Instituts thématiques

Inserm

Institut national
de la santé et de la recherche médicale

Université Montpellier 1

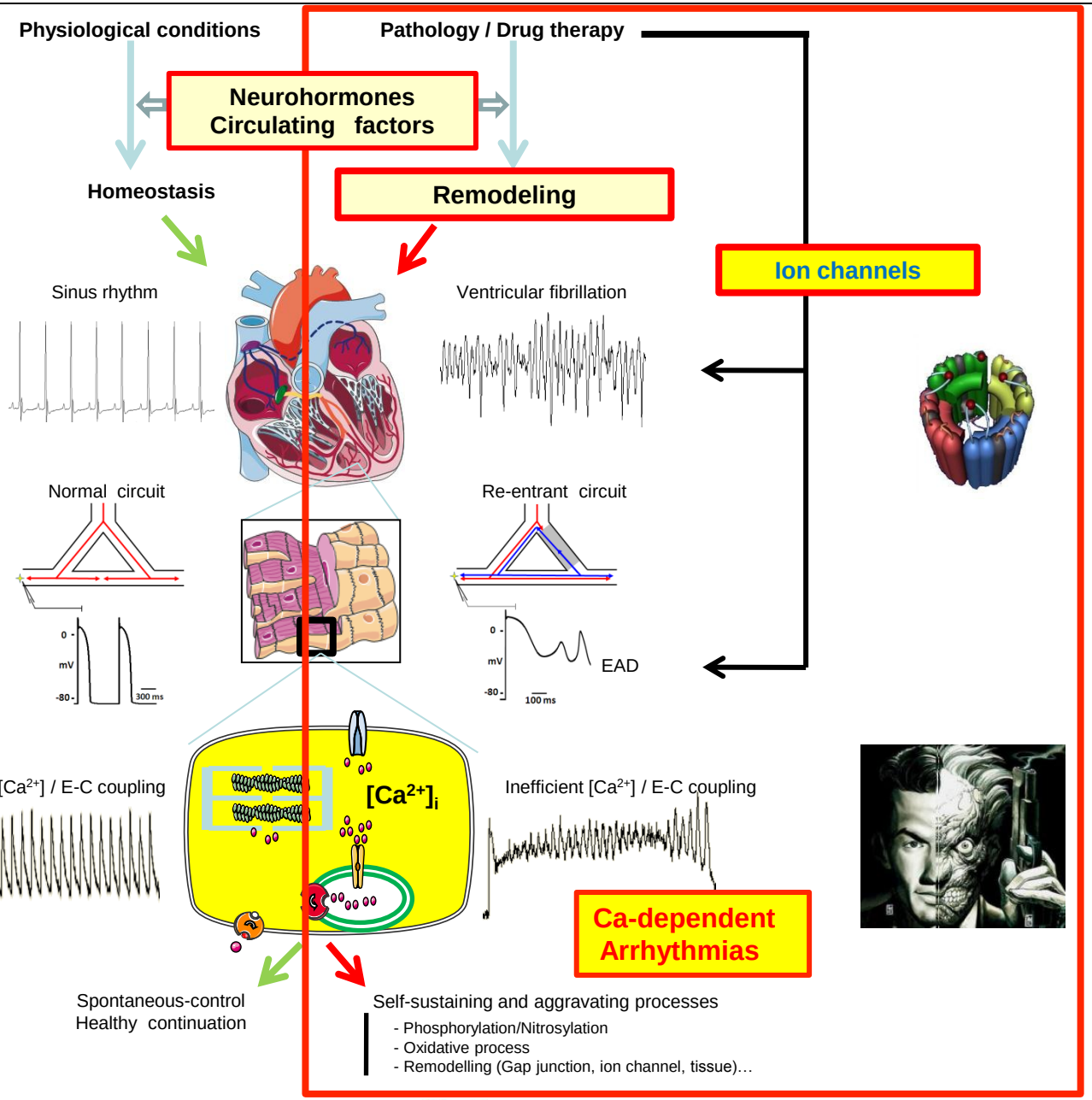
UNIVERSITÉ MONTPELLIER 2
SCIENCES ET TECHNIQUES

PHYSIOLOGIE
& MEDECINE EXPERIMENTALE
COEUR MUSCLES
MONTPELLIER

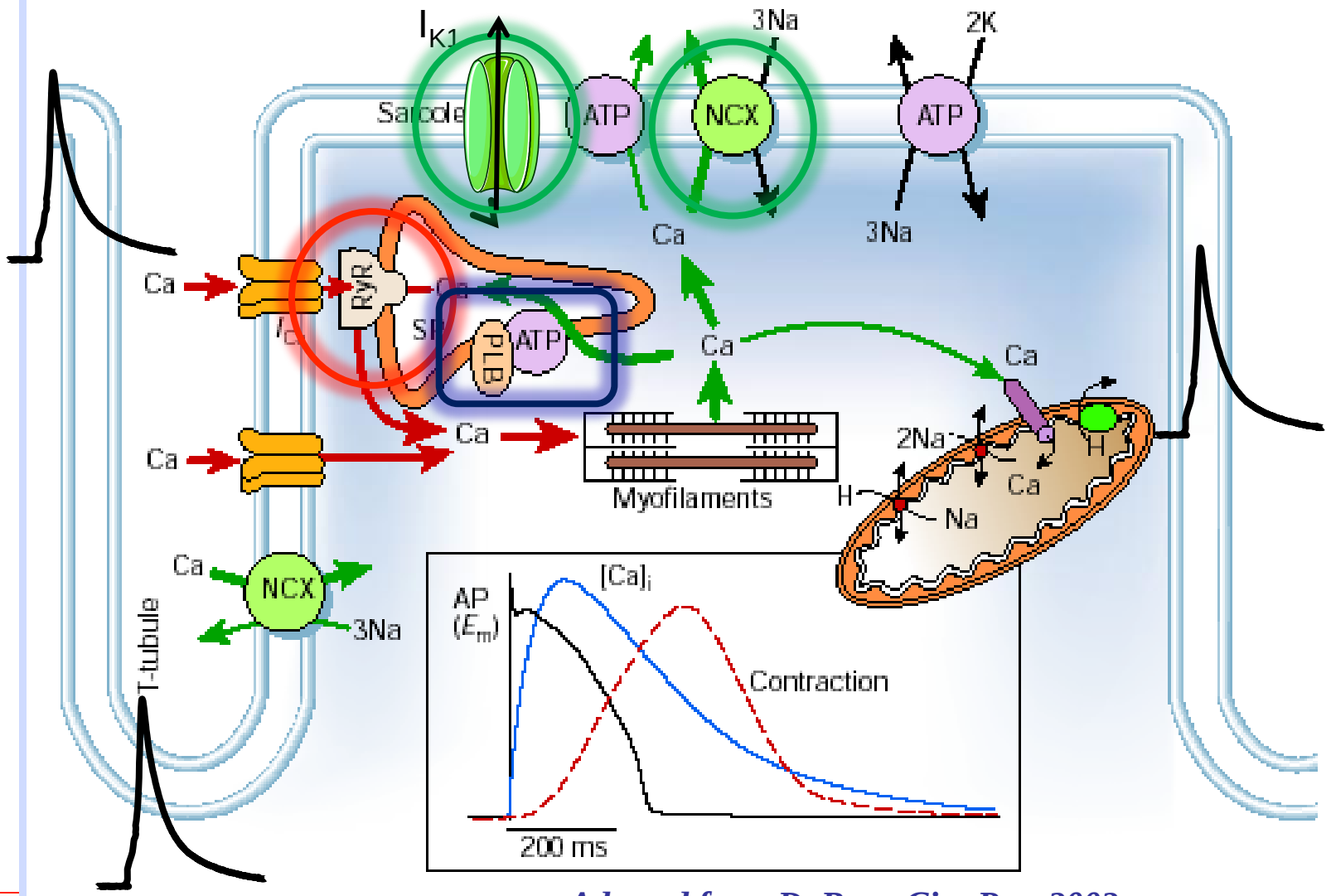
RYTHMOLOGIE : DE LA PHYSIOPATHOLOGIE À LA CLINIQUE

Mécanismes arythmogéniques : le rôle du calcium.

