geni identificati, coinvolgenti il Canale ionico o le Subunita' regolatorie
- Esiste almeno un 30% di LQT non codificate geneticamente

Mutazione geni in LQTS

LQT	gene	cro m	prod	Canale ionico	flusso	alterazi one	Prevale nza
LQT1	KCNQ1	11	Sub alfa	K	I Ks	Loss	57%
LQT2	KCNH2	7	Sub alfa	K	I Kr	Loss	23%
LQT3	SCN5A	3	Sub alfa	Na	I Na	Gain	16%
LQT4	ANKB	4	Prot mb	Ca	I Ca	Sovrac	
LQT5	KCNE1	21	Sub beta	K	I Ks	Loss	5%
LQT6	KCNE2	21	Sub beta	K	I Kr	Loss	
LQT7	KCJN	2	Sub alfa	K	I K1		
LQT8	CACNA1 C	12	Sub alfa	Ca	I Ca L		





LQTS

In sintesi in LQTS alterazioni
ioni che determinano la
ripolarizzazione , riduzione
correnti in uscita (I_{Kr}) o aumento
correnti in entrata (I_{Na} e I_{Ca})
prolungano la fase 2 e 3 del
plateau e allungano il QT

Dispersione della ripolarizzazione

- Esiste una eterogeneità fisiologica nella dinamica della ripolarizzazione a livello transmurale e zonale
- Il potenziale d'azione non ha la stessa durata in tutti i miociti, sebbene in vivo la propagazione elettrotonica e le gap junction riducano le differenze

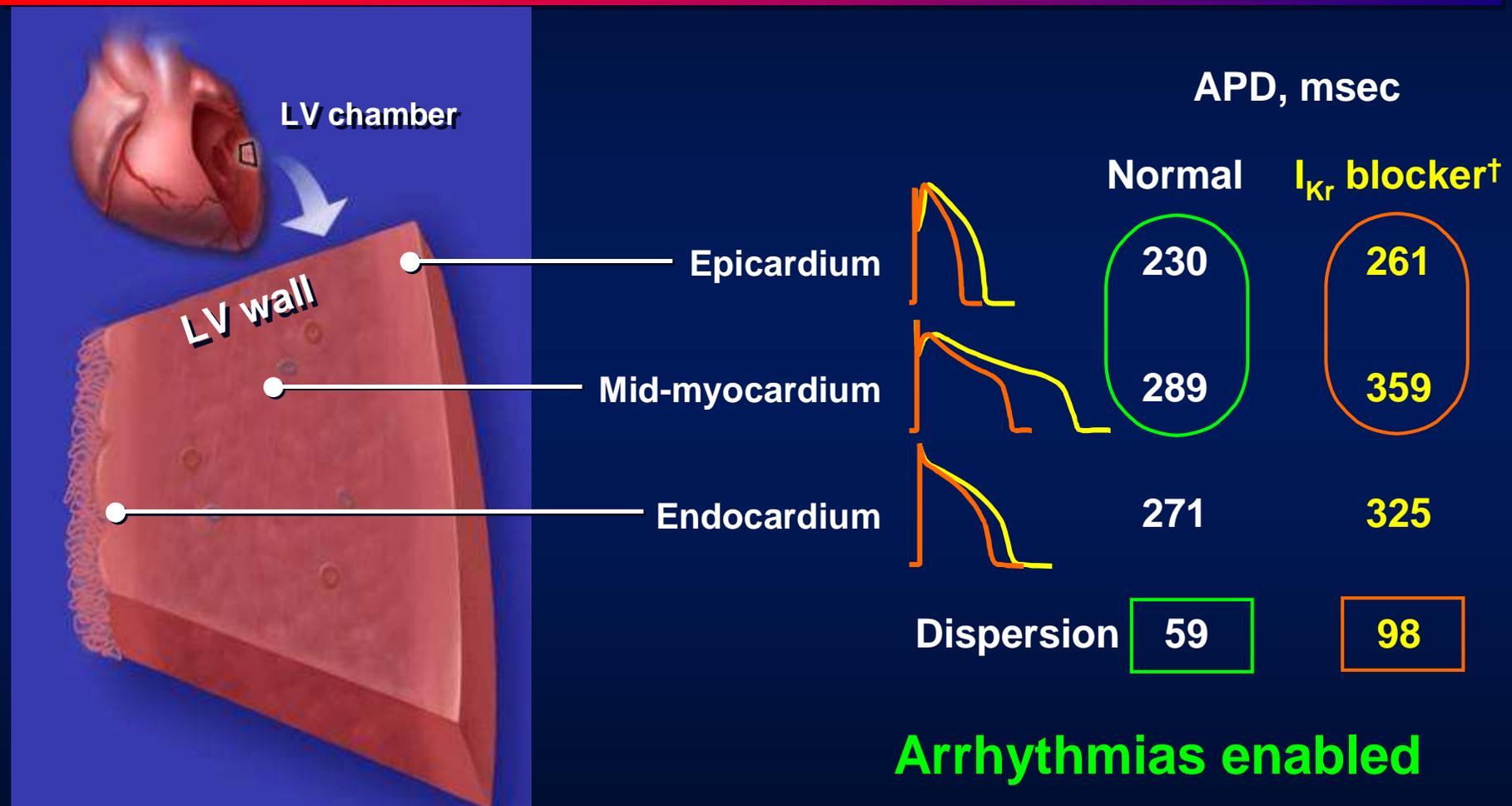
Dispersione QT

- A livello transmurale l'APD termina prima in Epicardio (apice T) poi subendocardio e poi Cellule M (termine QT)
- A livello regionale l'APD termina prima nelle regioni basali poi in quelle apicali

Dispersione QT

- Cellule M hanno meno rappresentate le correnti ripolarizzanti I_{Kr} e I_{Na} late, cio' le rende piu' sensibili ad agenti farmacologici o mutazioni geniche (es LQT) che influenzino tali canali
- Riserva di Ripolarizzazione

Differenze transmurali nella ripolarizzazione

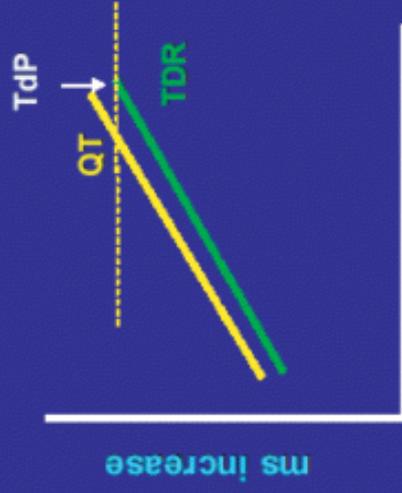


†d-Sotalol (I_{Kr} blockers) 100 μ M.

Shimizu et al. *JCE*. 1999;10:154-164.

Polymorphic VT (PVT)

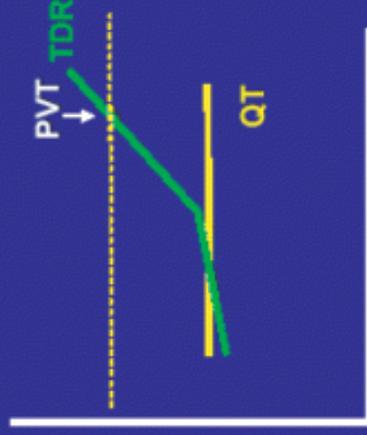
Long QT syndrome



(Drug)
(Disease)

↓ I_{Kr}
Sotalolol
Dofetilide

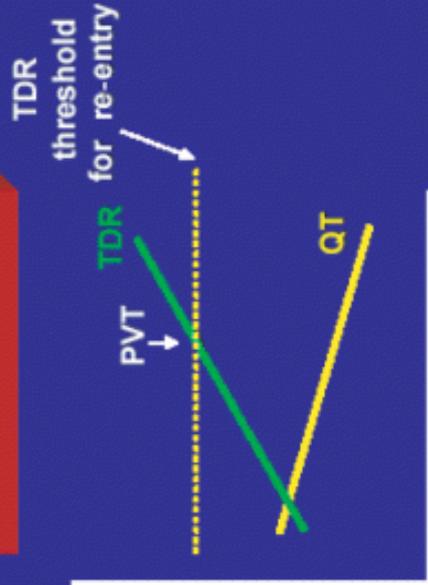
Brugada syndrome



(Drug)
(Disease)

↓ I_{Na} ↓ I_{Ca}
Flecainide
Procainamide
Terfenadine

Short QT syndrome



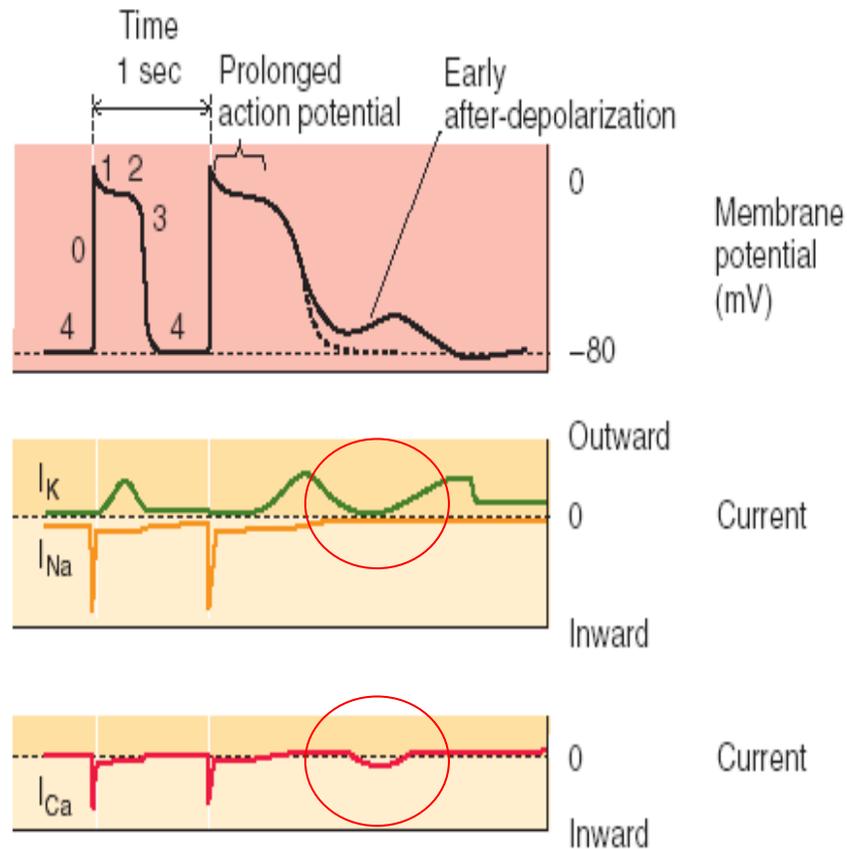
(Drug)
(Disease)

