



Università degli Studi di Firenze



**INVECCHIAMENTO
E LONGEVITÀ:
PIÙ GENI O
PIÙ AMBIENTE**

Firenze
Palazzo dei Congressi
30 Novembre
4 Dicembre 2010

55°
CONGRESSO
NAZIONALE

SOCIETÀ ITALIANA
DI GERONTOLOGIA
E GERIATRIA

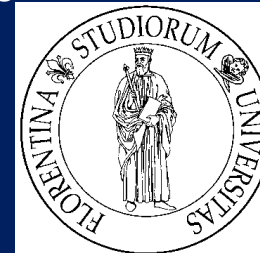
11° CORSO PER INFERMIERI
9° CORSO DI RIABILITAZIONE
8° CORSO PER PSICOLOGI
5° CORSO PER ASSISTENTI SOCIALI

PROGRAMMA AVANZATO

The poster features several images: a doctor with a stethoscope, an elderly woman, a couple jogging, a brain with red neural activity, a burger, and a DNA double helix.

La corrente tardiva del Na come nuovo target di terapia antiischemica: ruolo della ranolazina

Alessandro Mugelli*
Department of Preclinical and
Clinical Pharmacology
University of Florence
Florence (Italy)



* Disclosures: recipient of research funding by Gilead and Menarini.

Chronic stable angina

- Many patients **remain symptomatic** and at risk of major cardiac events despite optimal medical therapy and myocardial revascularization procedures¹
 - At 1 year ~10–25% of patients still have angina and 60–80% require antianginal therapy²
- In patients with comorbidities (HTA, DM, HF) it may be **difficult to uptitrate** the dose of traditional antianginal drugs
 - Dose-limiting adverse effects (i.e., hypotension, bradycardia, AVB) or associated intolerance before angina relief is achieved

(1) Gibbons RJ et al. J Am Coll Cardiol. 2003;41:159-168.

(2) Scirica, Morrow. Curr Cardiol Rep 2007; 9: 272-278

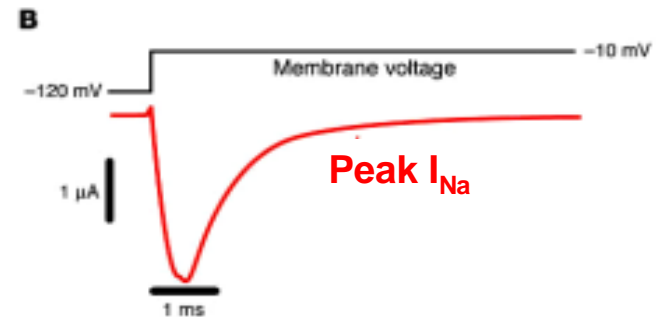
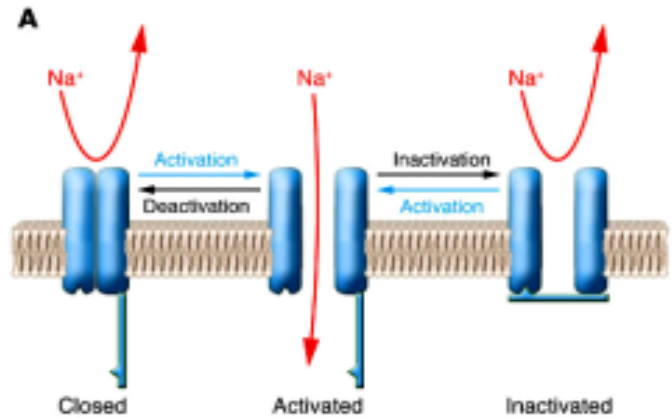
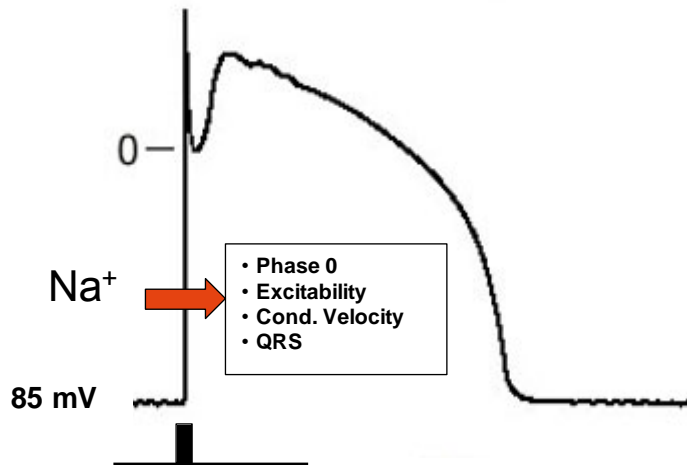
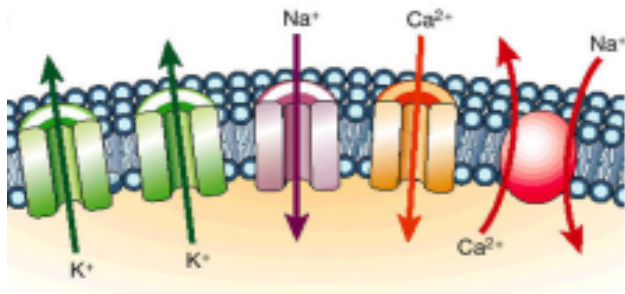
Chronic stable angina

We need new antianginal drugs with a different (and complementary) mechanism of action and without these limitations

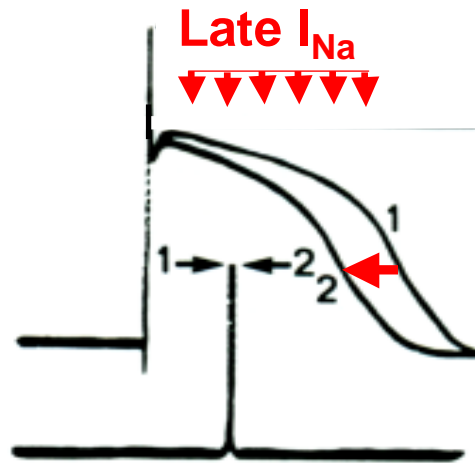
The late sodium current (late I_{Na}): A new therapeutic target in angina

1. The role of late I_{Na} under physiological conditions
2. Pathological conditions associated with an increase in late I_{Na}
3. The role of the late I_{Na} in the ischemic myocardium –
A Pathological Paradigm
4. Ranolazine, a novel antianginal and anti-ischemic agent with a **new mechanism** of action, the inhibition of the late I_{Na}

Cardiac Na⁺ channels



Tetrodotoxin, a selective blocker of Na⁺ channels, prolongs APD in Purkinje fibers at concentrations lower than those at which it inhibits the peak I_{Na}

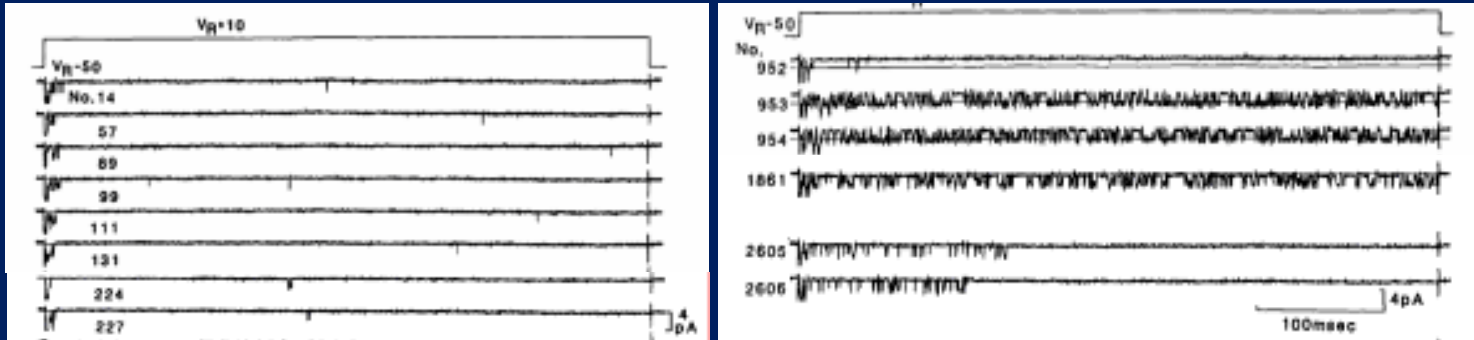


1: control. 2: TTX (0.03 μM)

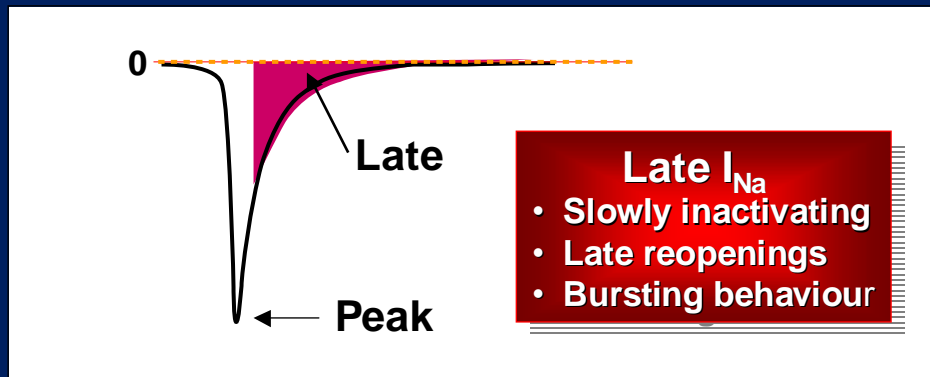
- “ The shortening was due to a TTX-sensitive **Na⁺ current flowing during the plateau** of the action potential”
- “ This current flows through a small proportion of Na⁺ channels with **no inactivation mechanism** (or inactivation different from normal), e.g. the late I_{Na}