Sylvain RICHARD, DR1 CNRS

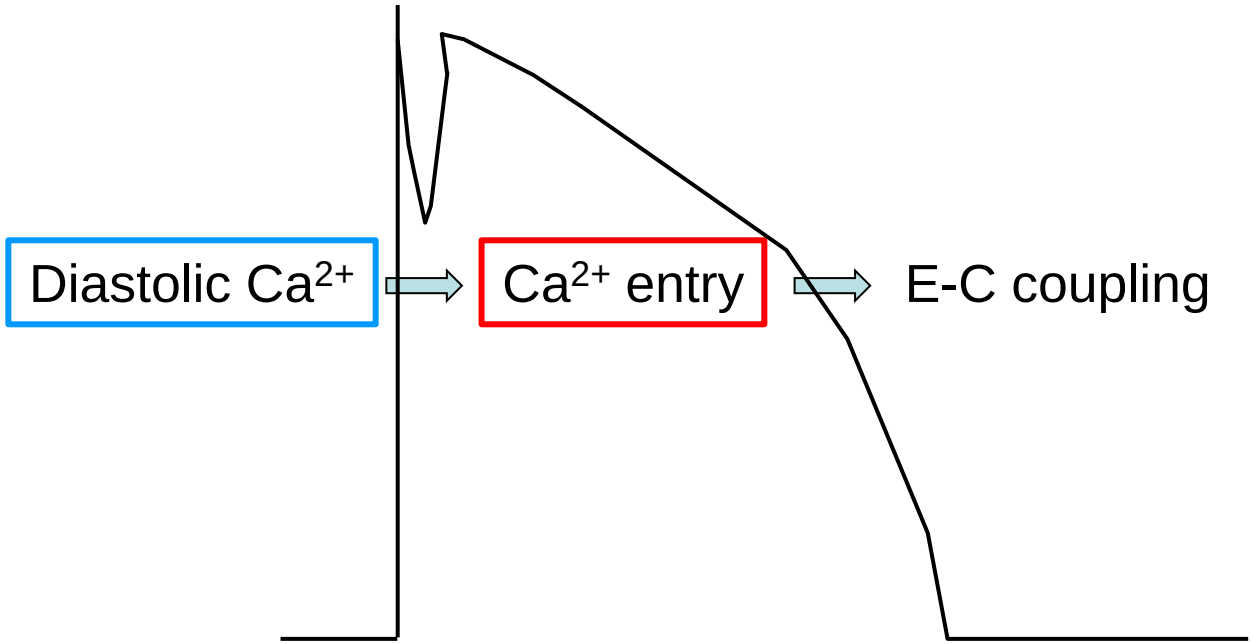

Physiological conditions
Pathology / Drug therapy
Neurohormones
Circulating factors
Homeostasis
Remodeling
Ion channels
Sinus rhythm
Ventricular fibrillation
Normal circuit
Re-entrant circuit
0
mV
-80
300 ms
100 ms
EAD
Normal [Ca2+] / E-C coupling
[Ca2+]i
Inefficient [Ca2+] / E-C coupling
Ca-dependent
Arrhythmias
Spontaneous-control
Healthy continuation
Self-sustaining and aggravating processes
- Phosphorylation/Nitrosylation
- Oxidative process
- Remodelling (Gap junction, ion channel, tissue)…

Role of Ca^{2+} in Cardiac Excitation-Contraction coupling



Adapted from D. Bers, Circ Res, 2002

Ca^{2+}-dependent Arrhythmias in cardiomyocytes



Ca^{2+}-dependent Arrhythmias

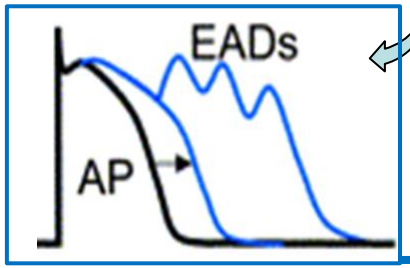
Sustained Depolarization

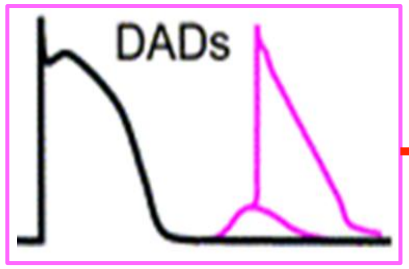
Diastolic Ca^{2+} → Ca^{2+} entry → E-C coupling

Ca^{2+} re-entry

Ca^{2+} waves

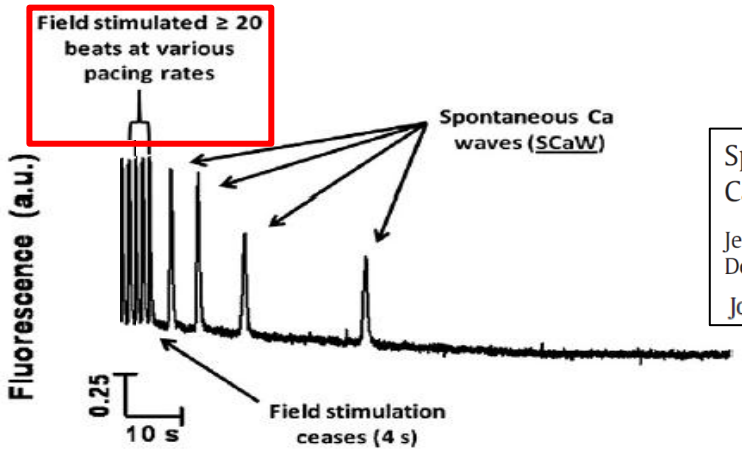
I_{ti} (NCX)