↑ I_{Kr} , I_{Ks}
↑ I_{K-ATP}
Pinnacidil

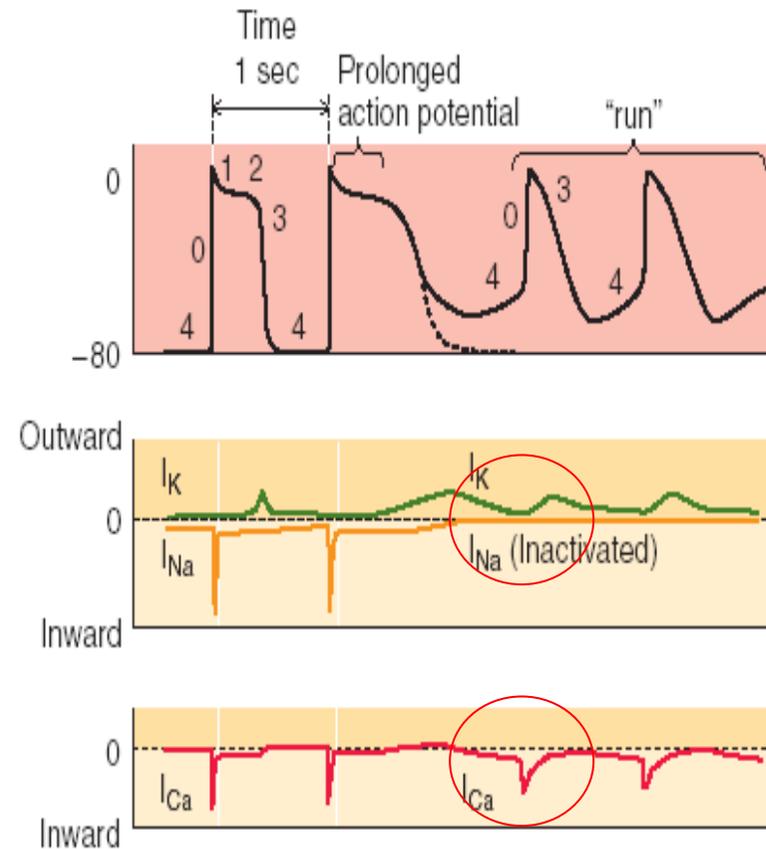
Meccanismi aritmie

- Allungamento QT favorisce EAD
predisporre a TdP
- TdP puo' terminare spontaneamente o se
avviene in un momento di particolare
dispersione della refrattarieta' che favorisce
il rientro , degenerare in FV

A PROLONGED ACTION POTENTIAL LEADS TO EARLY AFTER-DEPOLARIZATION



B PROLONGED ACTION POTENTIAL LEADS TO A "RUN" OF SPONTANEOUS ACTIVITY



Extended phase two cause long QT syndrome.

Aspetti fenotipici :