Coraboeuf et al. Am J Physiol 1979;236:H561-H567

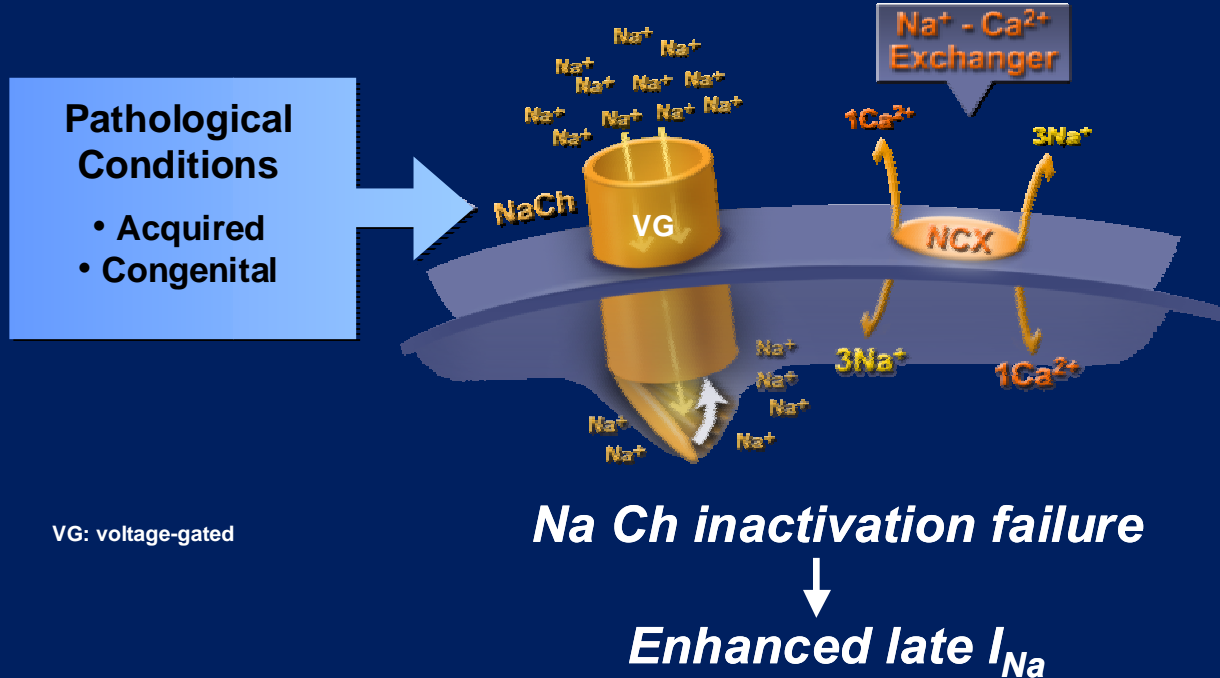
Late Na current in guinea pig ventricular myocytes



- Two types of Na⁺ channel activity: brief openings (PEAK) and sustained openings with rapid interruptions (burst type) (LATE)
- Channels that either do not close, or close and then reopen



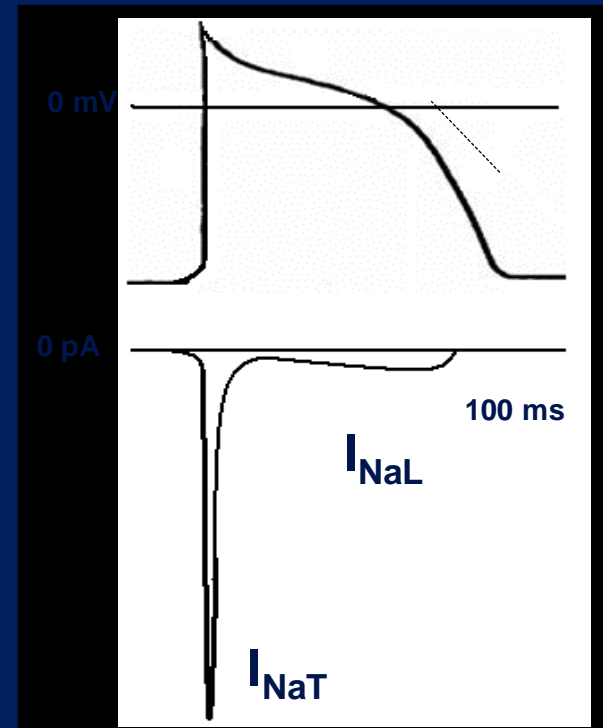
A Pathological Paradigm: Sodium Channelopathy



Role of I_{NaT} and I_{NaL} on AP

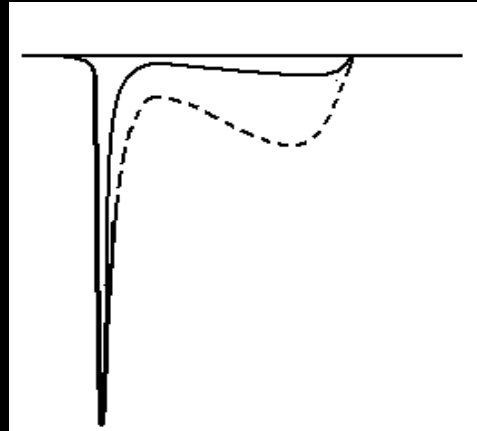
I_{NaT} : source of charges
for conduction

I_{NaL} : contributes to
the plateau phase

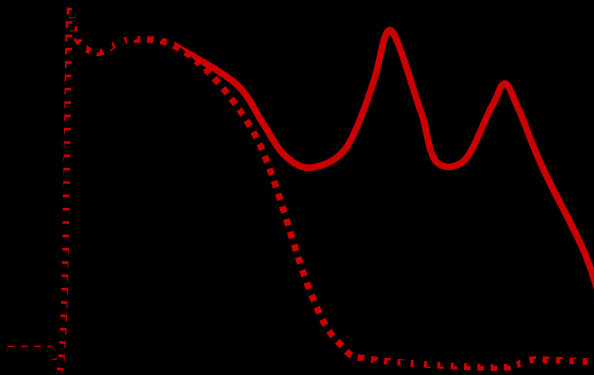


When I_{NaL} increases

↑ APD (QT)



↑ Na^+ influx



If I_{NaL} increases.....

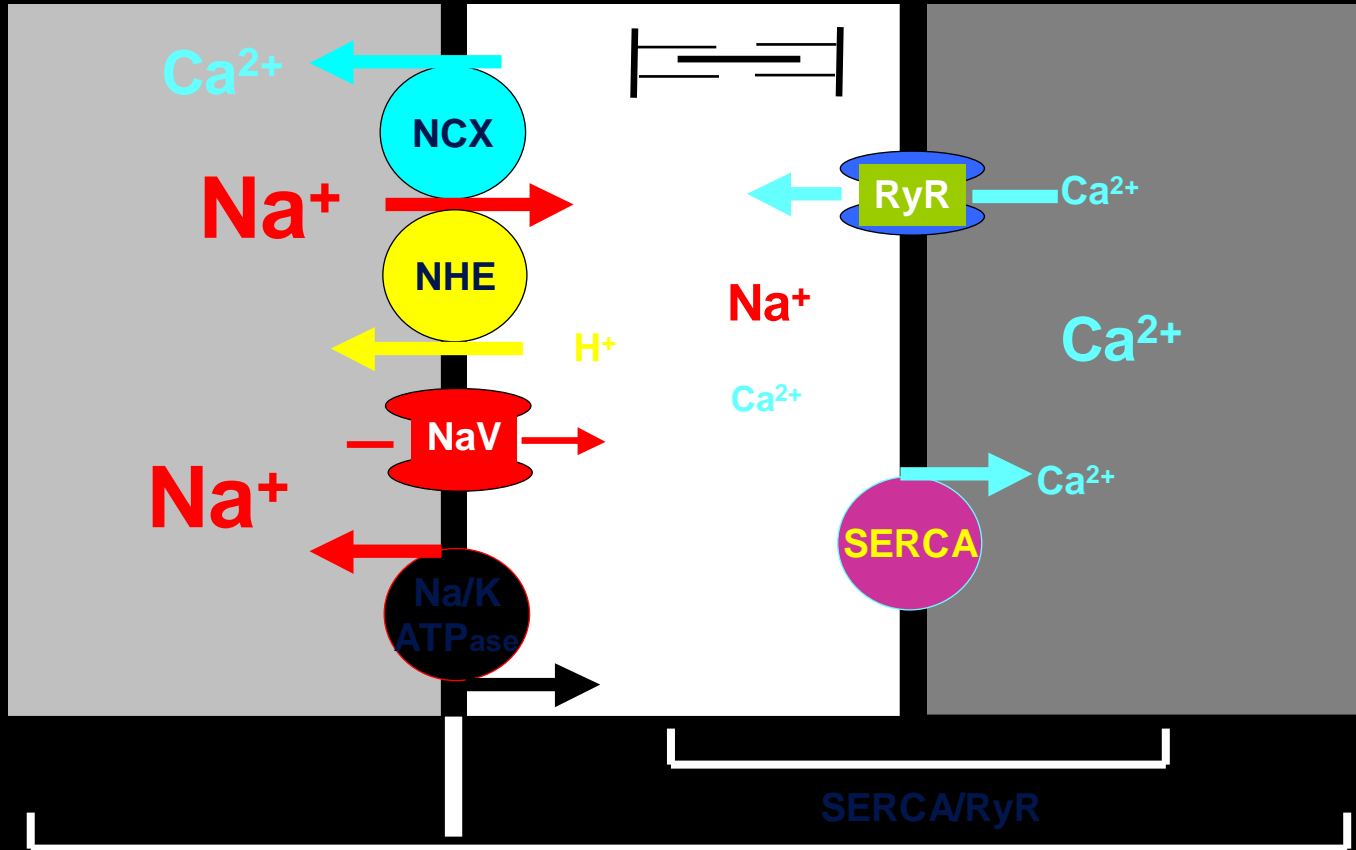
**Na⁺ entry into the cell
increases.....**