Ca^{2+} → Arrhythmias

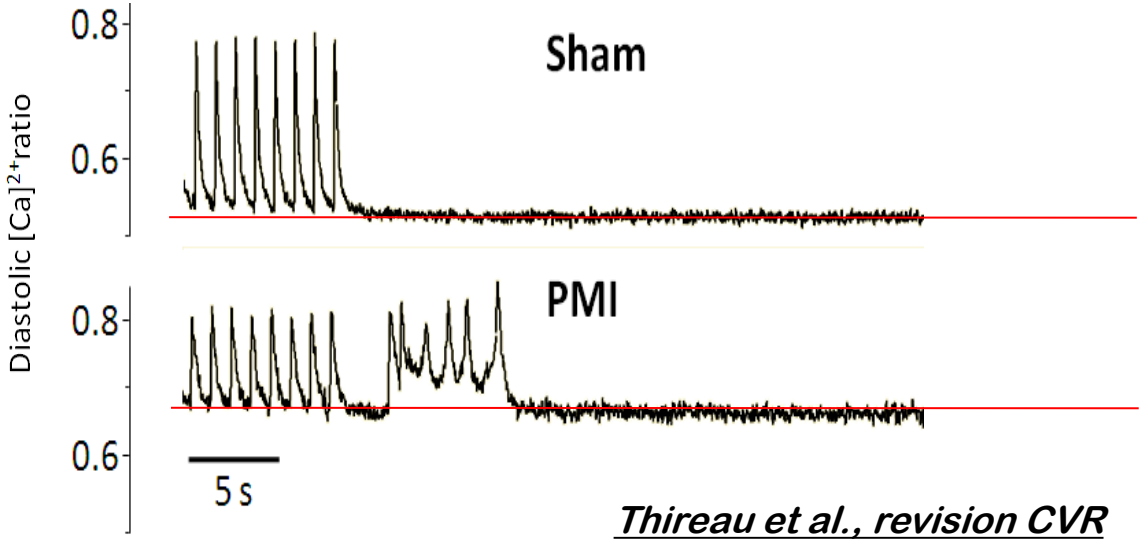
Spontaneous Ca^{2+} waves in cardiomyocytes



Spontaneous Ca waves in ventricular myocytes from failing hearts depend on Ca^{2+}-calmodulin-dependent protein kinase II

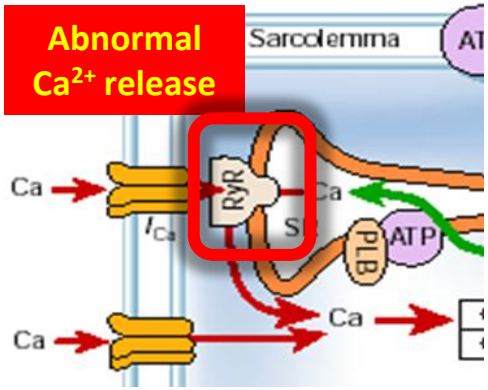
Jerry Curran [a], Kathy Hayes Brown [a], Demetrio J. Santiago [a], Steve Pogwizd [b], Donald M. Bers [c], Thomas R. Shannon [a,*]

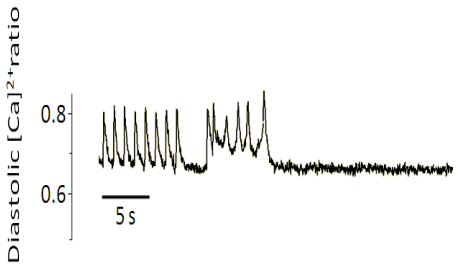
Journal of Molecular and Cellular Cardiology 49 (2010) 25–32



Thireau et al., revision CVR

Spontaneous Ca^{2+} waves in cardiomyocytes





1) CPVT (TV Catéchol. Polym)
(heart structurally normal ;
alterations of Ca^{2+} signaling)

2) CO
(heart with normal function ;
alterations of Ca^{2+} signaling)

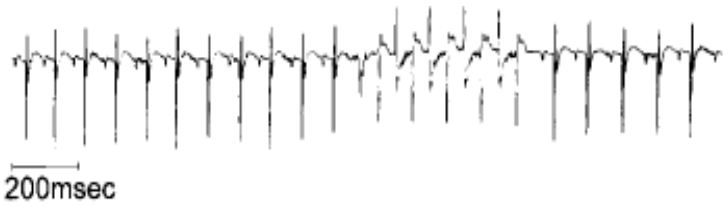
3) *Duchenne Muscular Dystrophy (mdx)*
(progressive cardiomyopathy;
fatal cardiac arrhythmias)