L'elettrocardiogramma

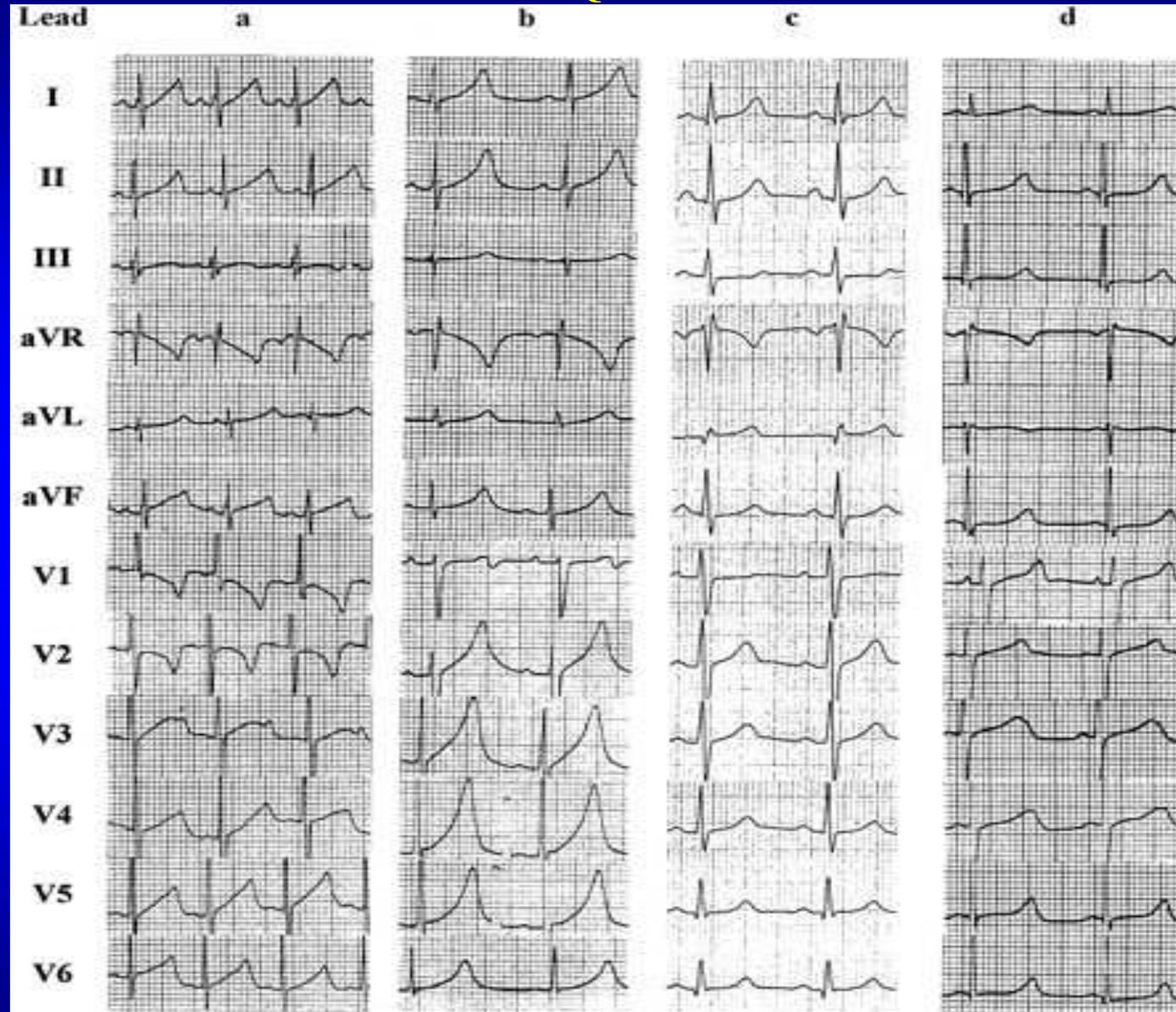
Il QT

La morfologia ST-T

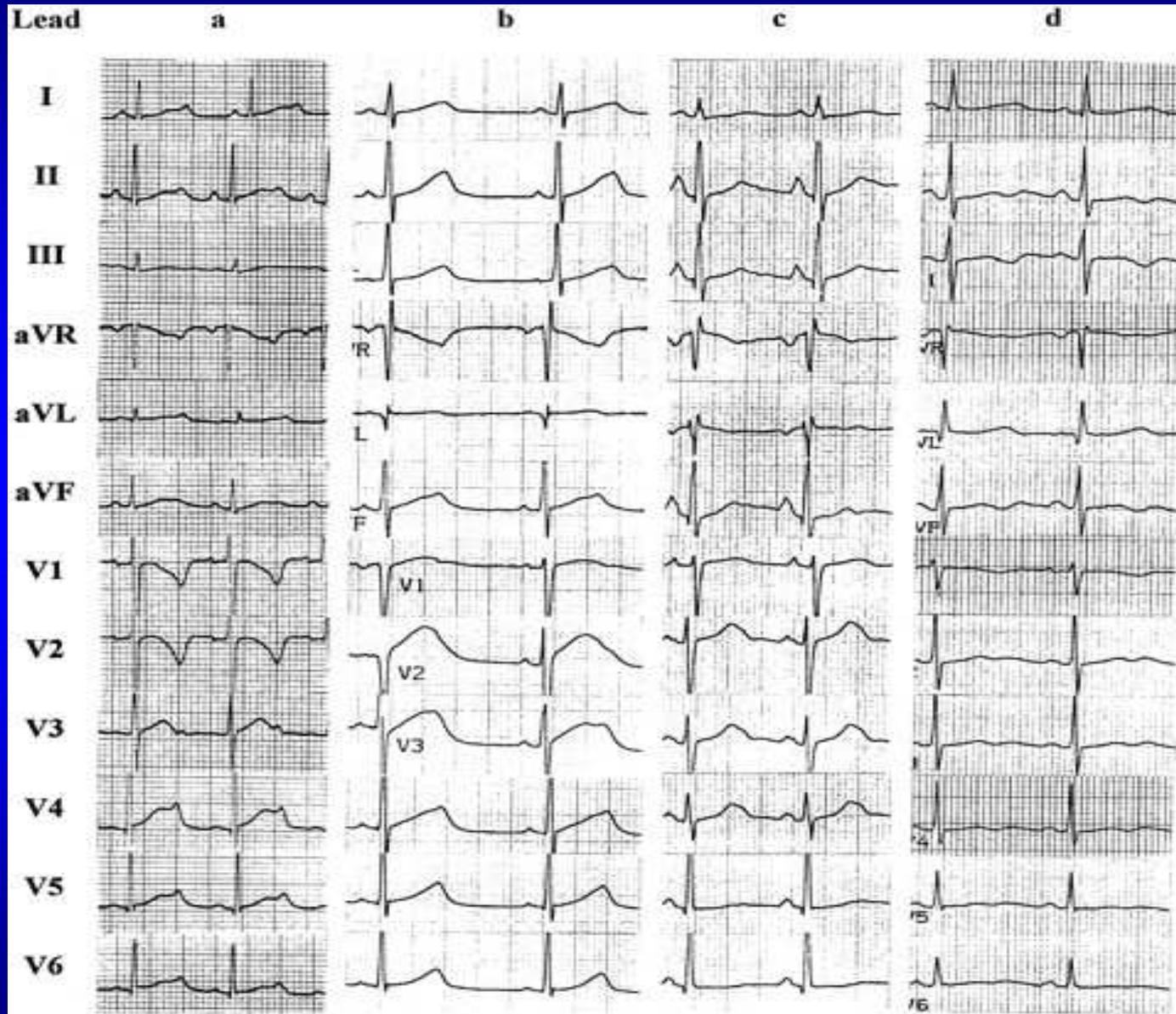
Correlazione Genotipo-fenotipo

- Oltre il 90% delle LQTS sono essenzialmente LQT1 LQT2 LQT3 ed esistono dati sufficienti per correlare genotipo a fenotipo
- Cio' puo' consentire di risalire dall'ECG (fenotipo) al tipo di LQT (genotipo)