EXTRACELLULAR

INTRACELLULAR

CYTOSOL

SR LUMEN



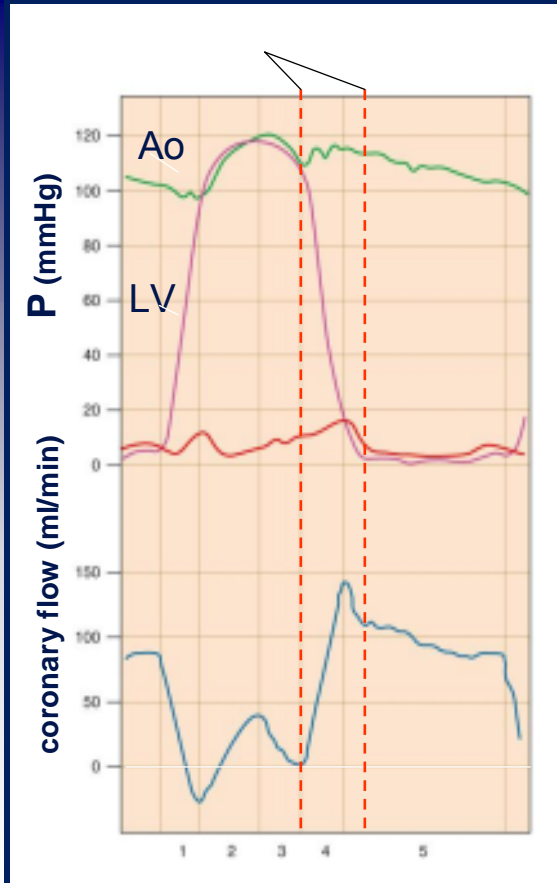
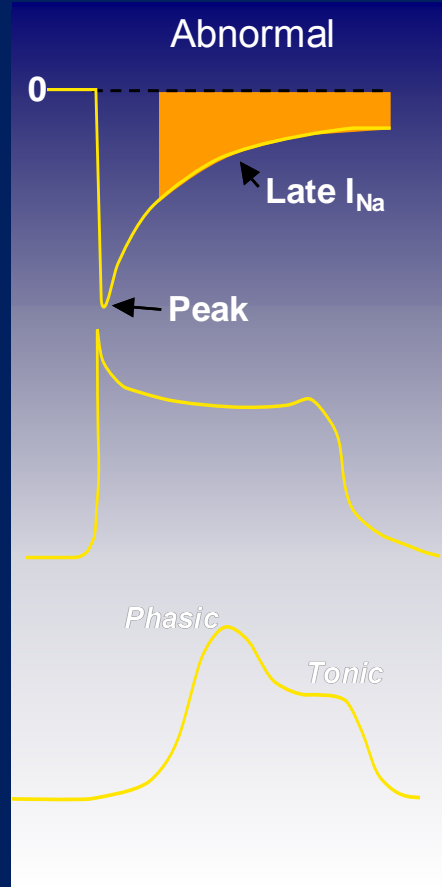
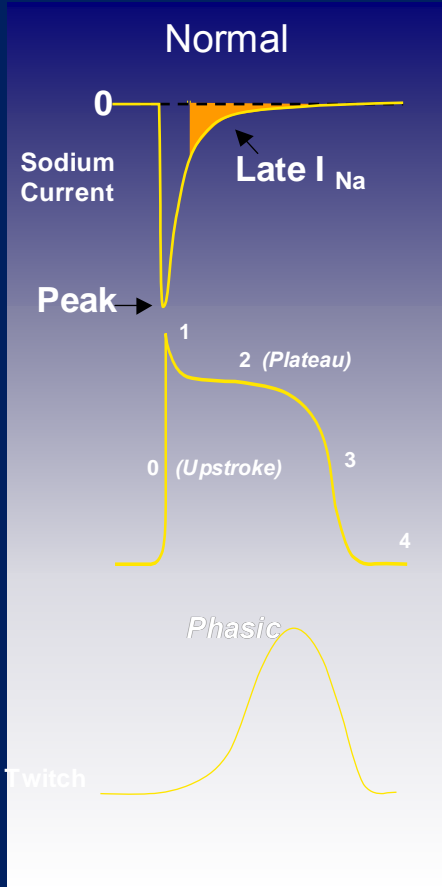
Na⁺ in/out

SERCA/RyR

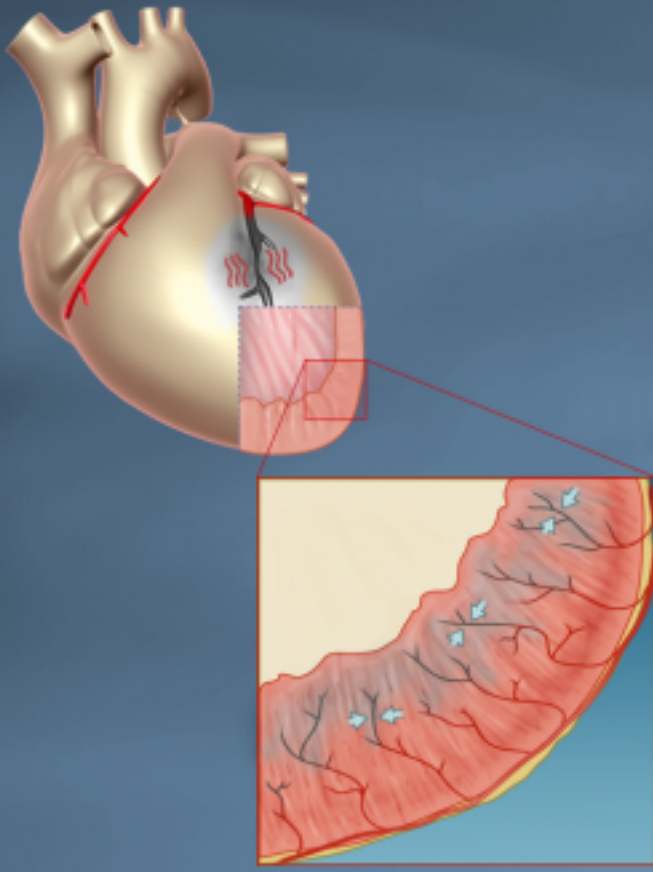
If I_{NaL} increases....

Ca²⁺ and H⁺ homeostasis is altered

L'aumento di I_{NaL} rallenta il rilassamento

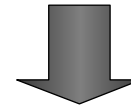


Diastolic relaxation failure increases O_2 consumption and reduces O_2 supply



Na^+ and Ca^{2+} overload Increased wall tension during diastole:

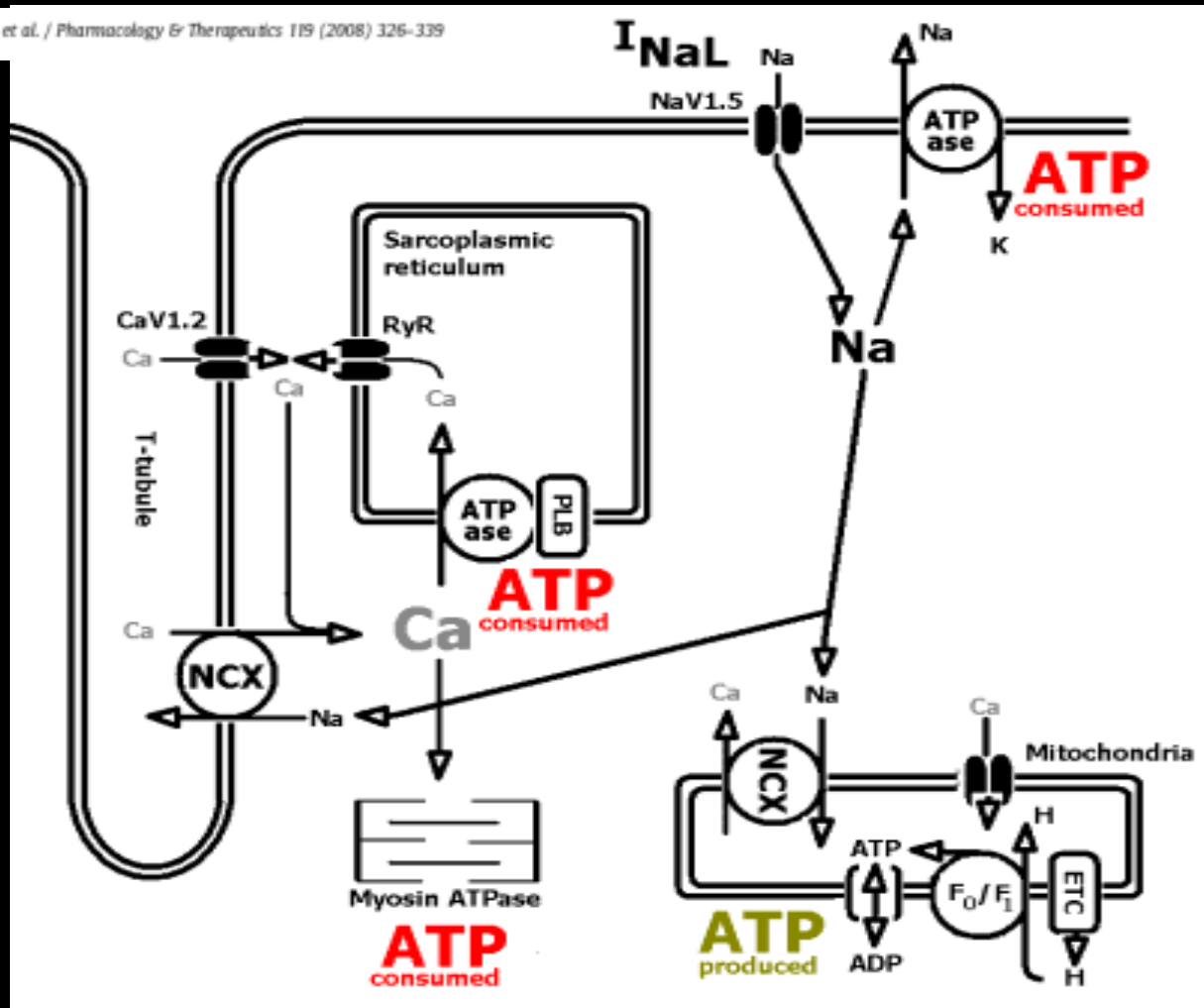
- Increases MVO_2
- Compresses intramural small vessels
- Reduces myocardial blood flow (subendocardium)



Worsens ischemia and angina

L'aumento di $[Na^+]_{cit}$ altera il bilancio energetico

A. Zaza et al. / Pharmacology & Therapeutics 119 (2008) 326-339



↓ Oxygen Supply / Demand

Ischemia

(Hypoxia, Ischemic metabolites, acidosis, and ROS)

↑ O₂ Consumption
↓ O₂ Supply

↑ Late I_{Na}

Vicious Cycle

↑ [Na⁺]_i

Contracture
(↑ LVEDP)