4) Heart Failure

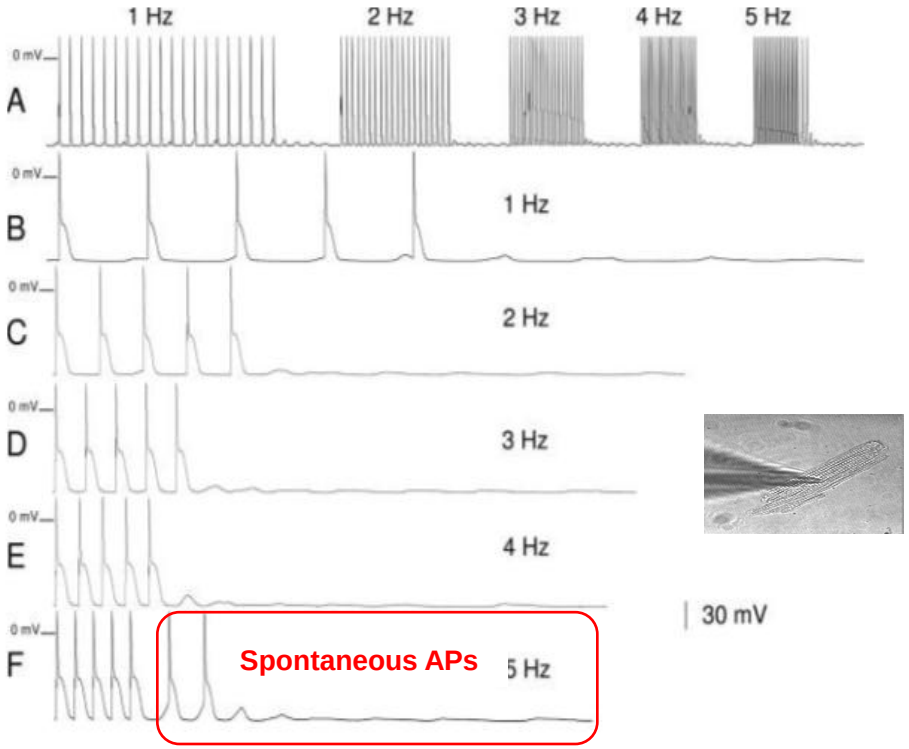
Arrhythmia in CPVT

SG. Priori, C. Napolitano

RyR2 **R4496C**



Cerrone et al., *Circ Res*. 2005;96:e77-82



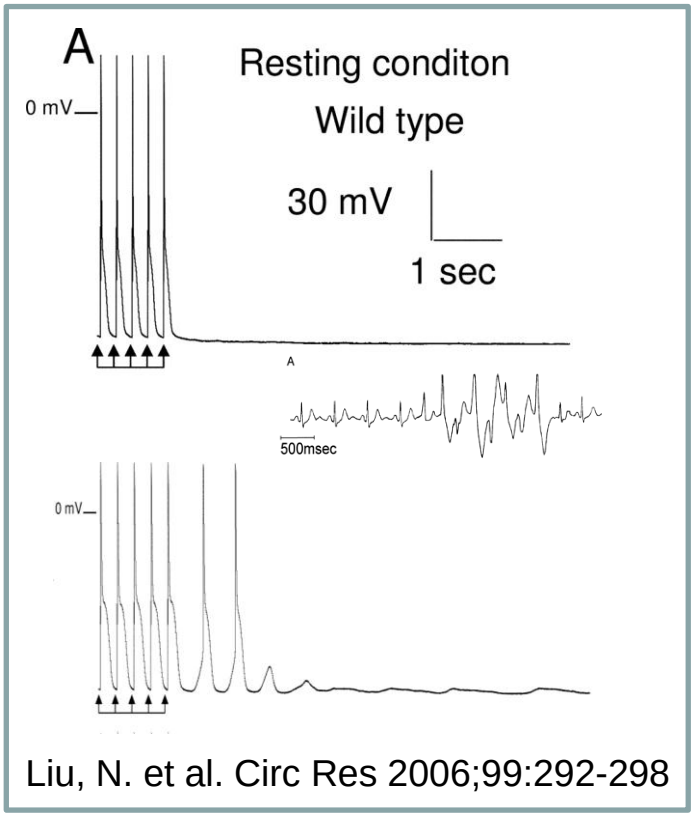
Arrhythmogenesis in Catecholaminergic Polymorphic Ventricular Tachycardia

Insights From a RyR2 R4496C Knock-In Mouse Model

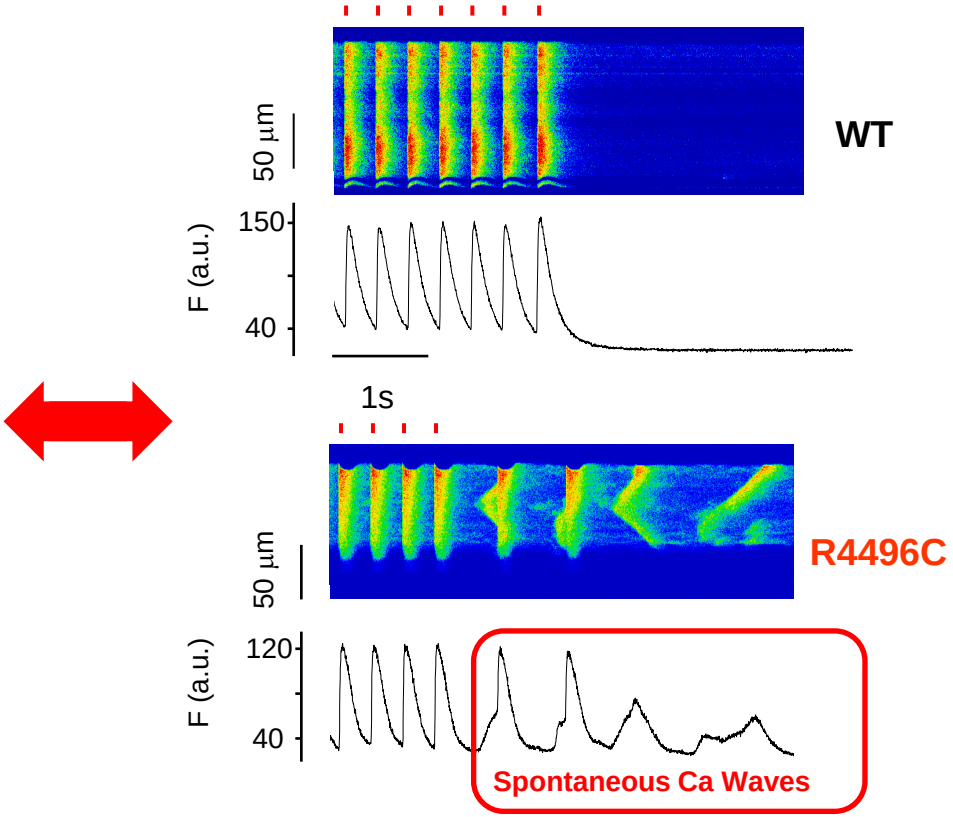
Nian Liu, Barbara Colombi, Mirella Memmi, Spyros Zissimopoulos, Nicoletta Rizzi, Sara Negri, Marcello Imbriani, Carlo Napolitano, F. Anthony Lai, Silvia G. Priori

(*Circ Res*. 2006;99:292-298.)

Spontaneous Ca^{2+} waves in $RyR^{R4496C\ +/-}$



Liu, N. et al. Circ Res 2006;99:292-298

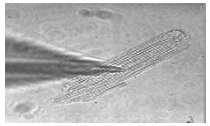


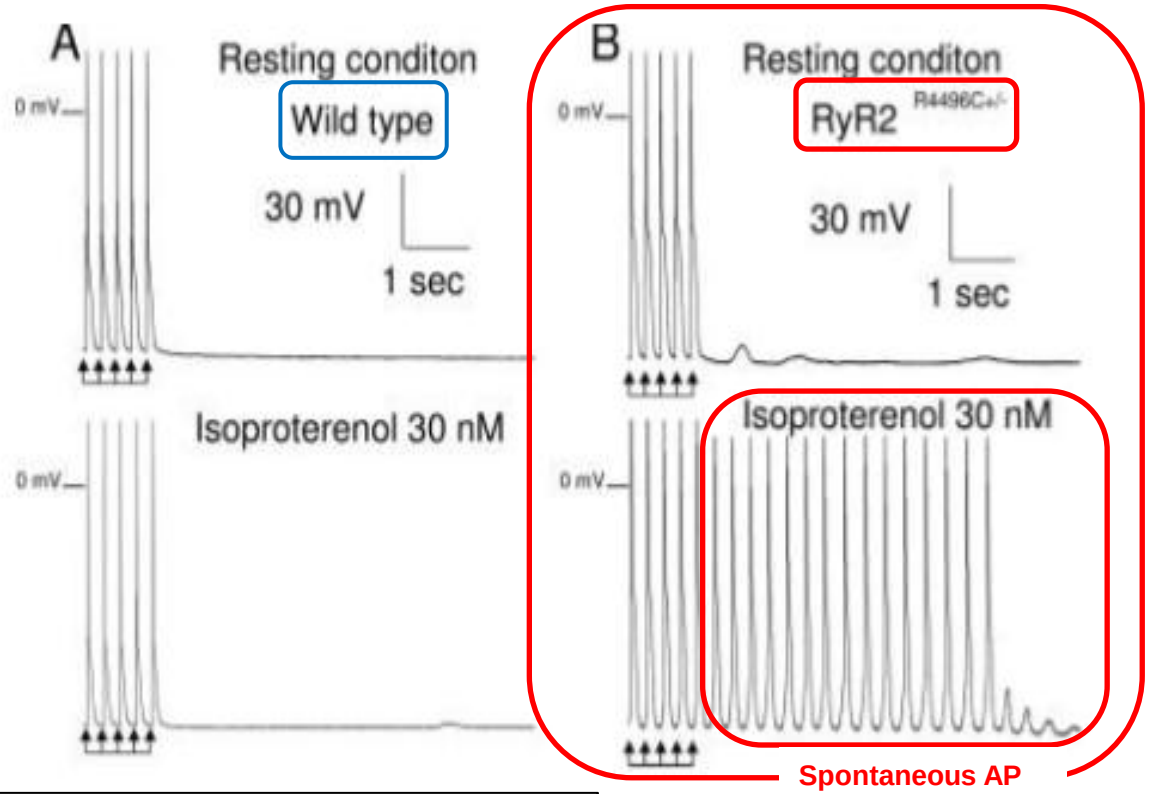
Increased Ca^{2+} Sensitivity of the Ryanodine Receptor Mutant $RyR2^{R4496C}$ Underlies Catecholaminergic Polymorphic Ventricular Tachycardia

Circ Res. 2009;104:201-209.