LQT1

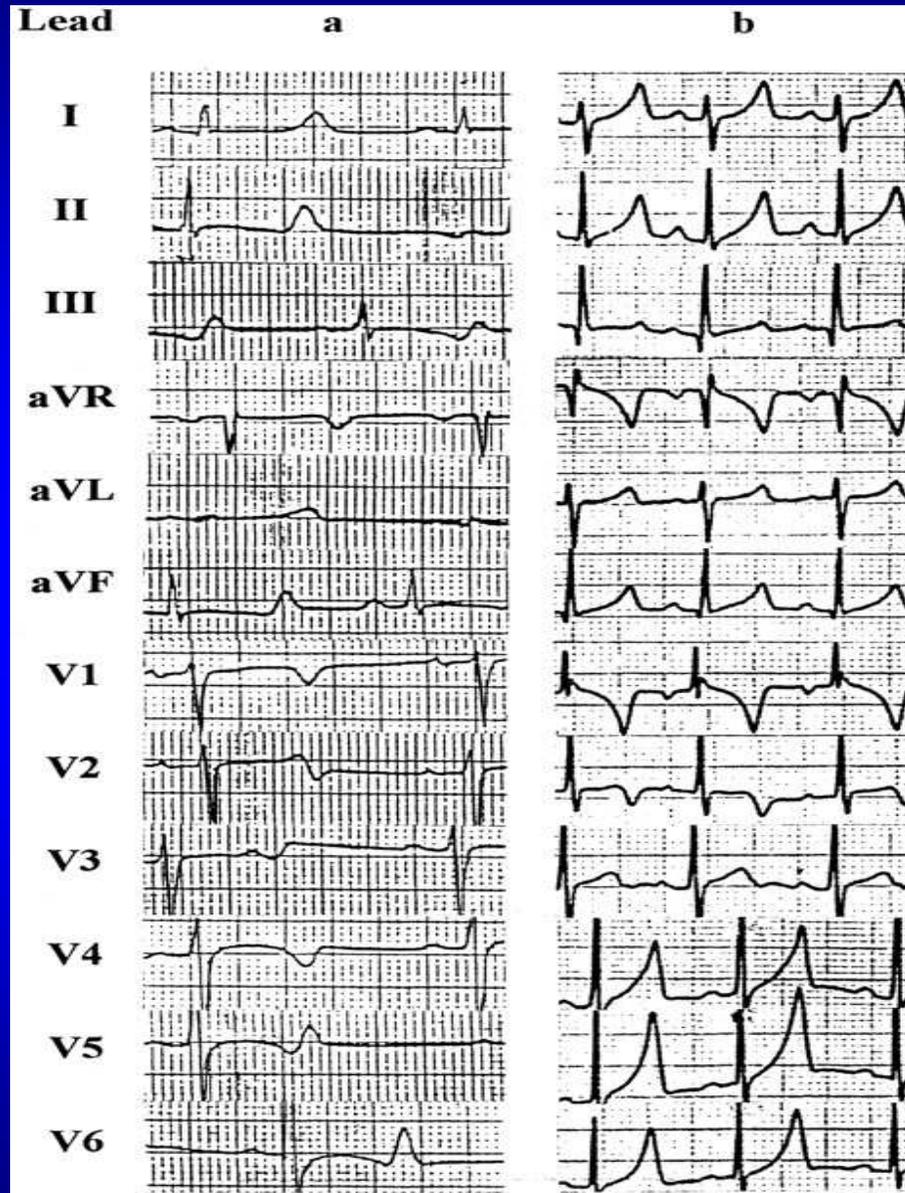


LQT2



Zhang, L. et al. *Circulation* 2000;102:2849-2855

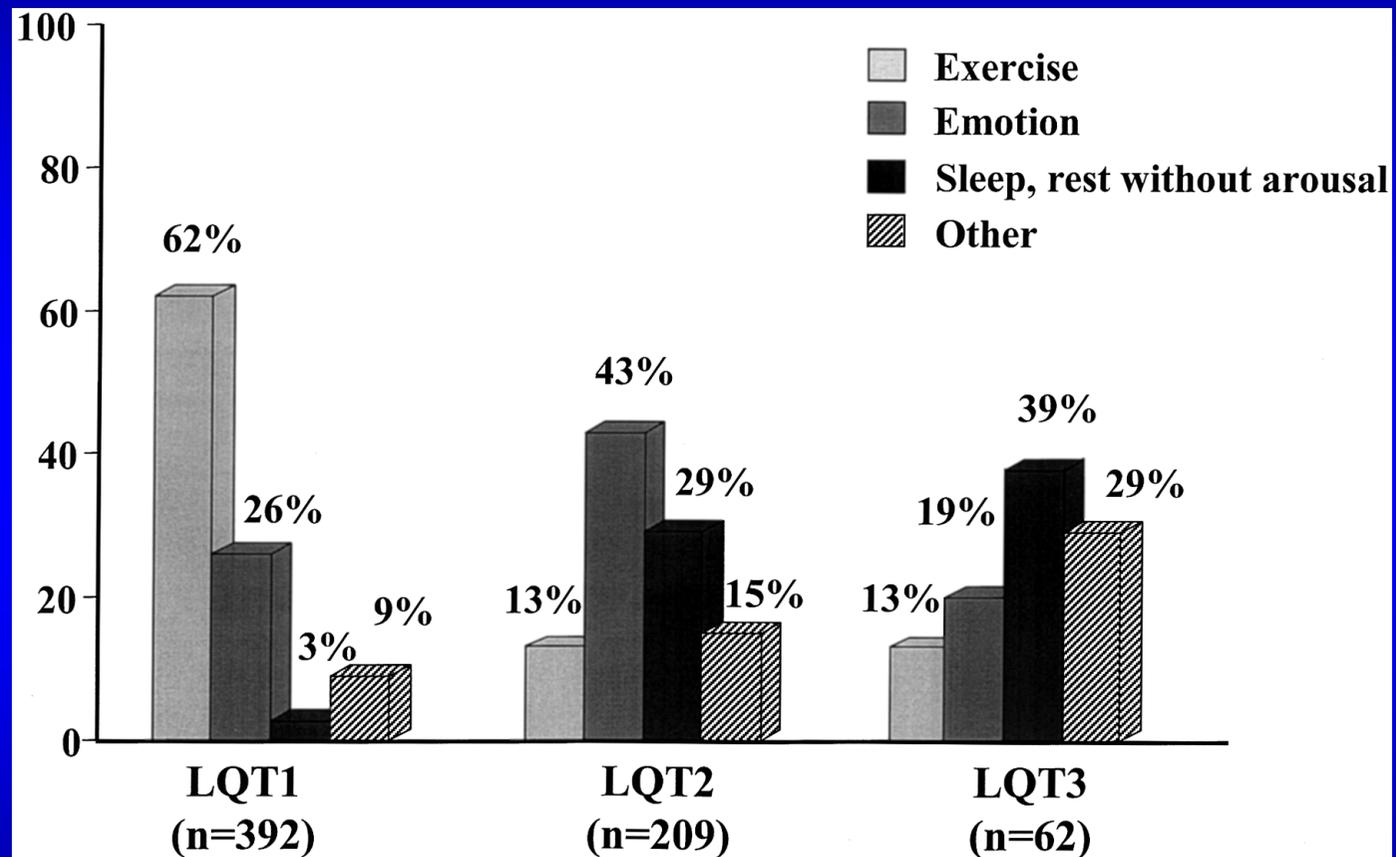
LQT3



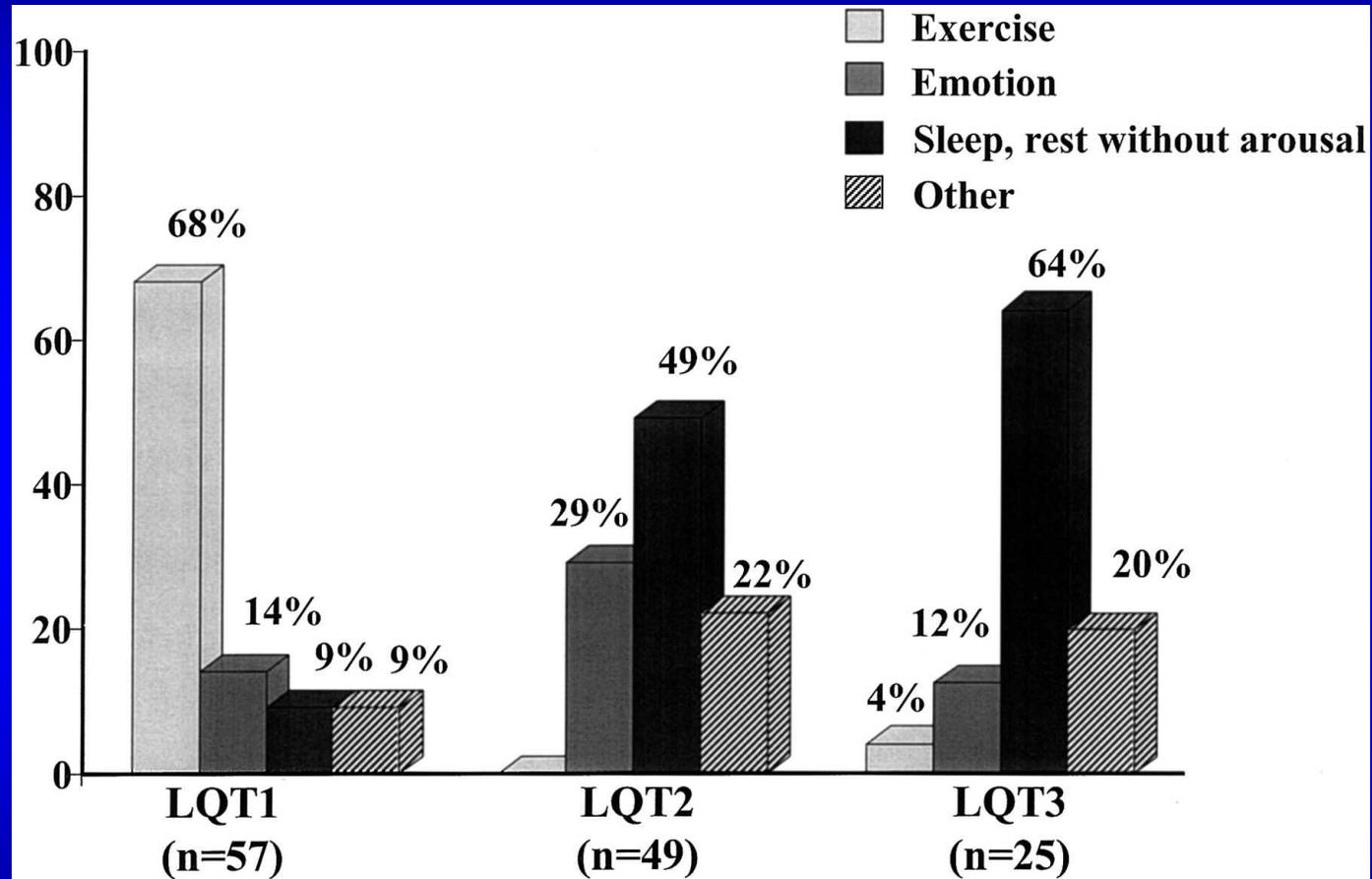
Presentazione clinica

- Asintomatico
- Sincope (Tdp si risolve)
- Arresto cardiaco (Tdp degenera in FV)
- Gli eventi sono in genere scatenati da *Trigger* , e sono piu' frequenti in *eta'* giovanile

Triggers for cardiac events according to 3 genotypes



Lethal cardiac events according to 3 classified triggers in 3 genotypes



Esistono quindi dei trigger che appaiono specifici per genotipo

La stimolazione simpatica (isoproterenolo, epinefrina), che aumenta I Ks via fosforilazione c- AMP mediata ha azioni diverse su QT e TDR secondo il genotipo:

LQT1 (I Ks) ↑ QT e TDR (..sforzo)

LQT2 (I Kr) ↑ QT e TDR solo all'inizio (..allarme)

LQT3 (I Na late) ↔ accorcia QT (..sonno)

Per LQT2 e soprattutto LQT3 Iks conservata e stimolata potrebbe avere un effetto compensatorio

Criteria diagnostici
e dati prognostici

Criteria diagnostici

	Points
<i>Electrocardiographic findings^a</i>	
QTc ^b	
>480 ms	3
460–470 ms	2
450 (male) ms	1
Torsades de pointes ^c	2
T-wave alternans	1
Notched T wave in 3 leads	1
Low heart rate for age ^d	0.5
<i>Clinical history</i>	
Syncope ^e	
With stress	2
Without stress	1
Congenital deafness	0.5
<i>Family history^f</i>	
A. Family members with definite LQTS	1
B. Unexplained sudden cardiac death below age 30 amongst immediate family members	0.5

Table 1. Incidence of a First Cardiac Arrest or Sudden Death before the Age of 40 Years and before Therapy among Patients with the Long-QT Syndrome, According to the Genetic Locus of the Mutation.

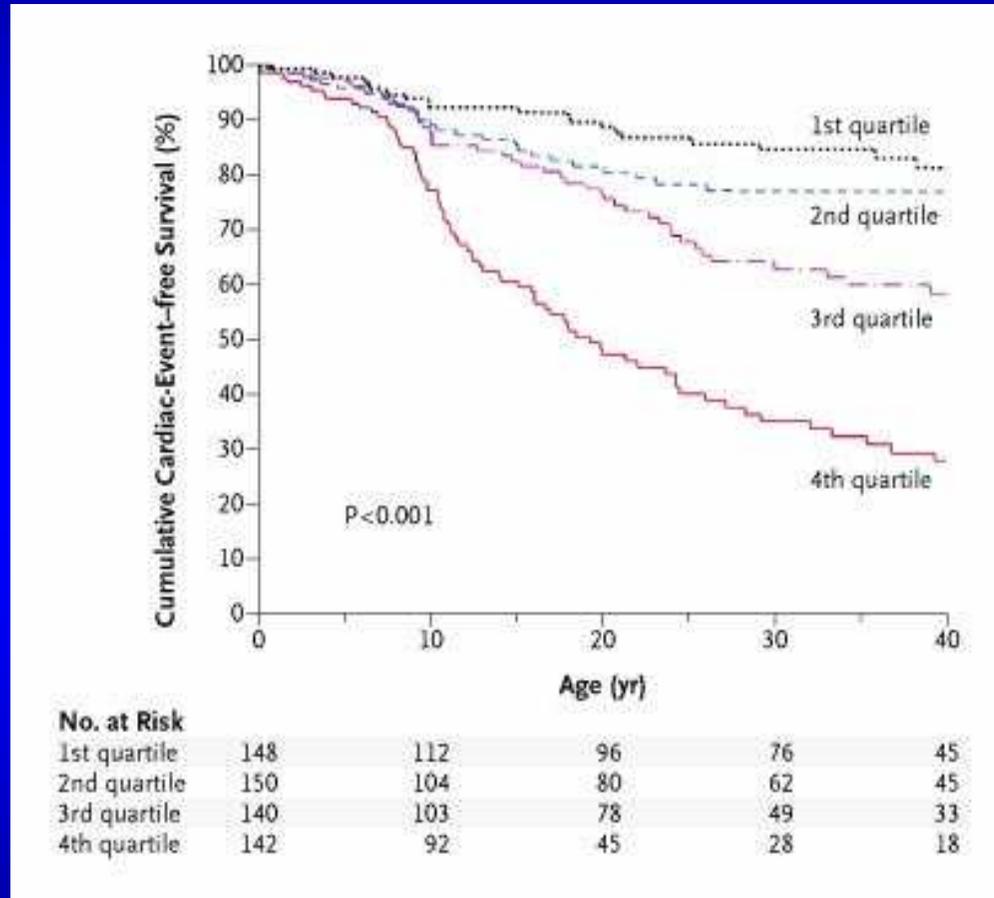
Locus and Sex	All Patients	Patients with Sudden Death or Cardiac Arrest	Incidence
		<i>number</i>	
LQT1			
Female sex	217	20	0.28
Male sex	169	17	0.33
Total	386	37	0.30
LQT2			
Female sex	125	30	0.82
Male sex	81	11	0.46
Total	206	41	0.60
LQT3			
Female sex	30	3	0.30
Male sex	25	6	0.96
Total	55	9	0.56