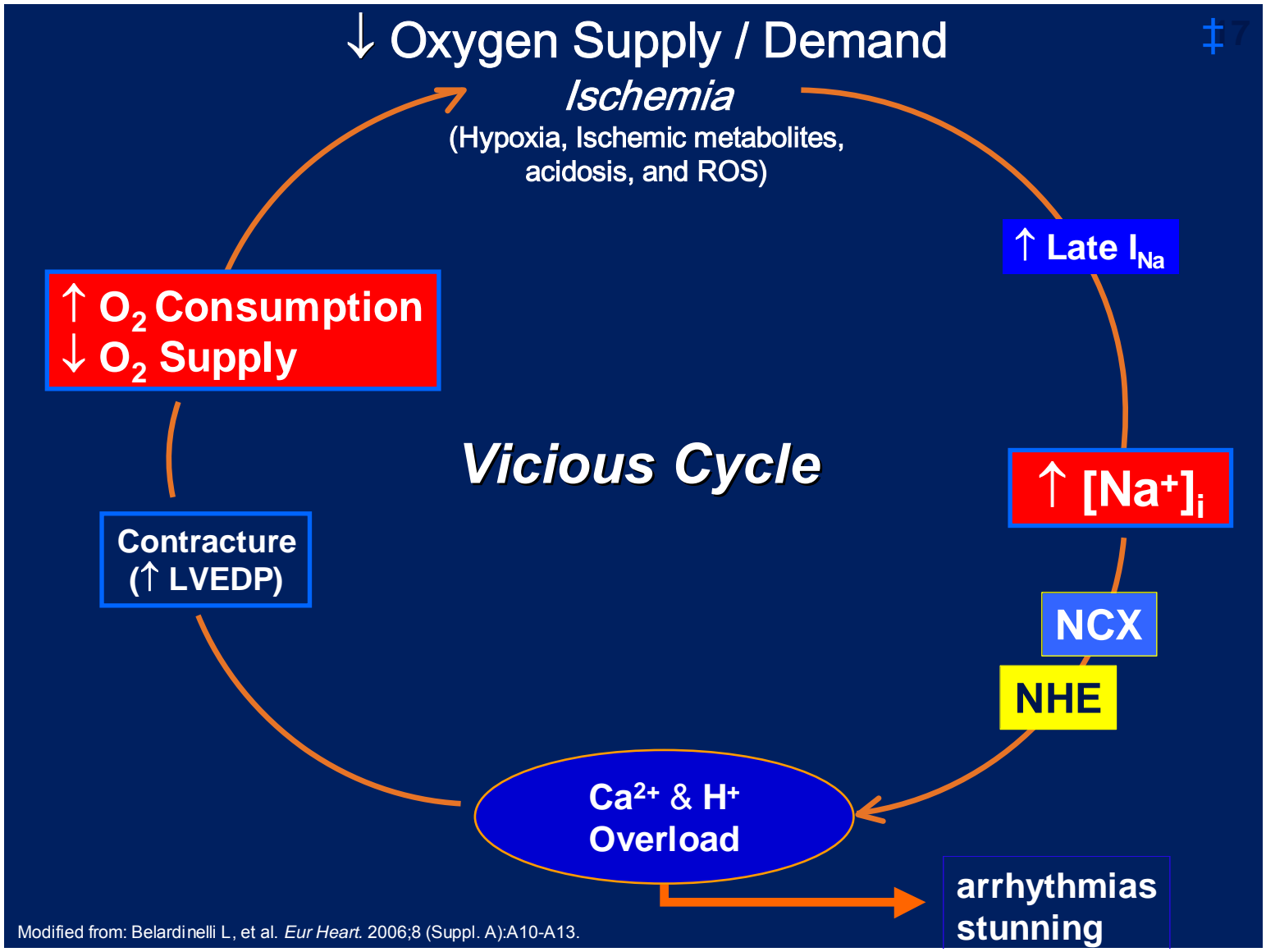
NCX

NHE

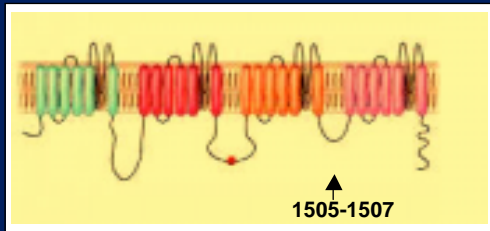
Ca²⁺ & H⁺ Overload

arrhythmias
stunning

Modified from: Belardinelli L, et al. *Eur Heart.* 2006;8 (Suppl. A):A10-A13.



Late I_{Na} is involved in the Long QTS



Δ KPQ: deletion of residues 1505 to 1507 in III-IV linker of NaCh (inactivation gating process)
K = lysine, P = proline, Q = glutamine

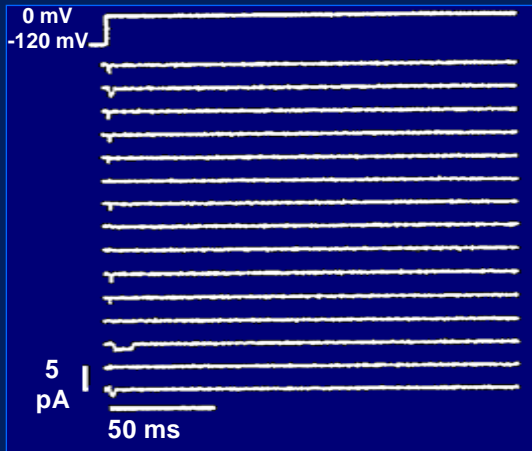
	Gene	Channel
LQT1	KCNQ1, KvLQT1	$\downarrow I_{Ks}$
LQT2	KCNH2, HERG	$\downarrow I_{Kr}$
LQT3	KCNQ1, KvLQT1	\uparrow Late I_{Na}
LQT4	KCNH2, HERG	$\uparrow Ca_i$, \uparrow Late I_{Na} ?
LQT5	KCNE1, minK	$\downarrow I_{Ks}$
LQT6	KCN2, MiRP1	$\downarrow I_{Kr}$
LQT7*	KCNJ2, Kir2.1	$\downarrow I_{K1}$
LQT8**	CACNA1C, $Ca_v1.2$	$\uparrow I_{Ca}$
LQT9	CAV3, Caveolin-3	\uparrow Late I_{Na}
LQT10	SCN4B, NavB4	\uparrow Late I_{Na}
LQT11	AKAP9, Yotiao	$\downarrow I_{Ks}$
LQT12	SNTA1, α -1 Syntrophin	\uparrow Late I_{Na}

* Andersen—Tawil Syndrome

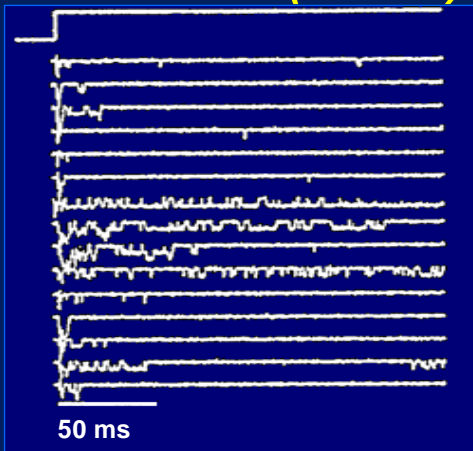
** Timothy Syndrome

Normal vs. Enhanced Late Sodium Current

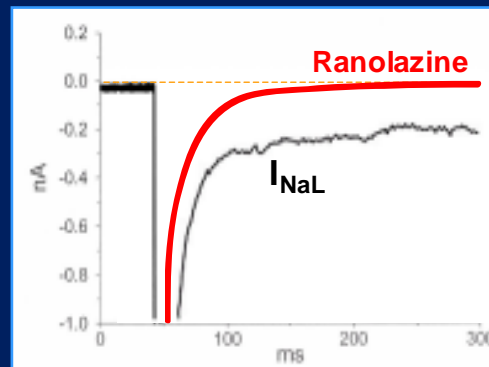
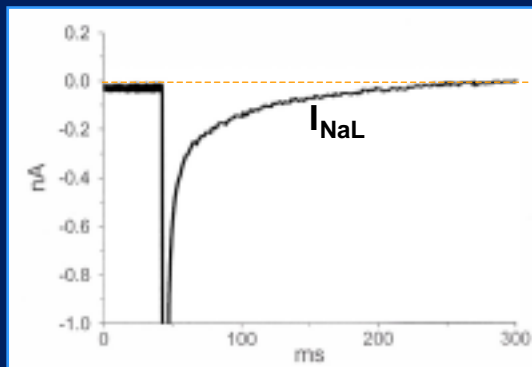
Normal



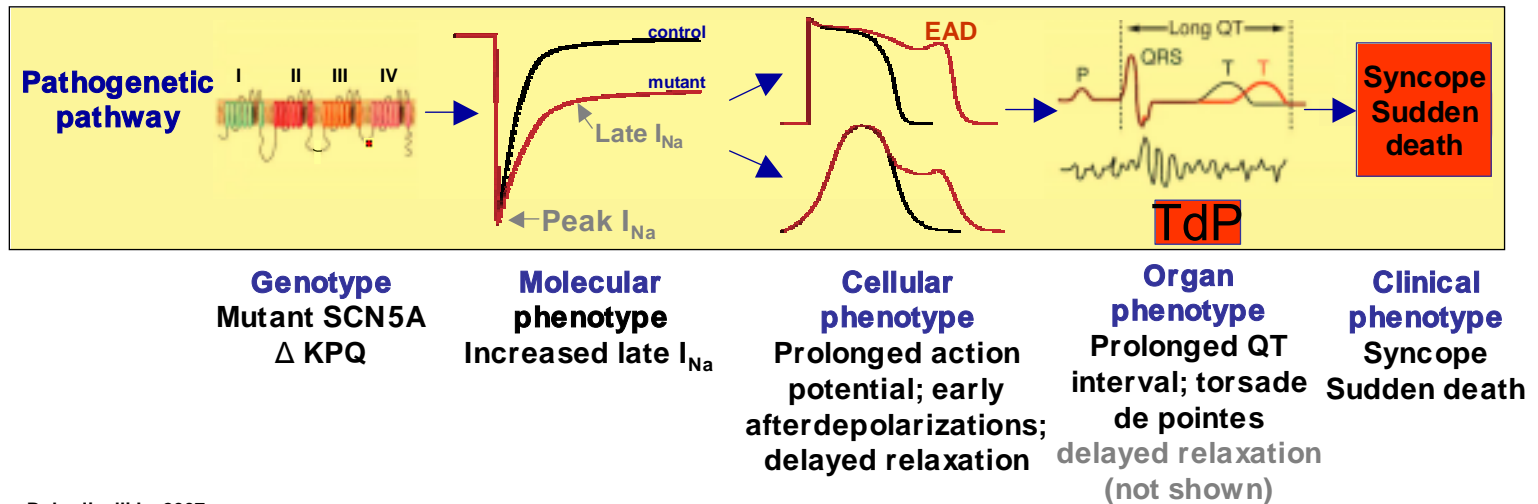
Enhanced (Δ KPQ)