María Fernández-Velasco, Angélica Rueda,* Nicoletta Rizzi,* Jean-Pierre Benitah, Barbara Colombi, Carlo Napolitano, Silvia G. Priori, Sylvain Richard, Ana María Gómez

Facilitating effect of Isoproterenol





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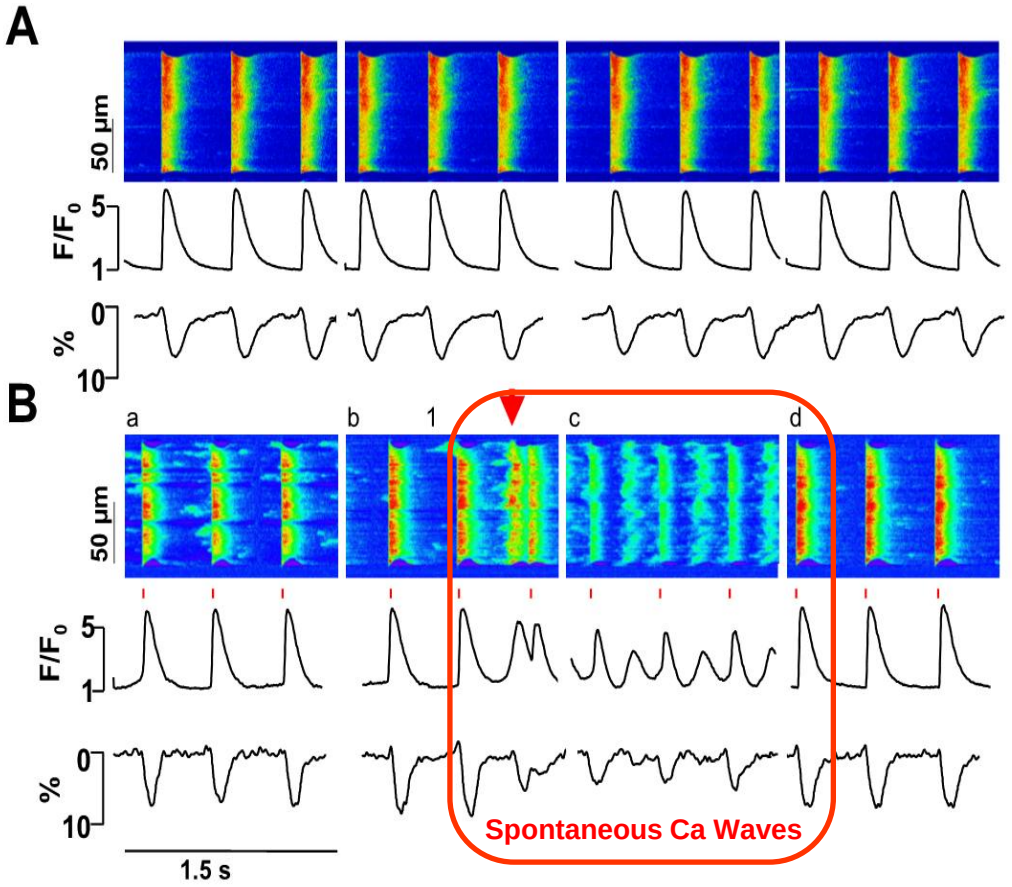
(*Circ Res*. 2006;99:292-298.)

… more Ca^{2+} waves with isoproterenol

WT + 1 µM Iso

$RyR^{24496C+/-}$ + 1 µM Iso



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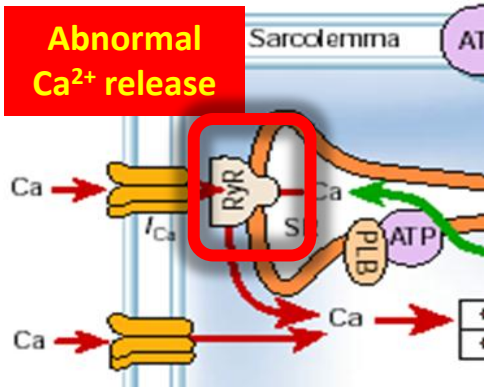
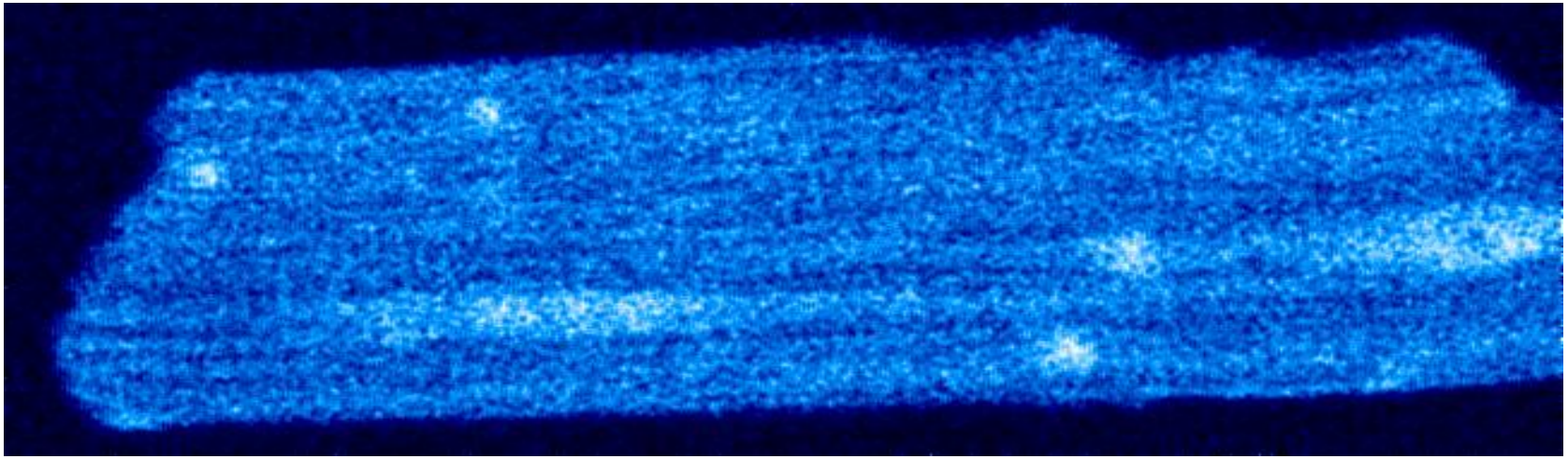
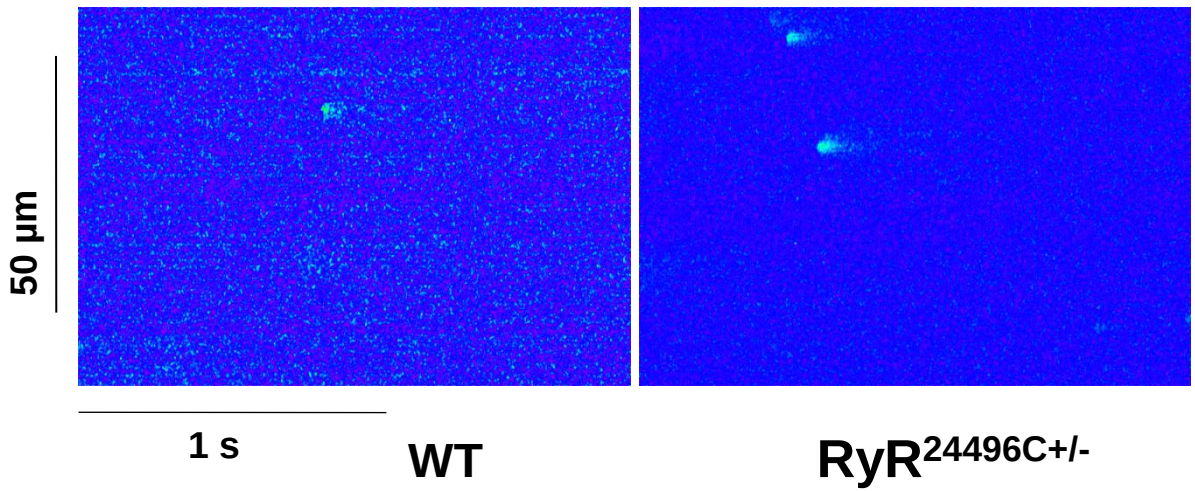
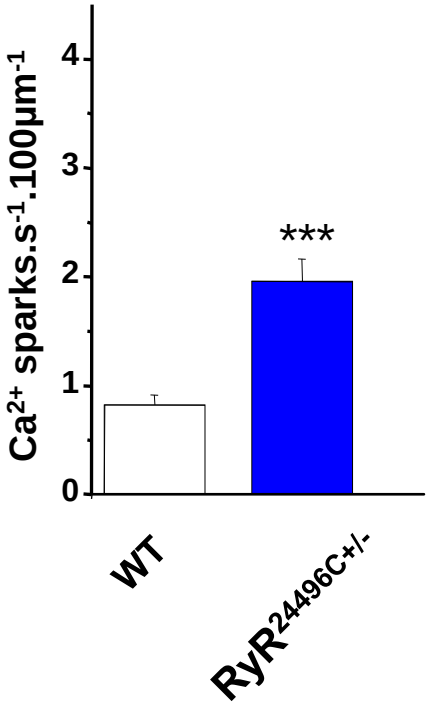
Spontaneous RyR2 activity = Ca^{2+} sparks