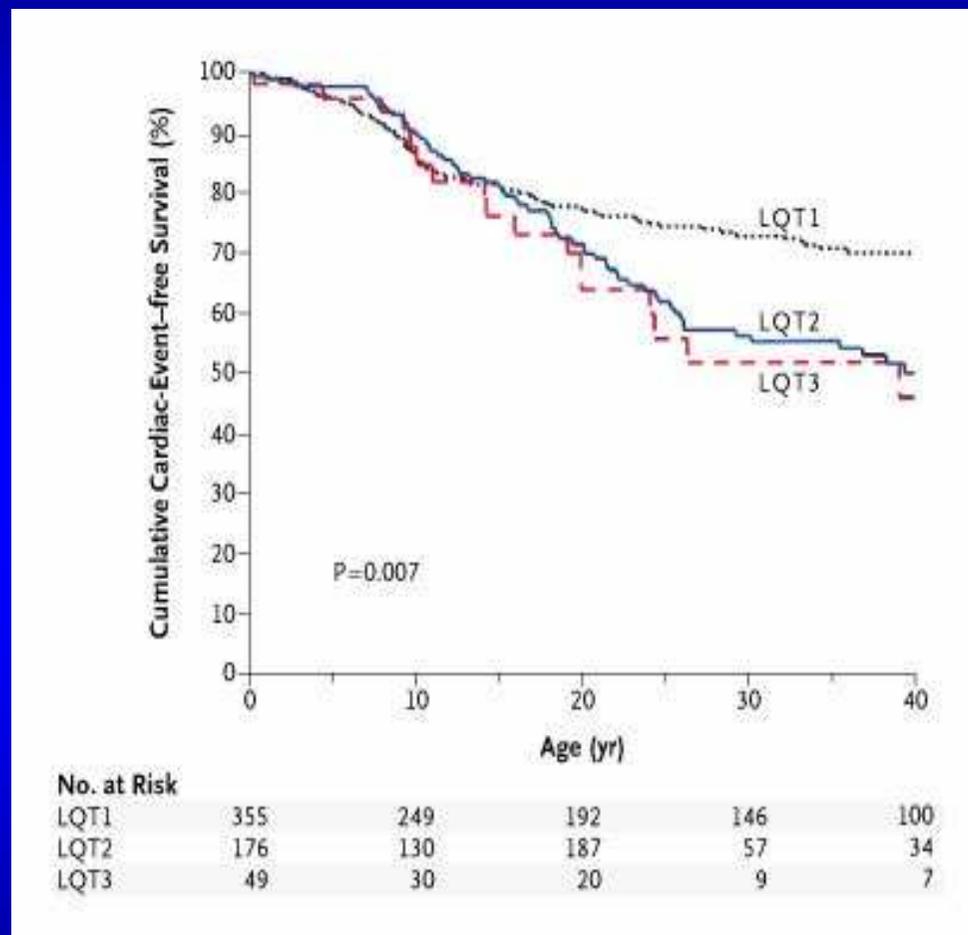
Table 2. Incidence of a First Cardiac Event before the Age of 40 Years and before Therapy in Patients with the Long-QT Syndrome, According to the Genetic Locus of the Mutation.*

Locus	Total No. of Patients	No. with an Event (%)
LQT1	386	116 (30)
LQT2	206	95 (46)
LQT3	55	23 (42)
Total	647	234 (36)

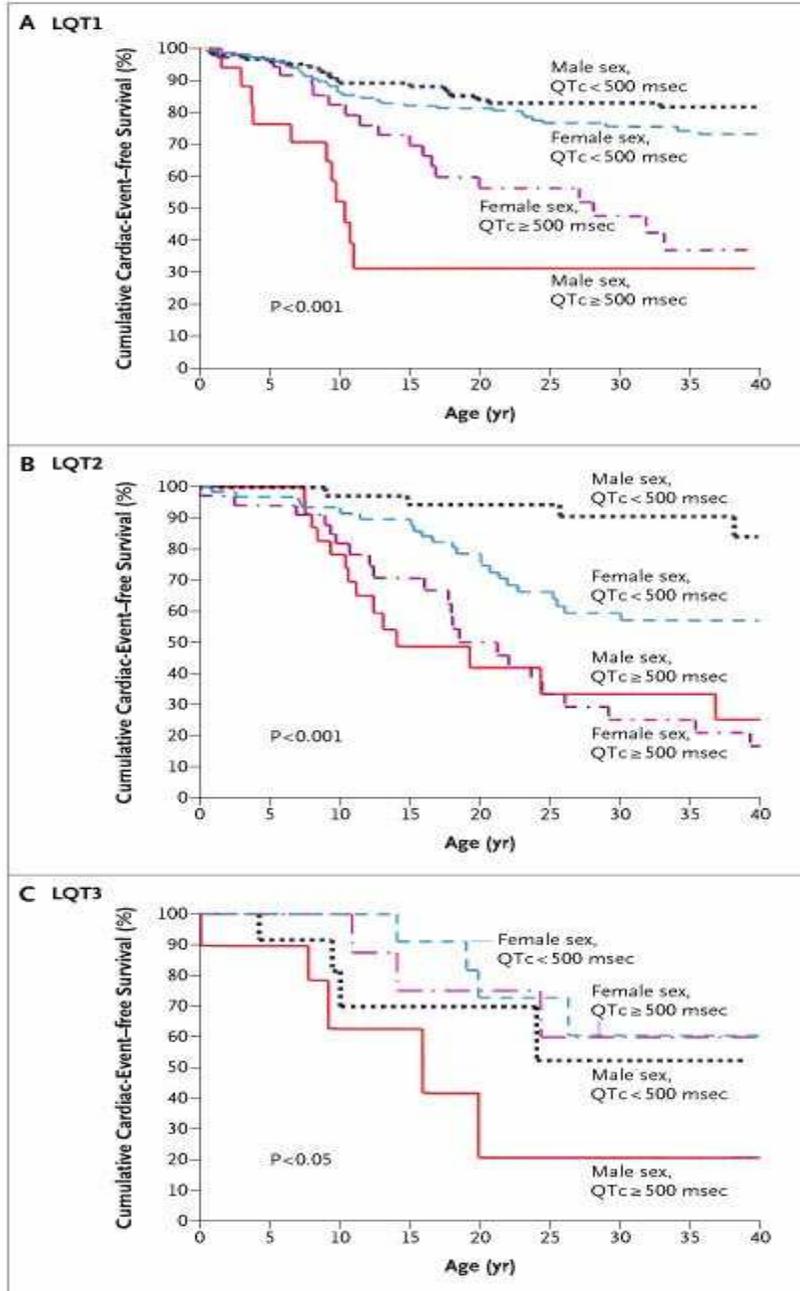
* Cardiac events include syncope, cardiac arrest, and sudden death.