Late openings of individual channels lead to increased whole cell macroscopic late I_{Na}

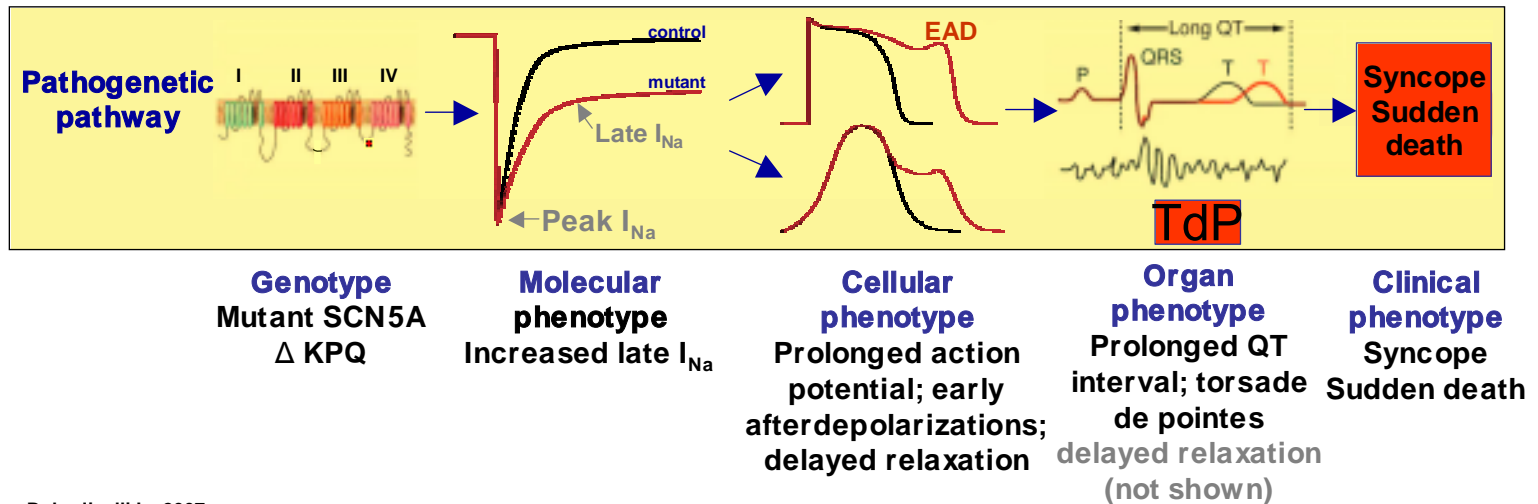


- LQT3 syndrome is a monogenetic disorder characterized by an abnormally prolonged QT interval and by life-threatening arrhythmias.



Effect of Ranolazine in the Congenital Long-QT Syndrome Type 3 Patients

- LQT3 syndrome is a monogenetic disorder characterized by an abnormally prolonged QT interval and by life-threatening arrhythmias.



Effect of Ranolazine in the Congenital Long-QT Syndrome Type 3 Patients



NIH Public Access

Author Manuscript

J Cardiovasc Electrophysiol. Author manuscript; available in PMC 2009 January 6.

Published in final edited form as:

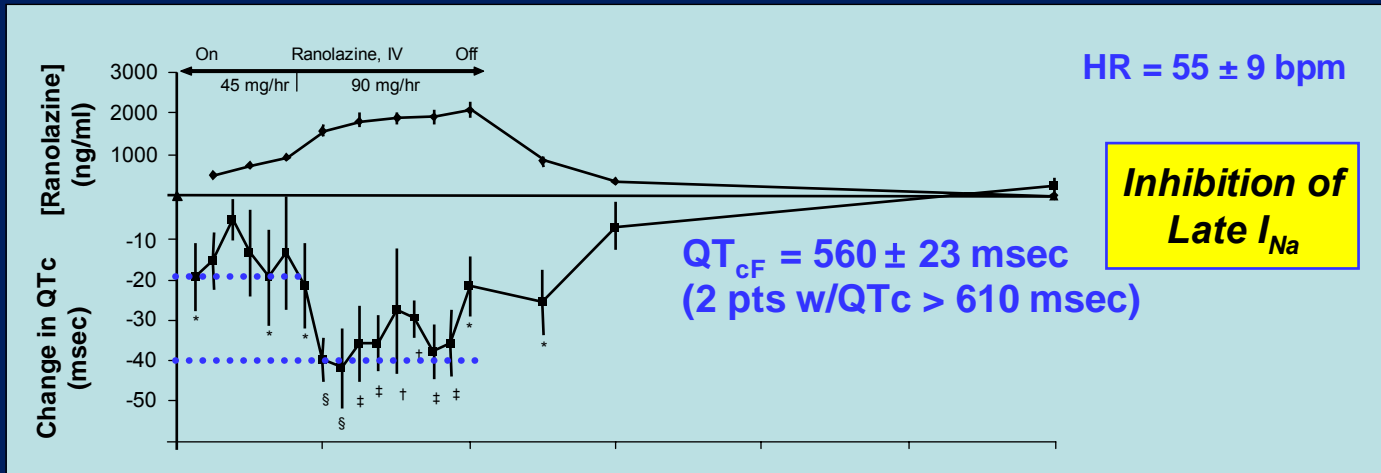
J Cardiovasc Electrophysiol. 2008 December ; 19(12): 1289–1293. doi:10.1111/j.1540-8167.2008.01246.x.

Ranolazine Shortens Repolarization in Patients with Sustained Inward Sodium Current Due To Type-3 Long QT Syndrome

Arthur J. Moss, MD, Wojciech Zareba, MD, PhD, Karl Q. Schwarz, MD, Spencer Rosero, MD, Scott McNitt, MS, and Jennifer L. Robinson, MS

From the Cardiology Division of the Department of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, NY

Ranolazine Is a Selective Late I_{Na} Inhibitor in Human Heart of LQT3 Patients



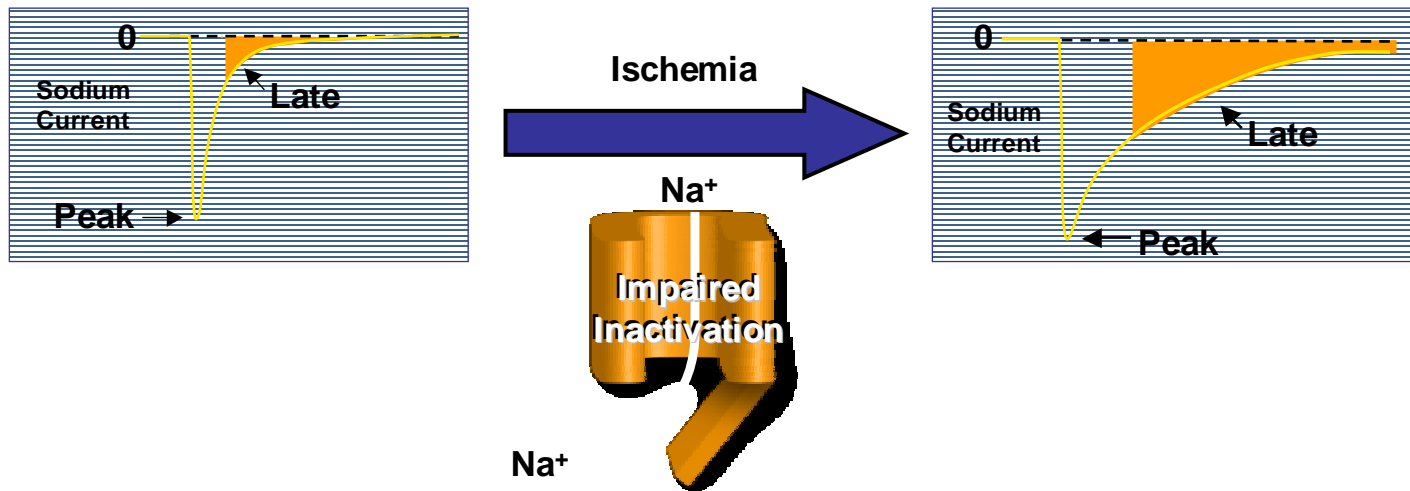
In humans ranolazine at therapeutic plasma levels inhibits late I_{Na} (\downarrow QTc) but does not inhibit $I_{Ca,L}$ or peak I_{Na} (no effect on P-R or QRS intervals)