Spontaneous RyR2 activity is increased





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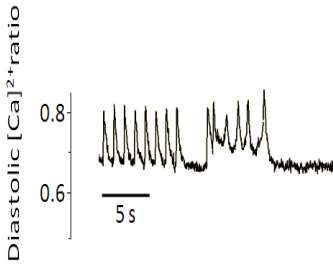
Circ Res. 2009;104:201-209.

Spontaneous Ca^{2+} waves in cardiomyocytes



1) CPVT

(heart structurally normal ;
alterations of Ca^{2+} signaling)

2) CO

(heart with normal function ;
alterations of Ca^{2+} signaling)

3) Duchenne Muscular Dystrophy

(mdx)

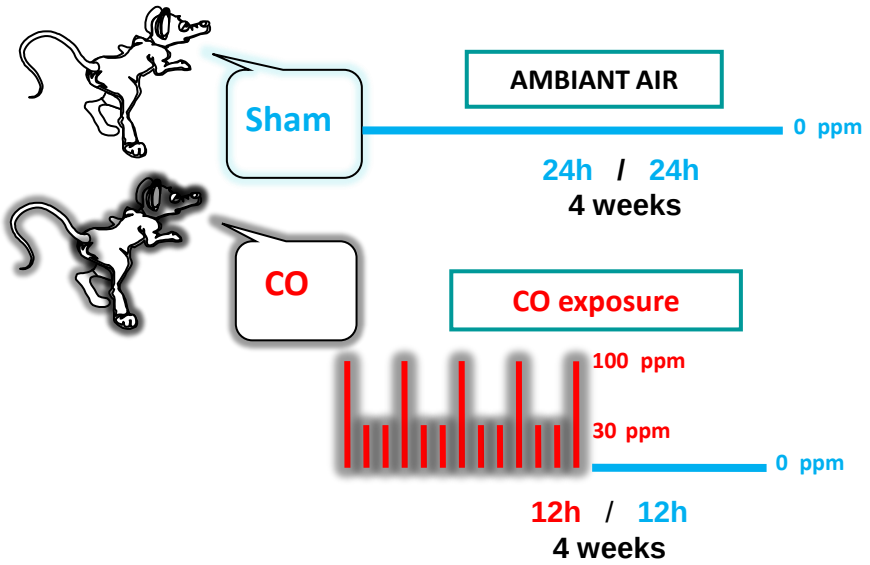
(progressive cardiomyopathy;
fatal cardiac arrhythmias)

4) Heart Failure

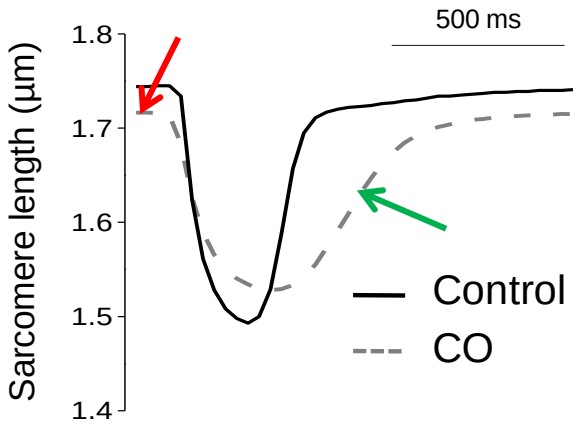
Carbon Monoxide Pollution Promotes Cardiac Remodeling and Ventricular Arrhythmia in Healthy Rats

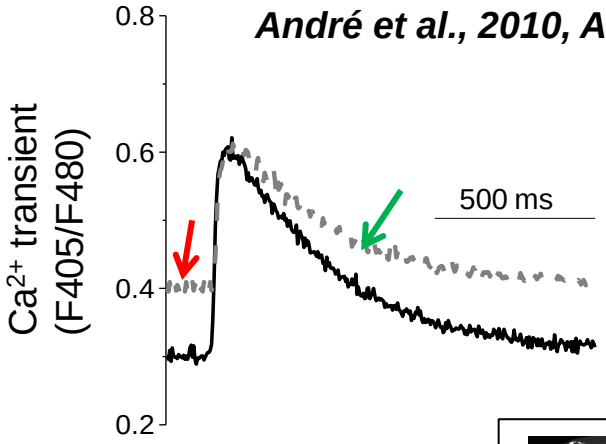
Lucas Andre[1*], Julien Boissière[1,2*], Cyril Reboul[2], Romain Perrier[1], Santiago Zalvidea[1], Gregory Meyer[2], Jérôme Thireau[1], Stéphane Tanguy[2], Patrice Bideaux[1], Maurice Hayot[3], François Boucher[4], Philippe Obert[2], Olivier Cazorla[1], and Sylvain Richard[1]