Correlazione tra Qtc e sopravvivenza

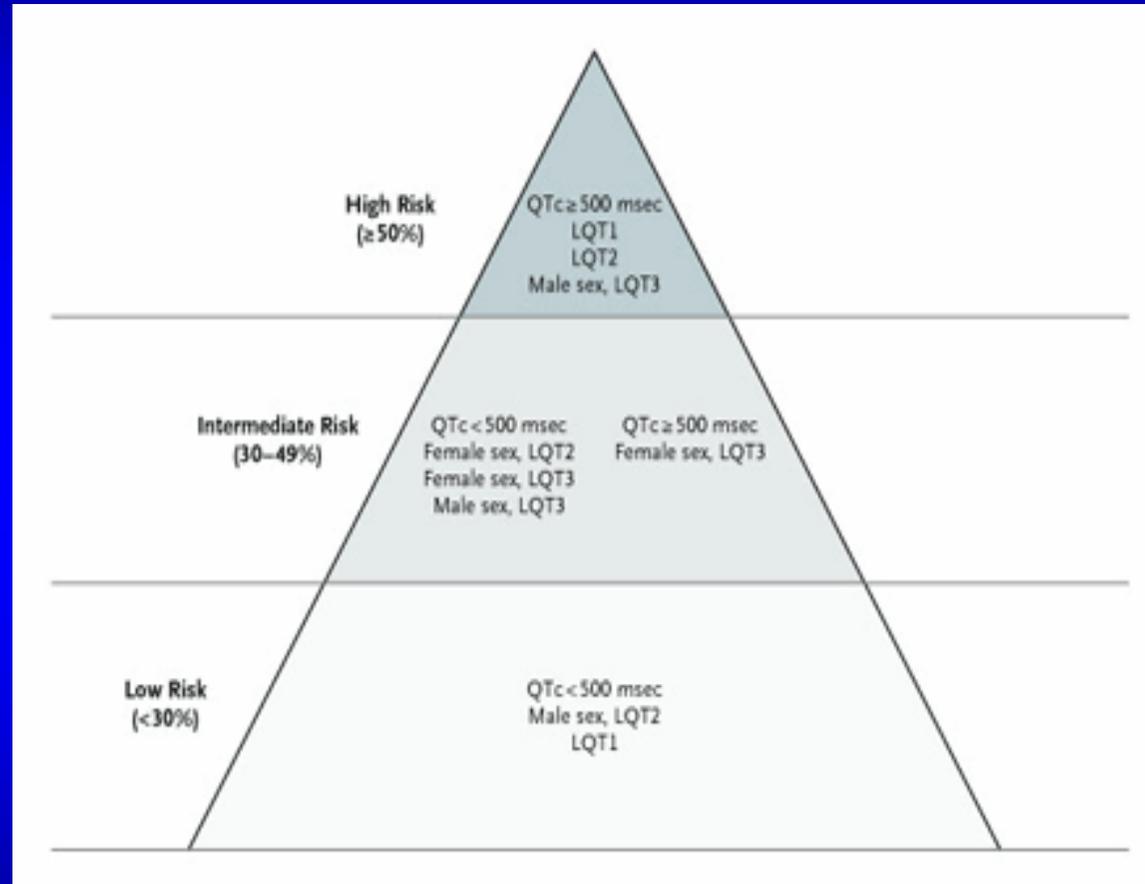




Priori et al , NEJM 2003



Priori et al , NEJM 2003



La Terapia

Anche la terapia si avvale della
tipizzazione genetica

Nessuna terapia

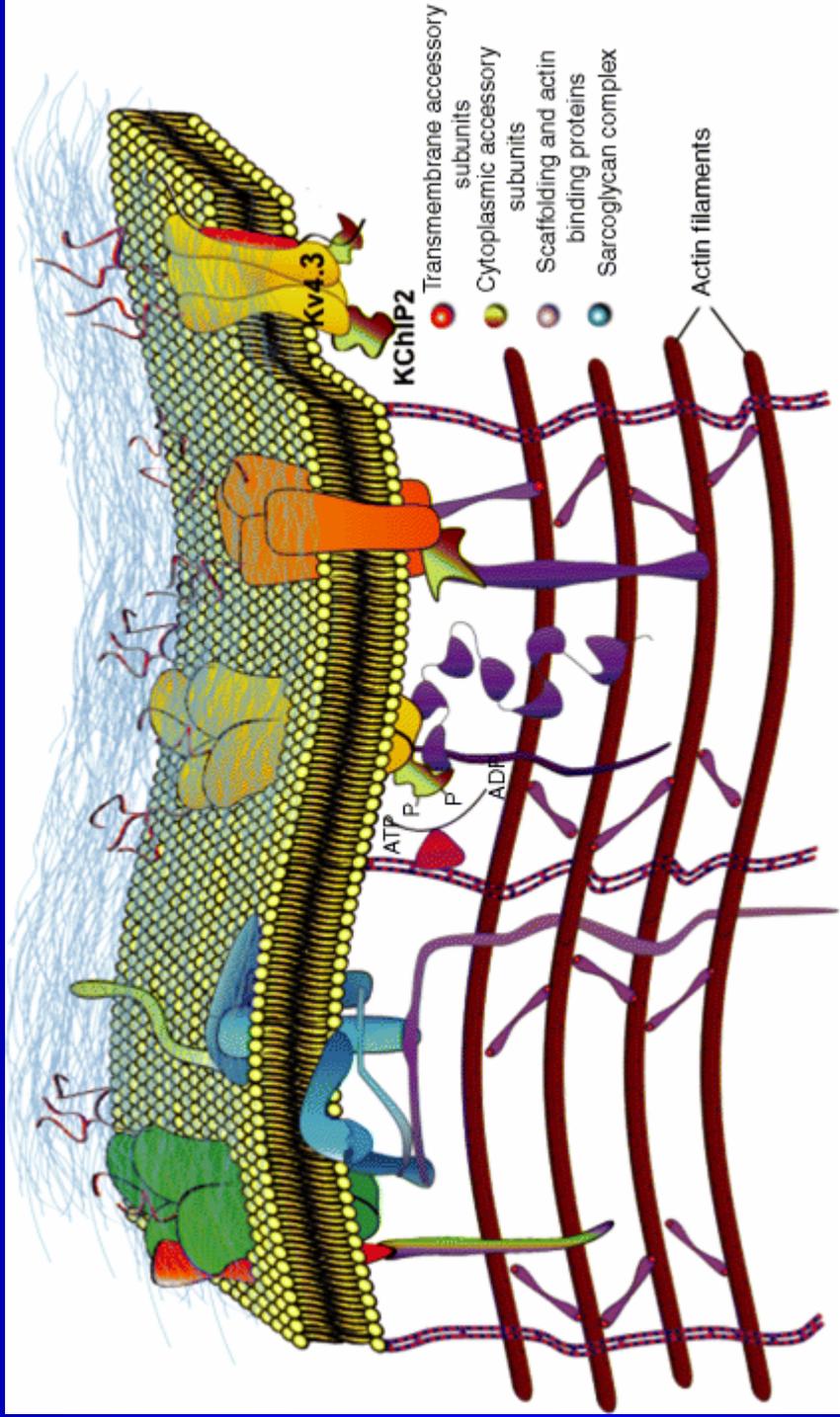
Beta bloccante

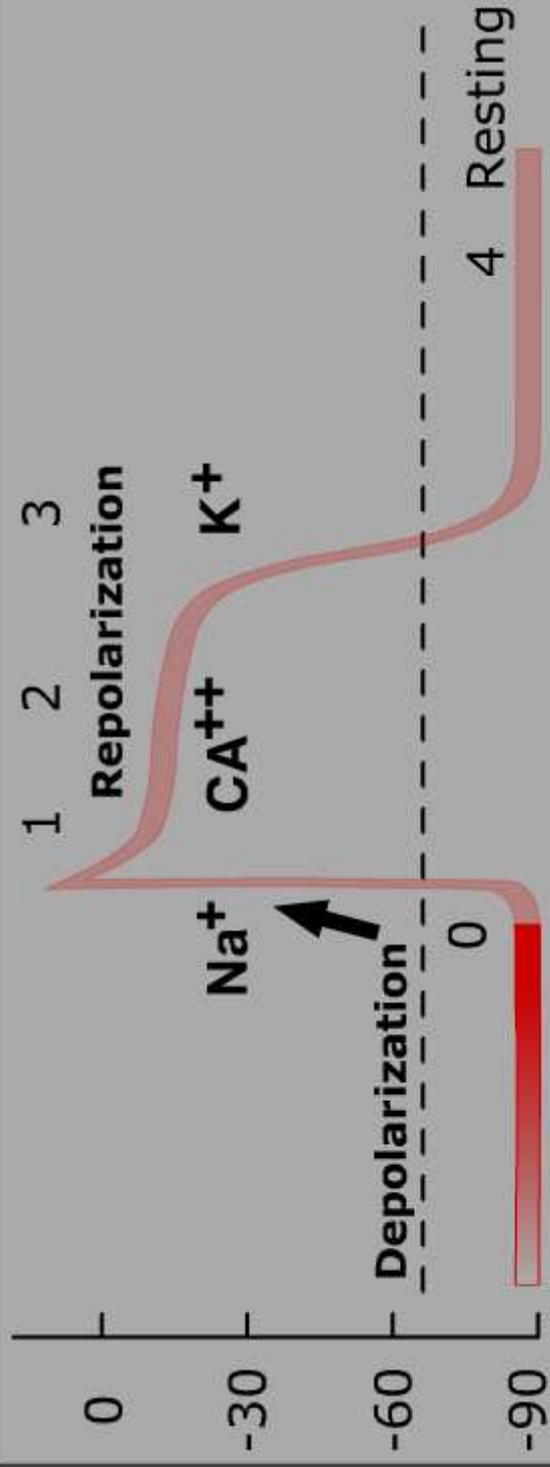
Altri farmaci

PM

ICD