¹ QTc (Fridericia) change from baseline

² Δ KPQ

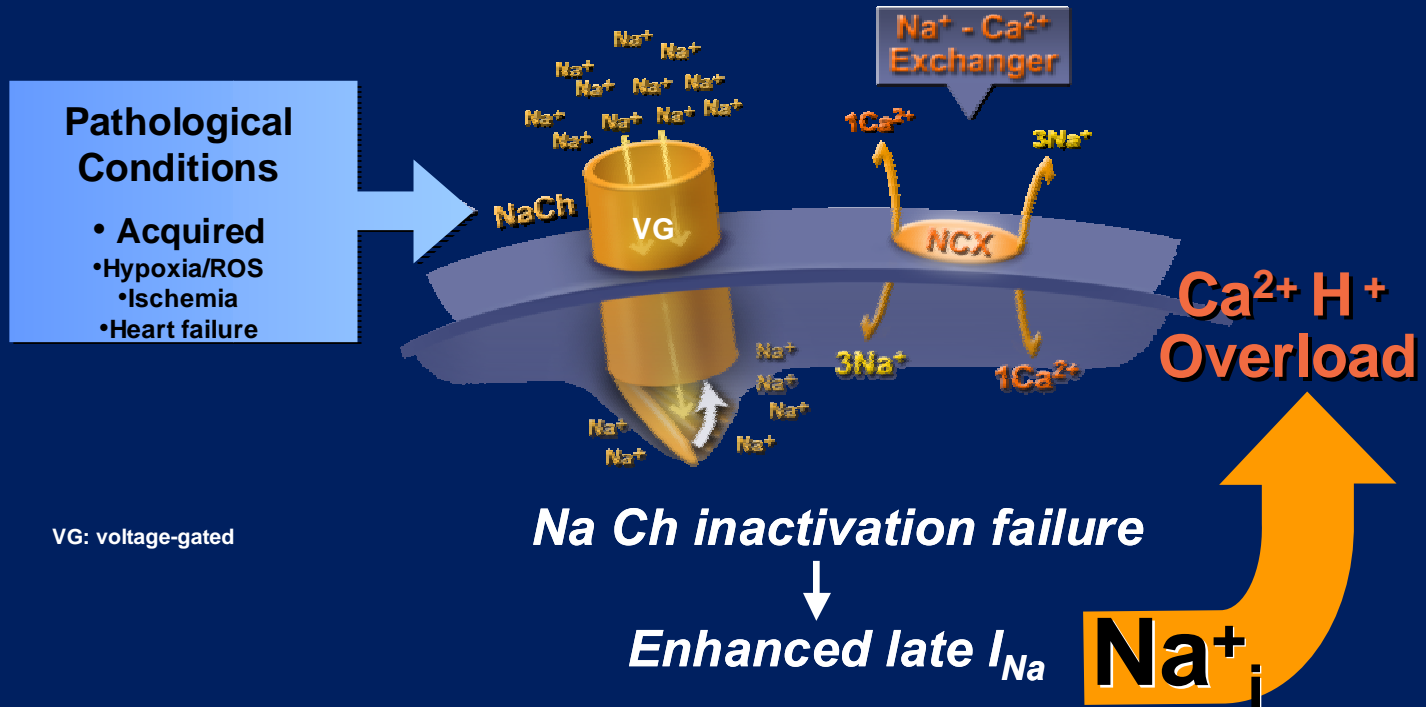
Role of the late I_{Na} in ischemia

Myocardial ischemia causes enhanced late I_{Na}



Adapted from Belardinelli L et al. *Eur Heart J Suppl.* 2006;(8 suppl A):A10-13.
Belardinelli L et al. *Eur Heart J Suppl.* 2004;6(suppl I):13-7.

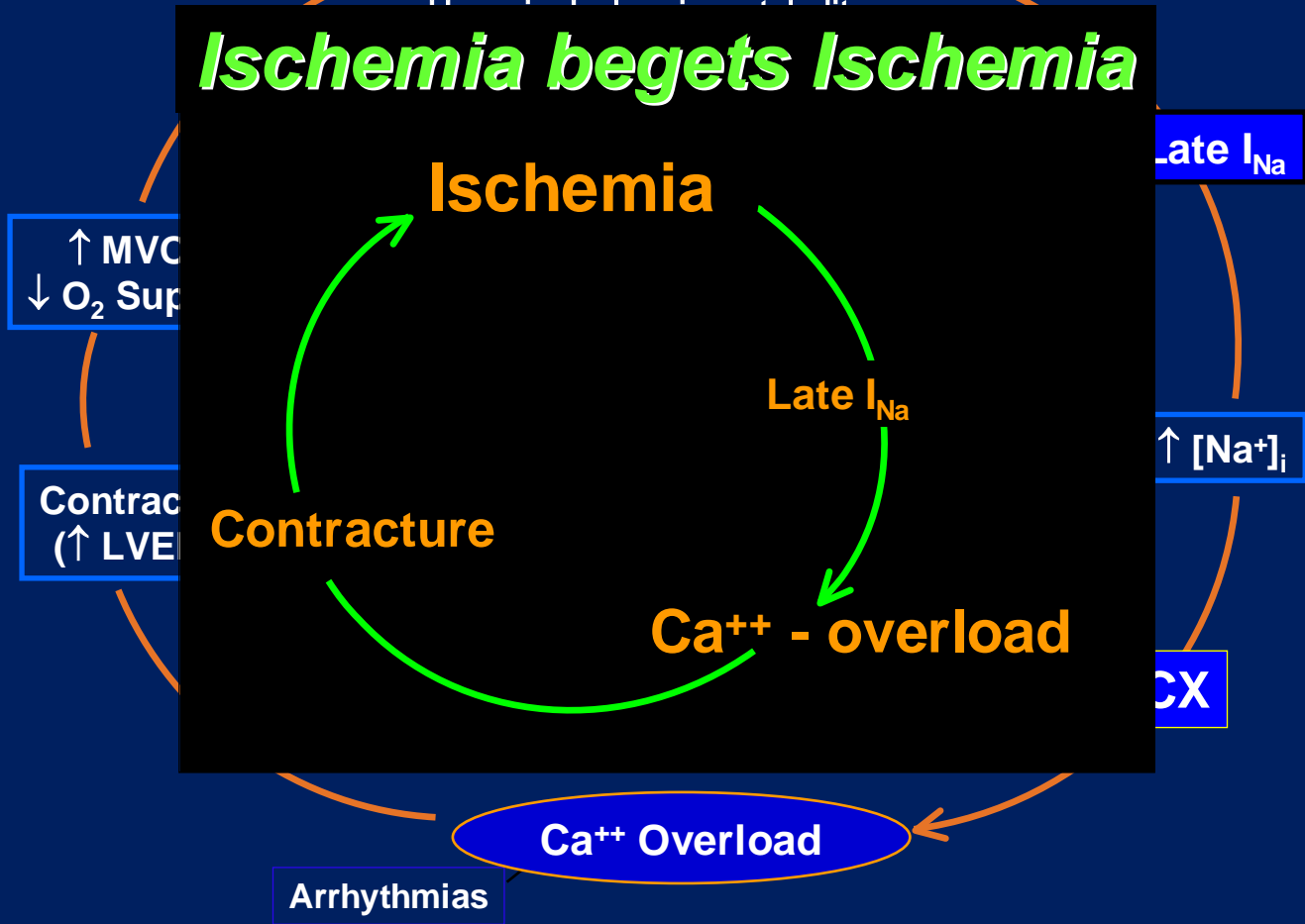
A Pathological Paradigm: Sodium Channelopathy



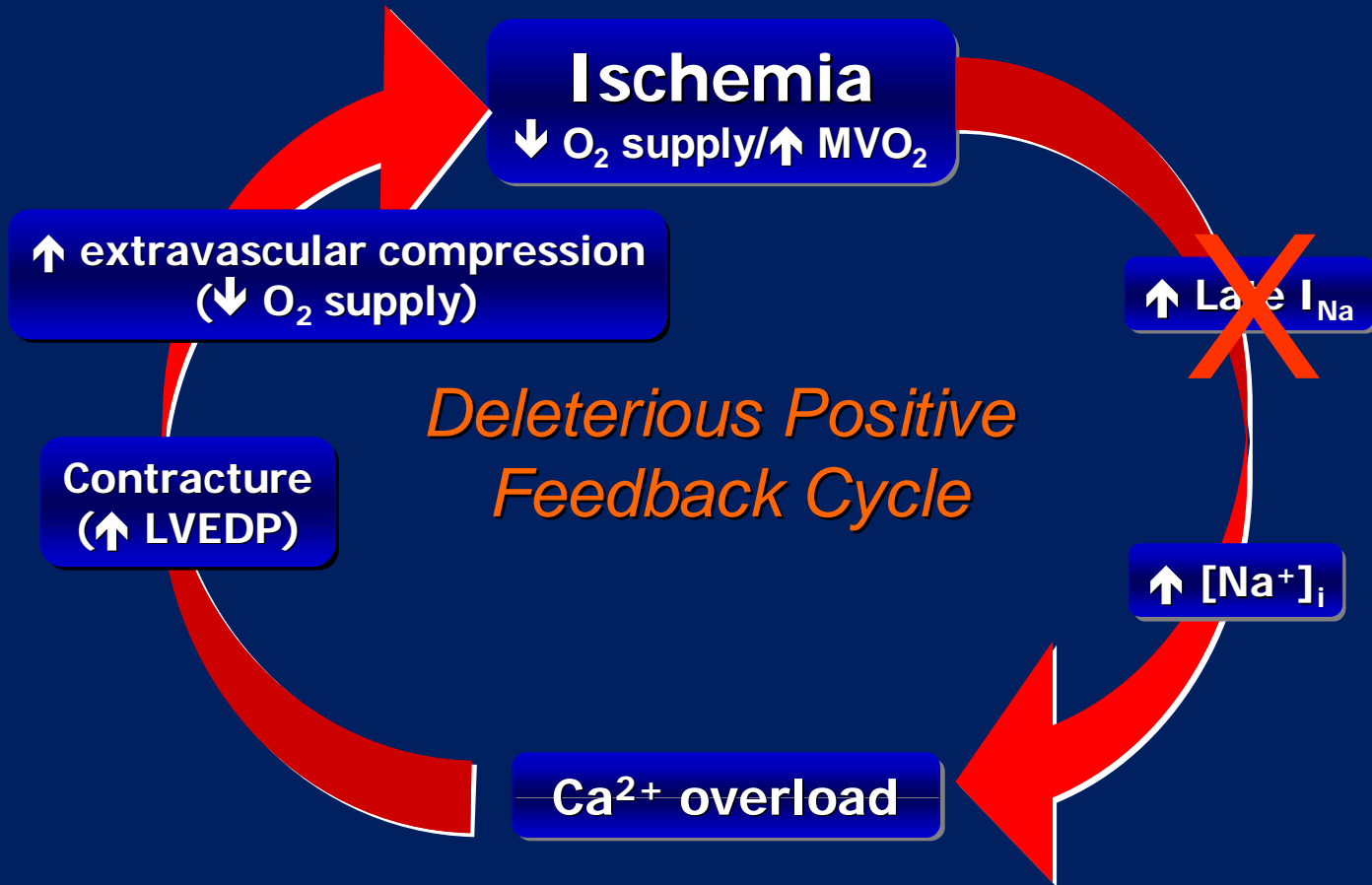
↓ Oxygen Supply: Demand

Ischemia

Ischemia begets Ischemia



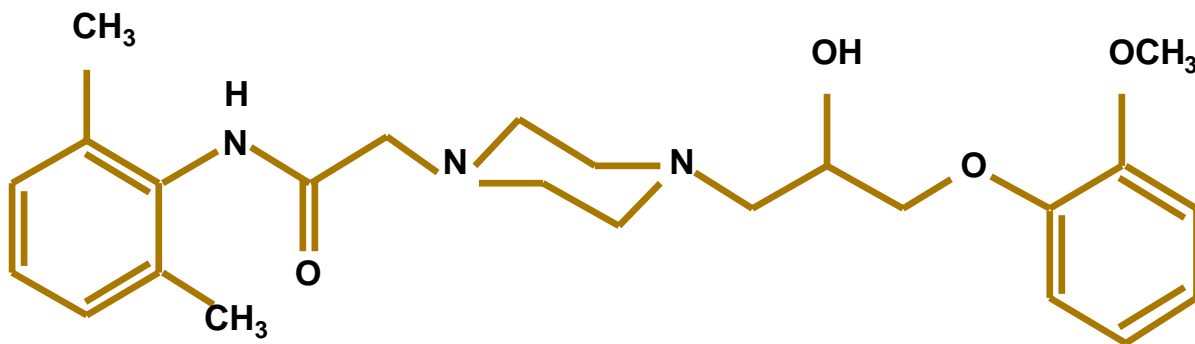
28 **Positive feedback during ischaemia increases the imbalance between myocardial O₂ supply and demand**