Am J Respir Crit Care Med Vol 181. pp 587–595, 2010

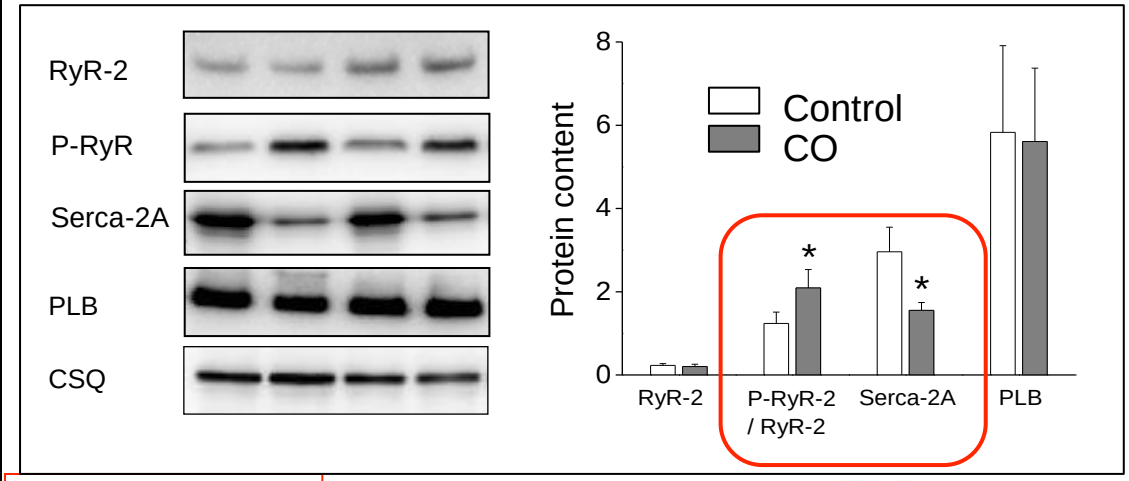


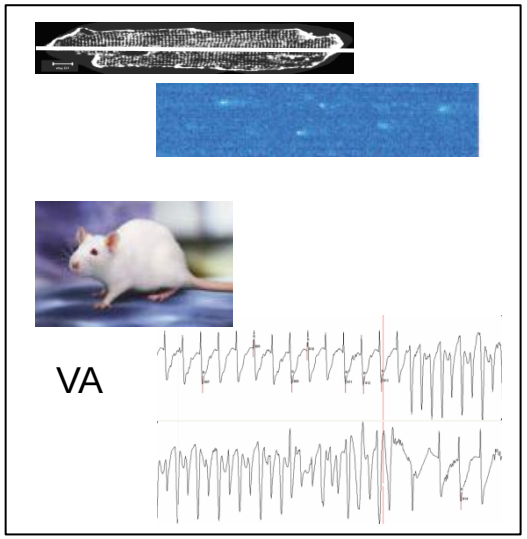
Chronic CO alters cell contraction and Ca^{2+} transients (both RyR2 and SERCA2a involved)



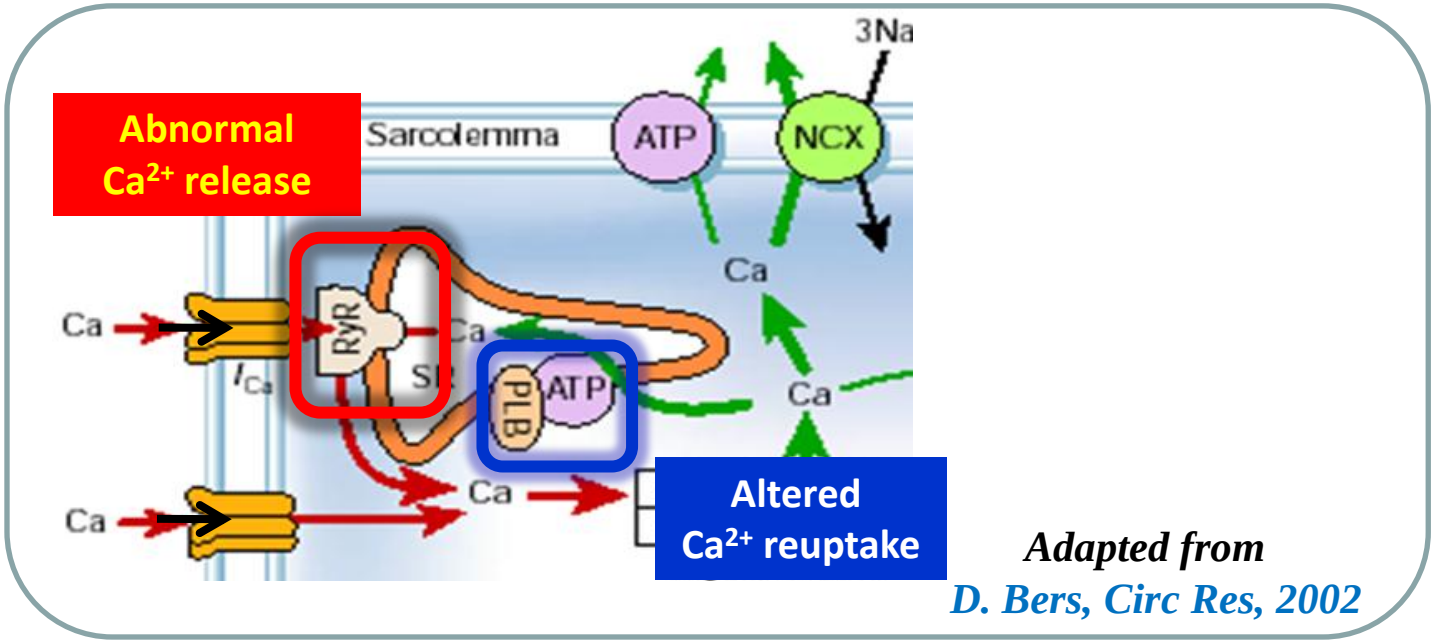


André et al., 2010, Am J Respir Crit Care Med



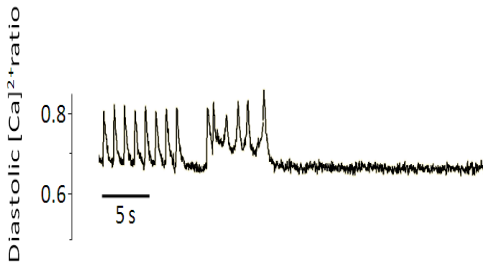


Origin of Ca^{2+} overload and related arrhythmias



Adapted from
D. Bers, Circ Res, 2002

Spontaneous Ca^{2+} waves in cardiomyocytes



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3) Duchenne Muscular Dystrophy (mdx)