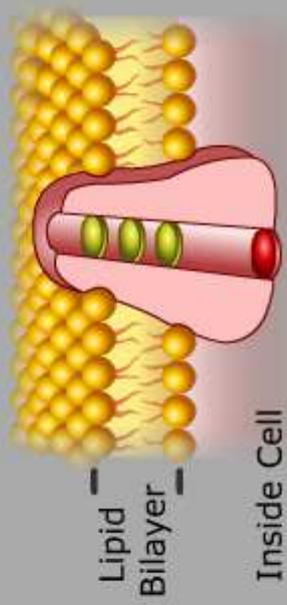




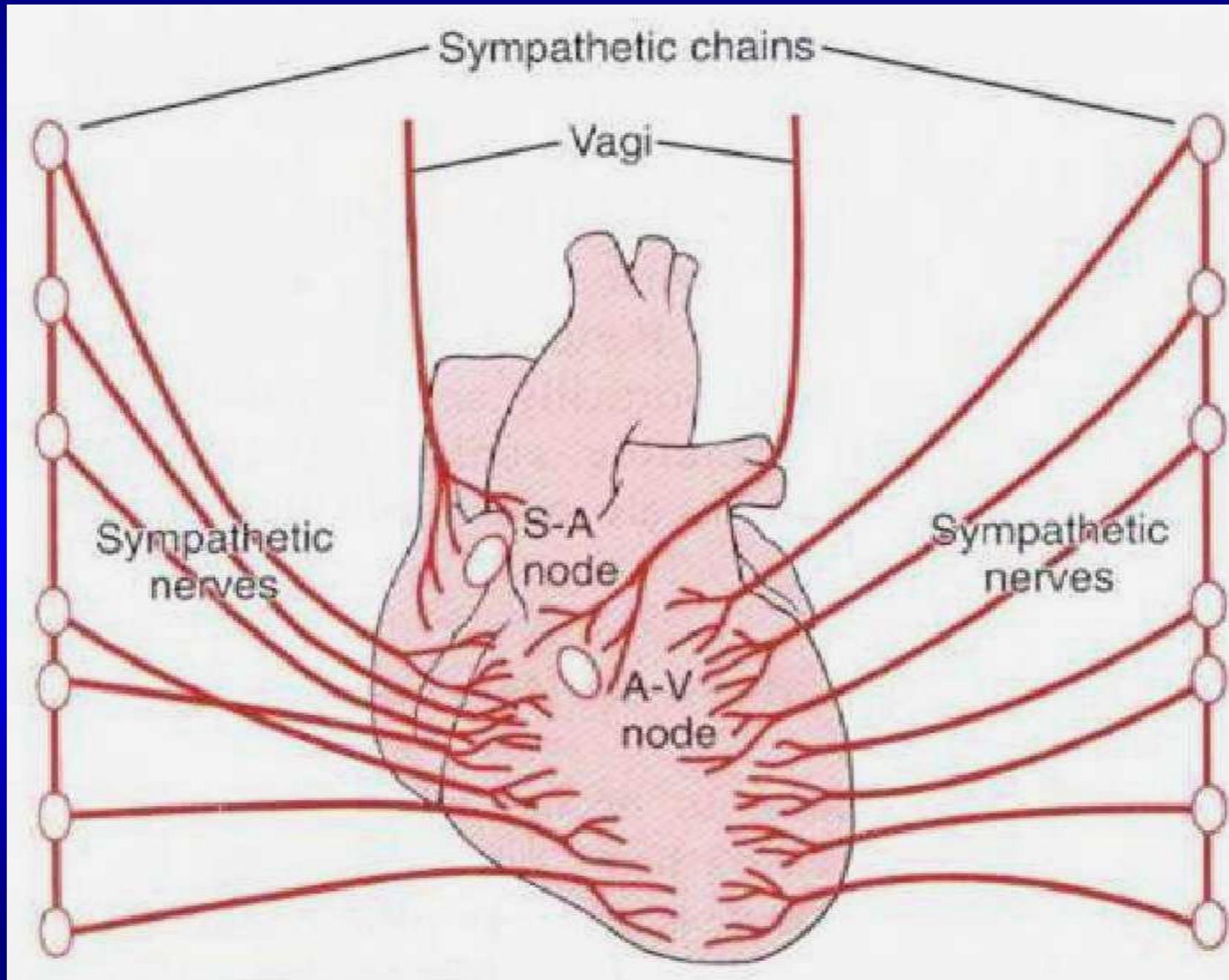


Na⁺ Outside Cell

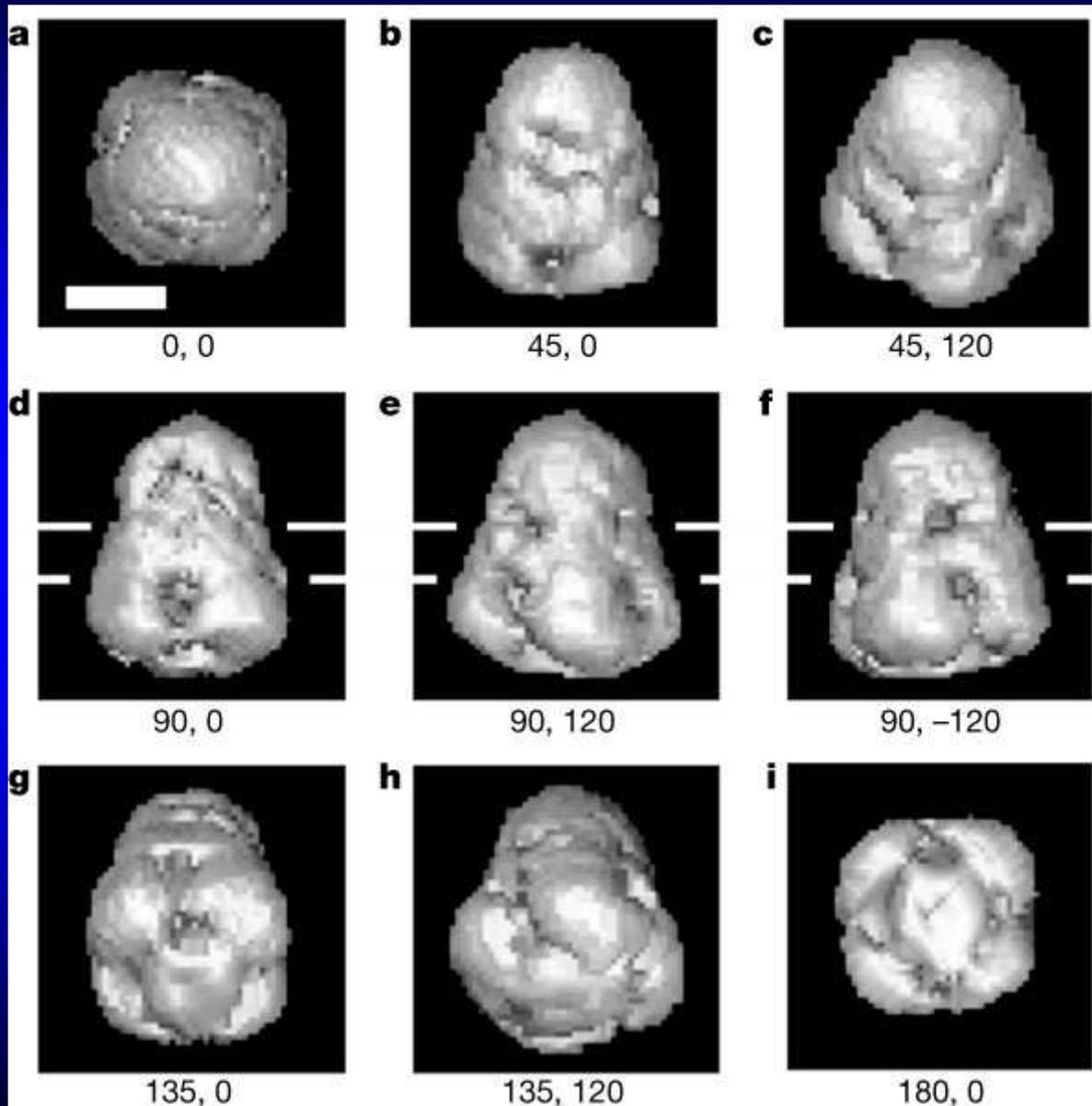
Na⁺ Sodium Channel

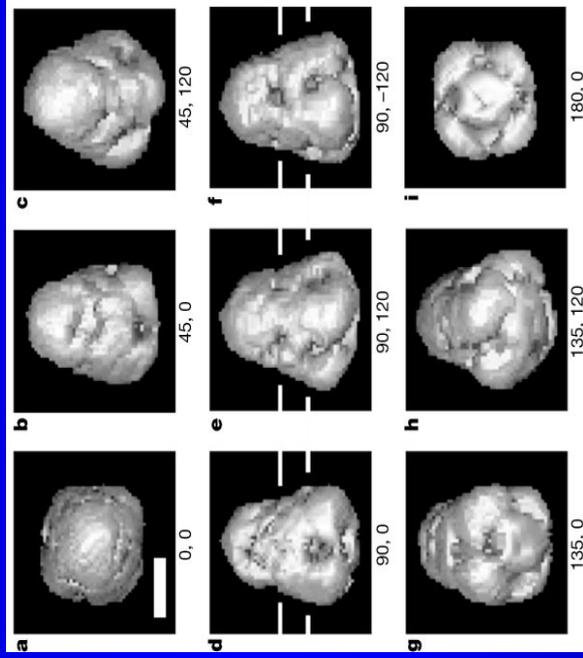
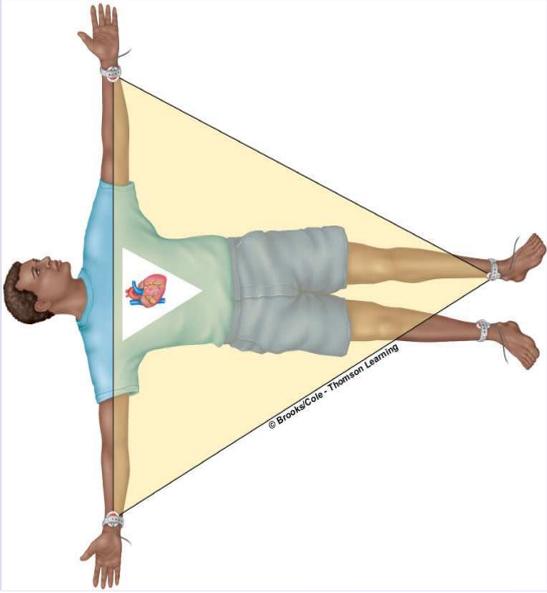


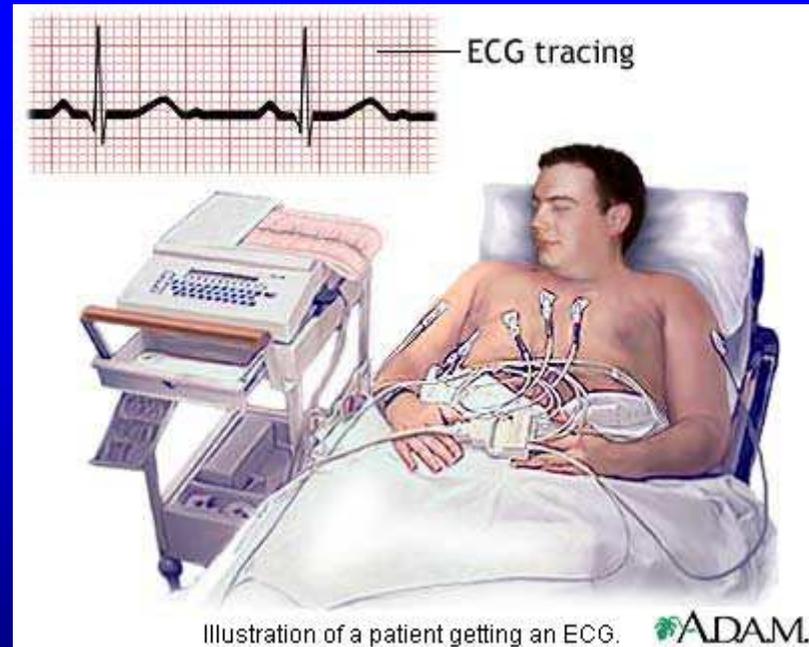
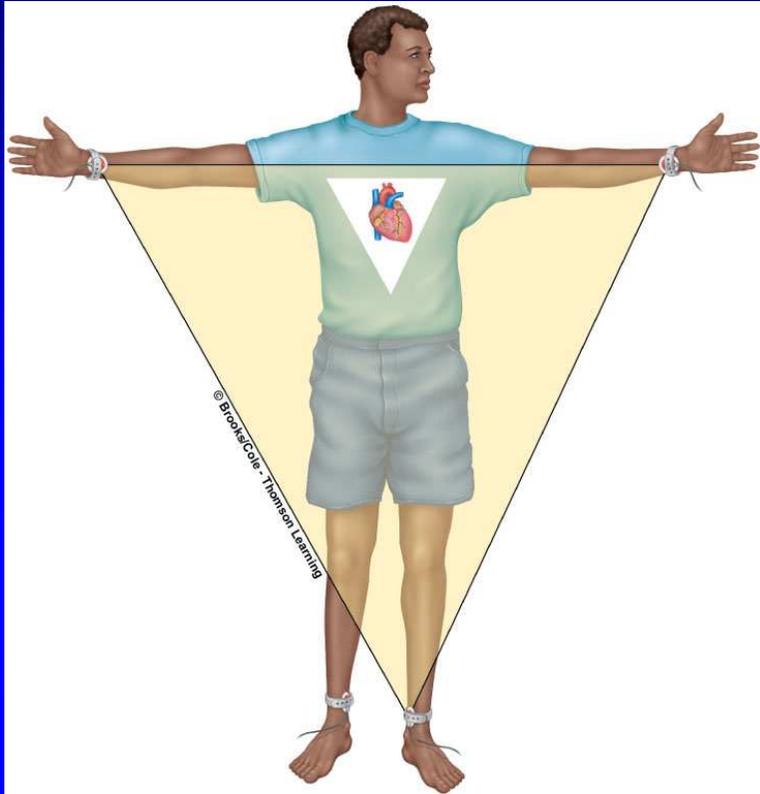
Sistema Nervoso Autonomo Cardiaco