Ranolazine

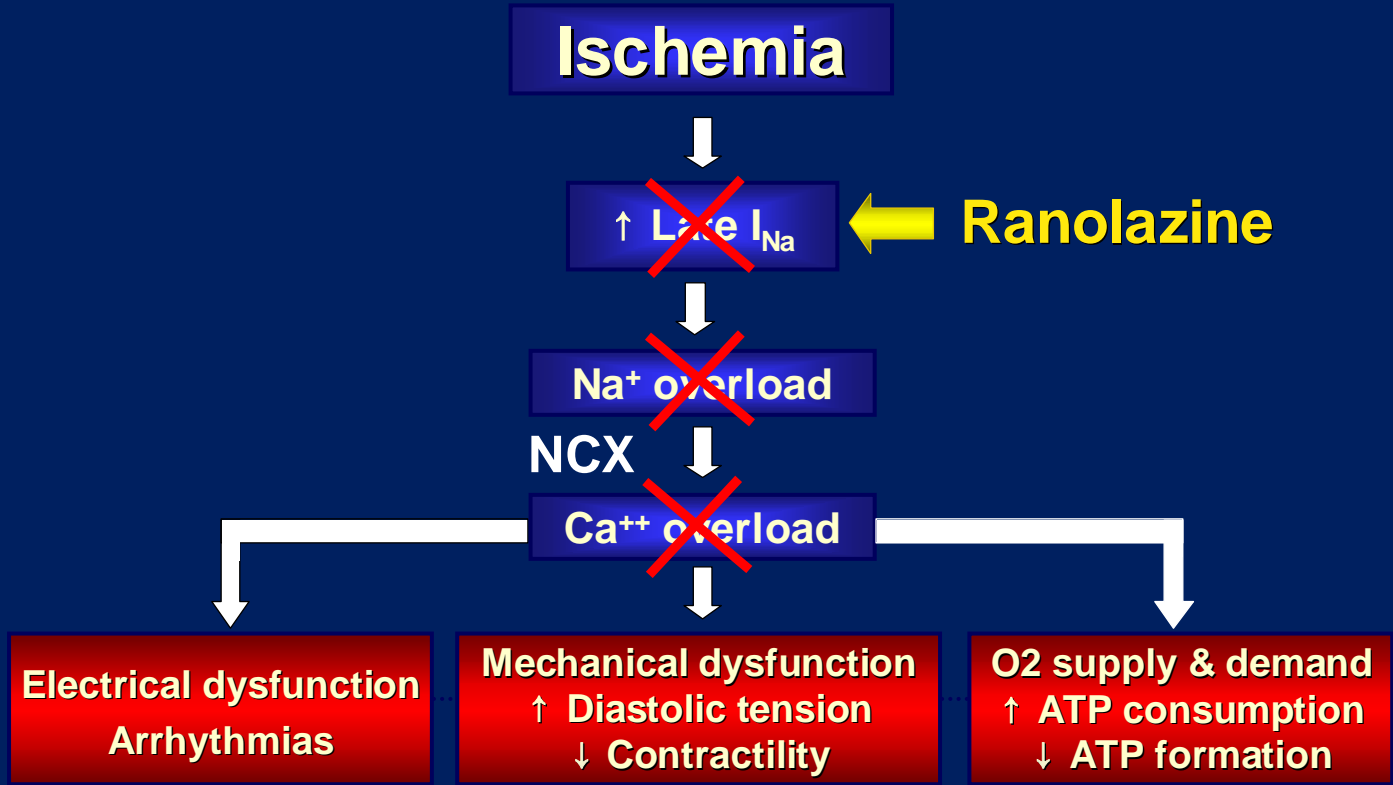
First “**SELECTIVE Late cardiac sodium current (I_{Na})**” inhibitor

A NEW CLASS OF ANTI-ANGINAL AGENTS



Film-coated prolonged release tablets containing
375 mg, 500 mg or 750 mg

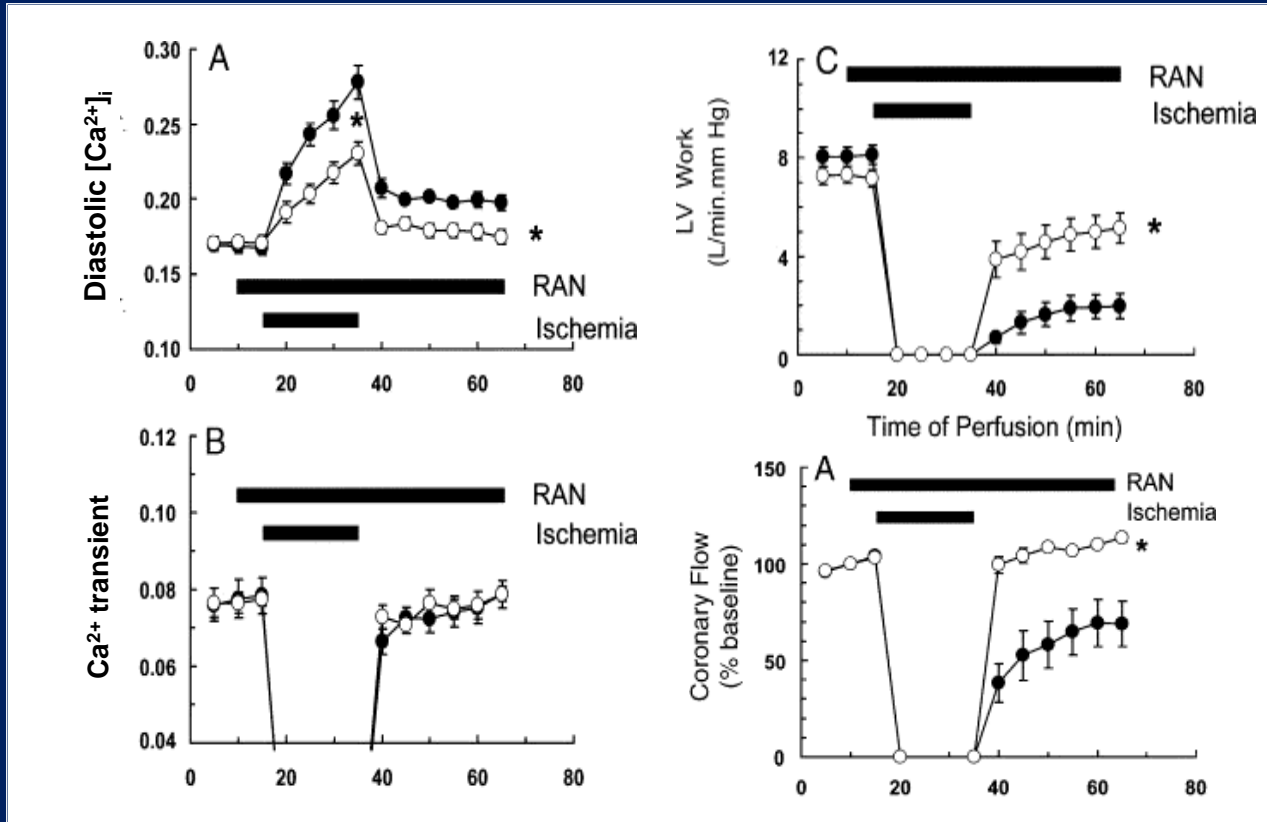
Ranolazine: mechanism of action



Hasenfuss G, Maier LS. Clin Res Cardiol 2008;97:222-26
Maier LS. Cardiol Clin 2008;26:603-14.