Cryo-EM Structure of Na Channel

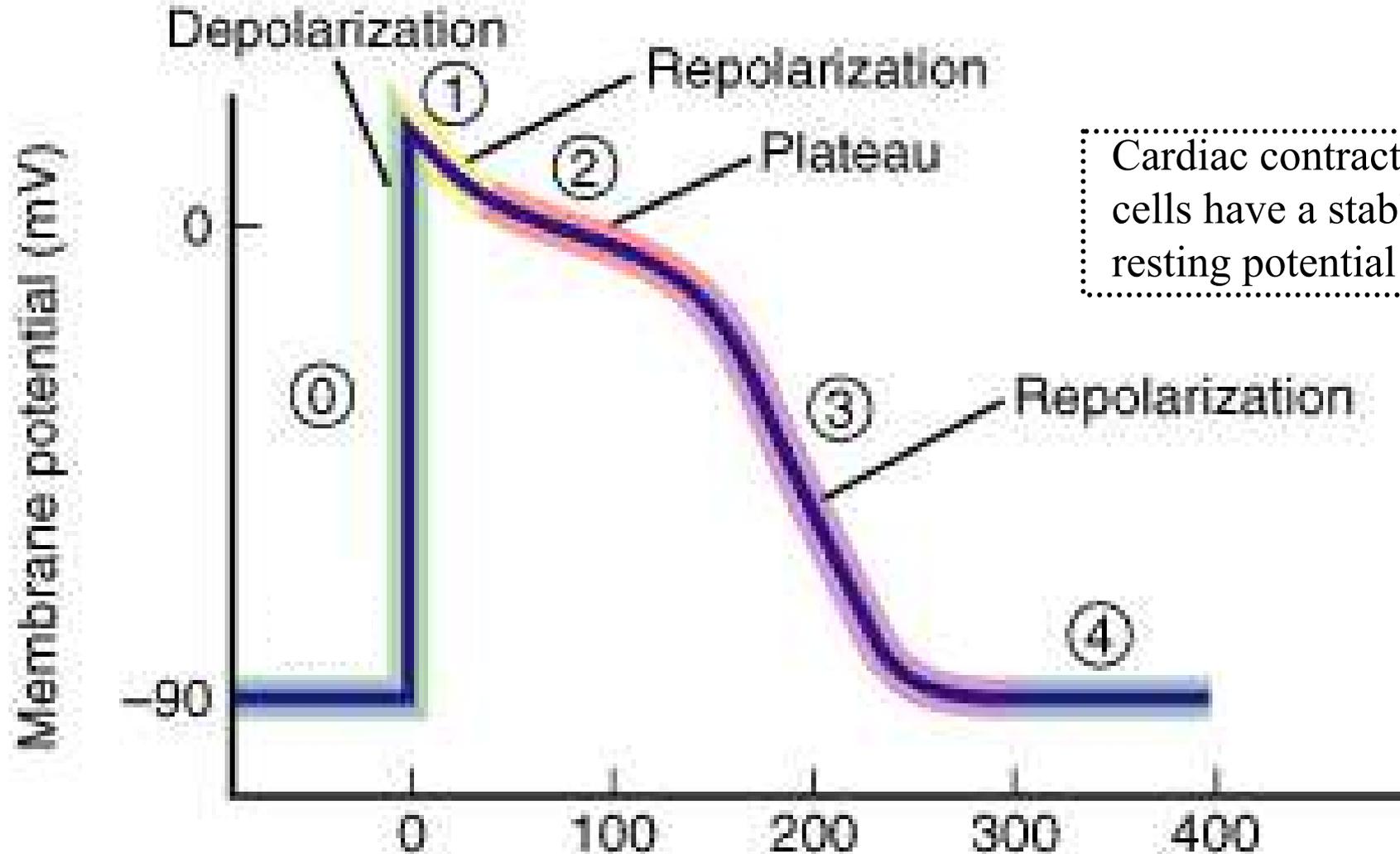




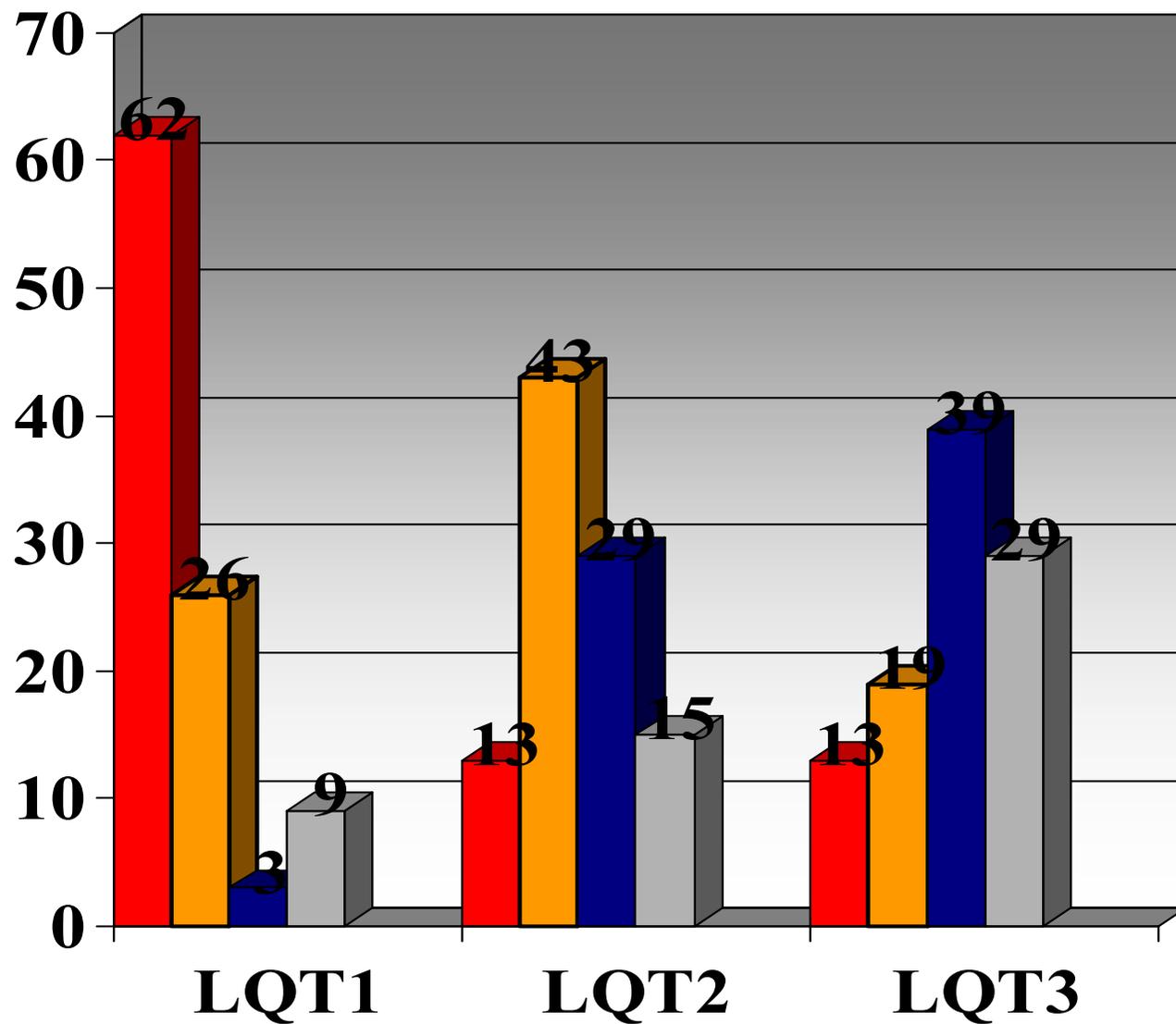


Cardiac Action Potential

Length
Plateau
 Ca^{++} (E_m and contraction)
 K^+ channel closure



Cardiac contractile cells have a stable resting potential



Potenziale d'azione cardiaco