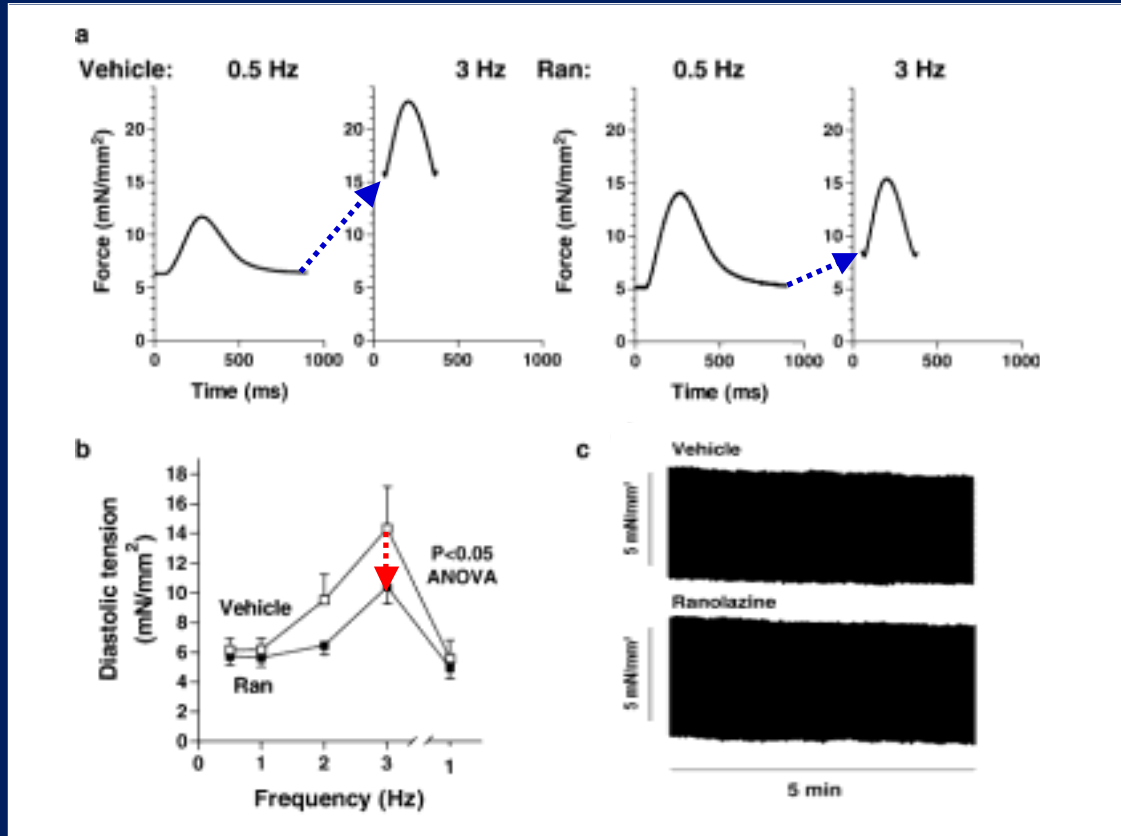
NCX: sodium-calcium exchanger

Ranolazine reduces the effects of ischemia on $[Ca^{2+}]_i$, Ca^{2+} transients, LV function and coronary flow



Fraser H et al. J Mol Cell Cardiol. 2006;41:1031–1038.

Ranolazine reduces the increase in diastolic tension in LV trabeculae from human failing heart



Sossalla S et al. J Mol Cell Cardiol 2008; 45: 32-43.

Effetti del blocco di I_{NaL}

(RILEVANTI PER ISCHEMIA)

➤ *positivizzazione del bilancio fra apporto e consumo di O_2 in condizioni di aumento di I_{NaL}*

Ciò consegue a normalizzazione di:

- *1) rilassamento diastolico;*
- *2) efficienza contrattile (lavoro/ MVO_2);*
- *3) controllo del pH intracellulare;*

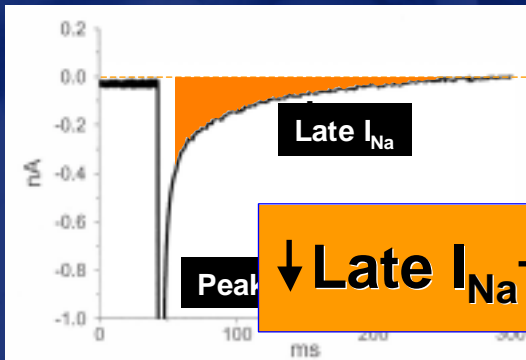
Quindi, blocco I_{NaL} NON:

- *1) cambia la frequenza cardiaca*
- *2) cambia le resistenze periferiche (post- carico)*
- *3) deprime la contrattilità miocardica*
- *4) intereferisce con il controllo nervoso*

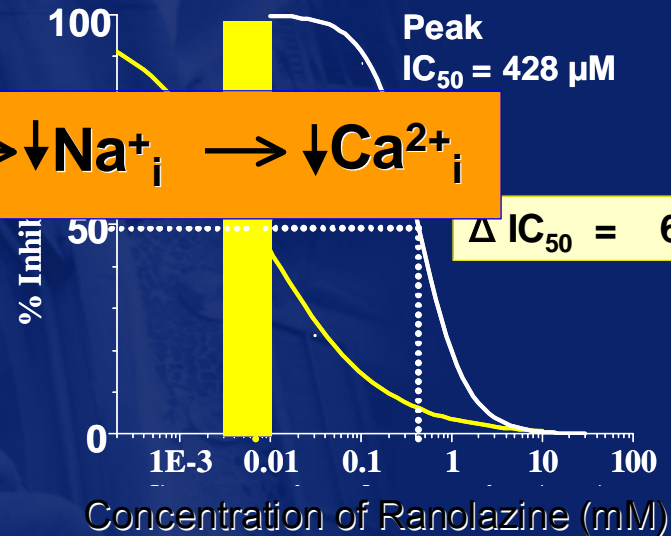
Selective Inhibition of Late Sodium Current by Ranolazine

Therapeutic Range
2 to 8 μM

A. Normal Late Sodium Current

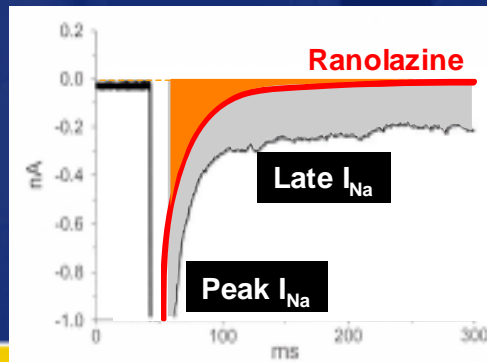


C. Human Cardiac NaCh in HEK293 Cells



$\downarrow \text{Late } I_{\text{Na}} \rightarrow \downarrow \text{Na}^+_i \rightarrow \downarrow \text{Ca}^{2+}_i$

B. Enhanced Late Sodium Current



E' questione di selettività...

BLOCCO RELATIVO

$$I_{NaL}/I_{NaT}$$

Ranolazine

62

SELETTIVO

Amiodarone

13

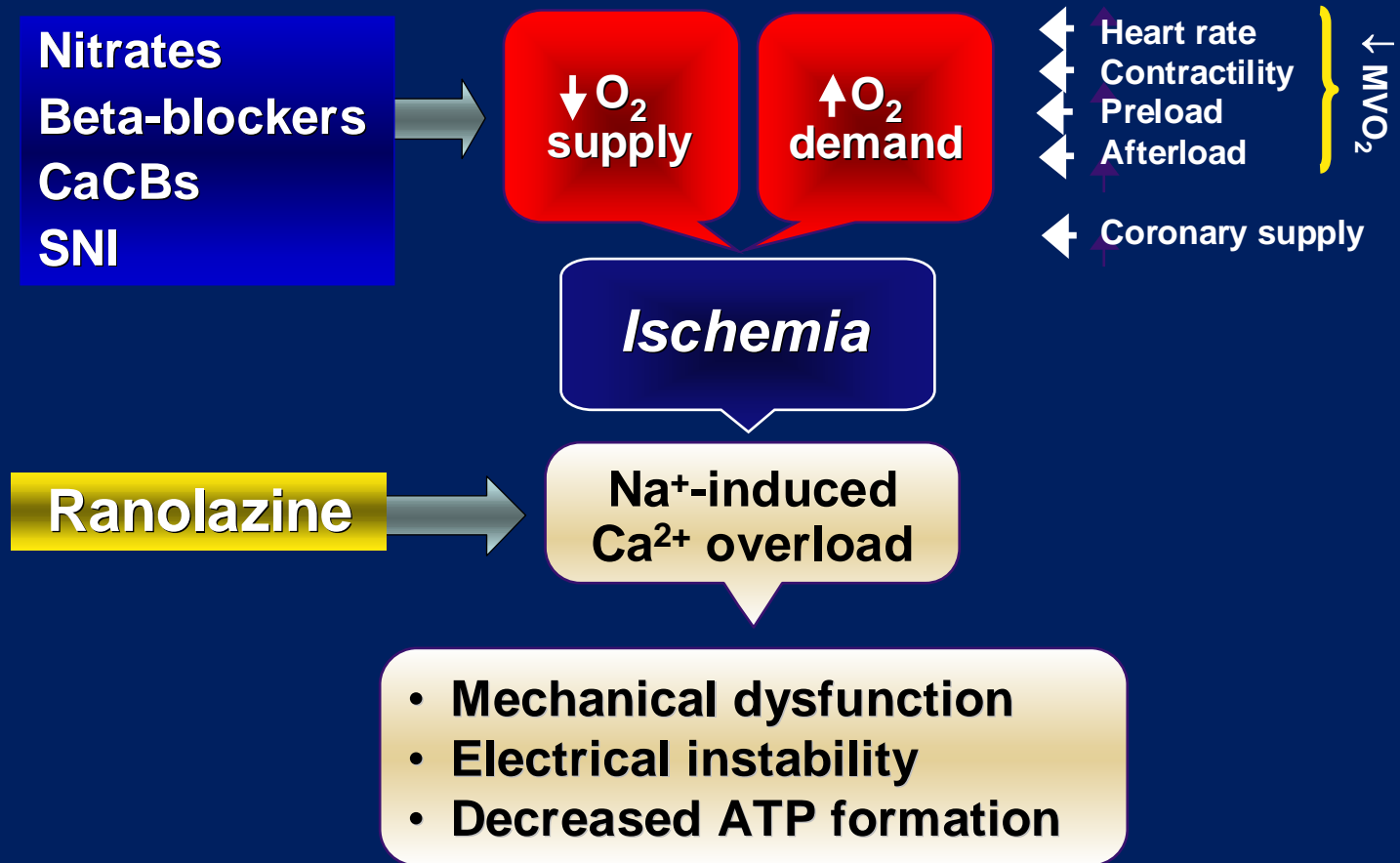
Flecainide

2.9-5

NON SELETTIVO



A new and complementary mechanism



Late Na⁺ current inhibition - A new antianginal approach

1. The enhanced late I_{Na} plays a critical role in Na⁺-induced Ca²⁺ overload in the ischemic myocardium
 - Contributes to electrical, mechanical and metabolic dysfunction
 - It **represents a new therapeutic target** in patients with Chronic Stable Angina

Late Na⁺ current inhibition - A new antianginal approach

2. **Ranolazine**, a selective late I_{Na} inhibitor, blocks Na⁺-dependent Ca²⁺ overload

- It improves LV function, decreasing diastolic tension
- Unlike other antianginal drugs, it has no significant effects on
 - Coronary blood flow, heart rate, blood pressure or venous return

Late Na⁺ current inhibition - A new antianginal approach

This distinct and complementary mechanism represents an alternative approach in patients with Chronic Stable Angina who are not controlled by conventional antianginal drugs or who do not tolerate those drugs