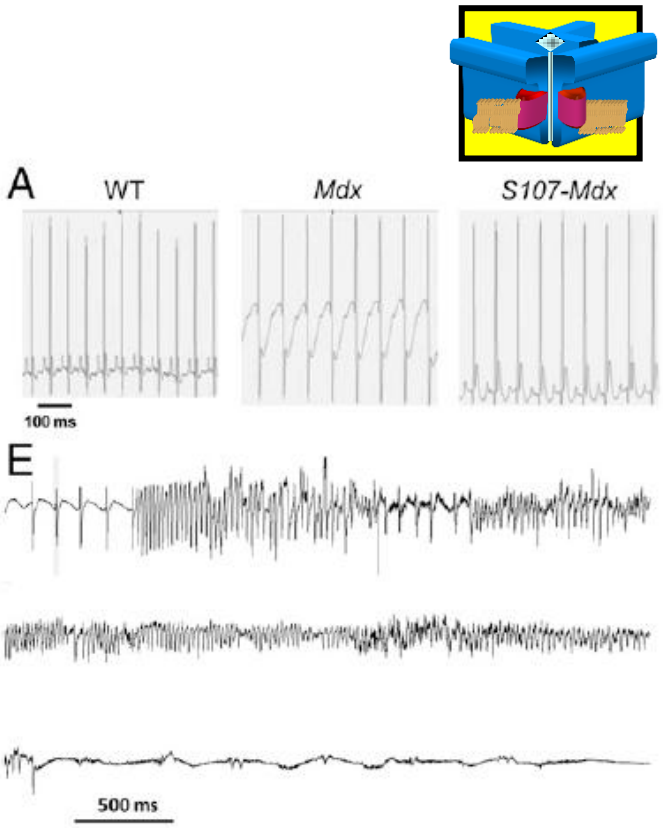
(progressive cardiomyopathy;
fatal cardiac arrhythmias)

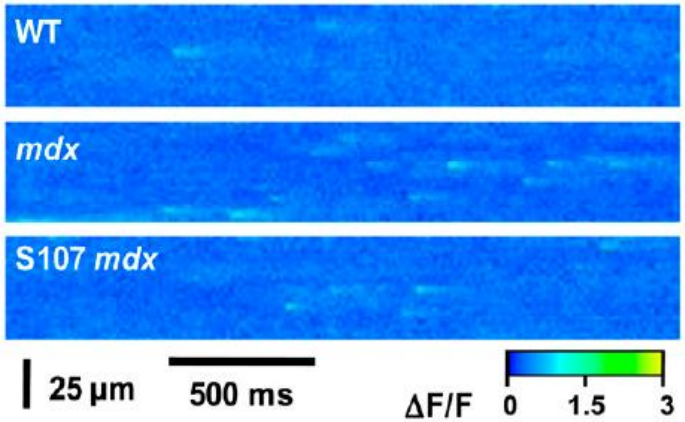
4) Heart Failure

Leaky RyR2 trigger ventricular arrhythmias in Duchenne muscular dystrophy

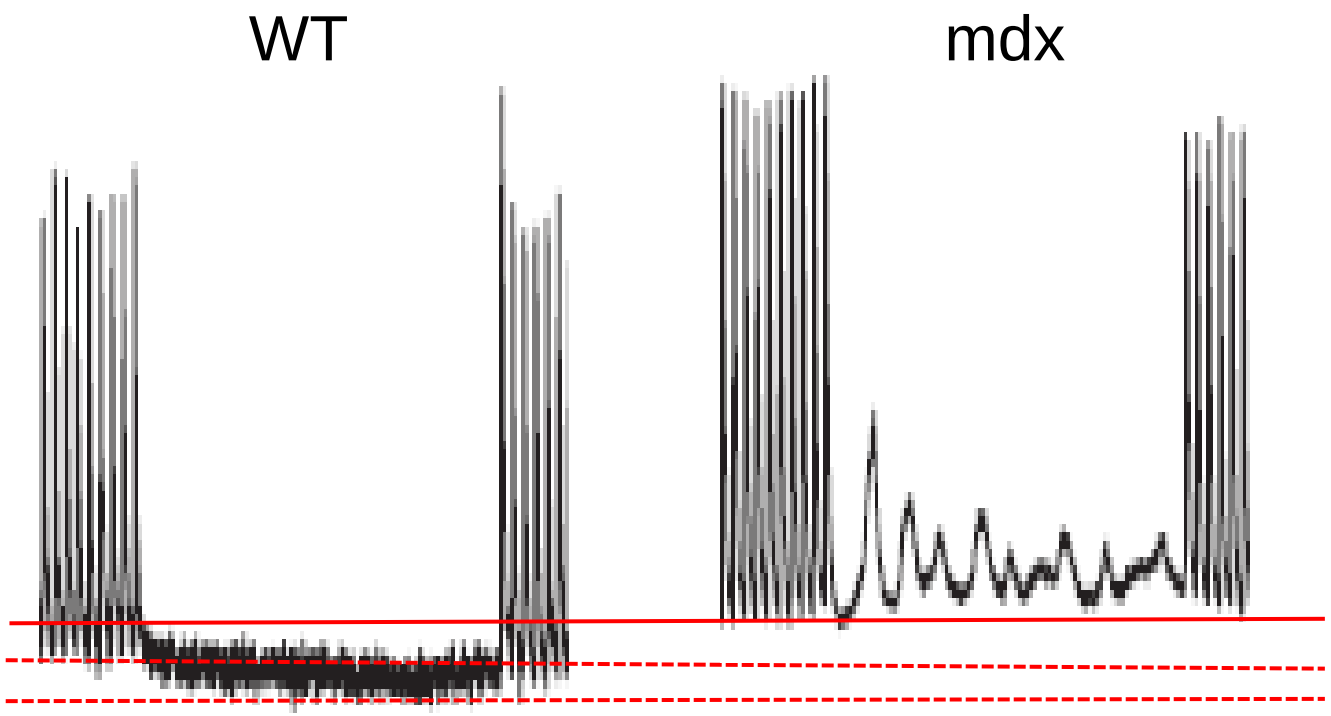
Jérémy Fauconnier[a,b,1], Jérôme Thireau[a,1], Steven Reiken[c], Cécile Cassan[a,b], Sylvain Richard[a,b], Stefan Matecki[b,d], Andrew R. Marks[c], and Alain Lacampagne[a,b,2]

PNAS | January 26, 2010 | vol. 107 | no. 4 | 1559–1564



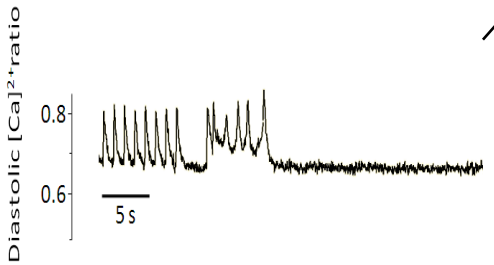


High diastolic Ca^{2+} and Ca^{2+} waves



Fauconnier et al., 2010, PNAS

Spontaneous Ca^{2+} waves in cardiomyocytes



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3) *Duchenne Muscular Dystrophy (mdx)*

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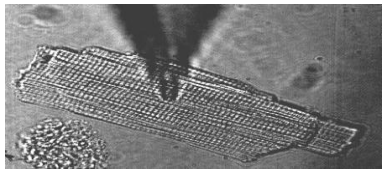
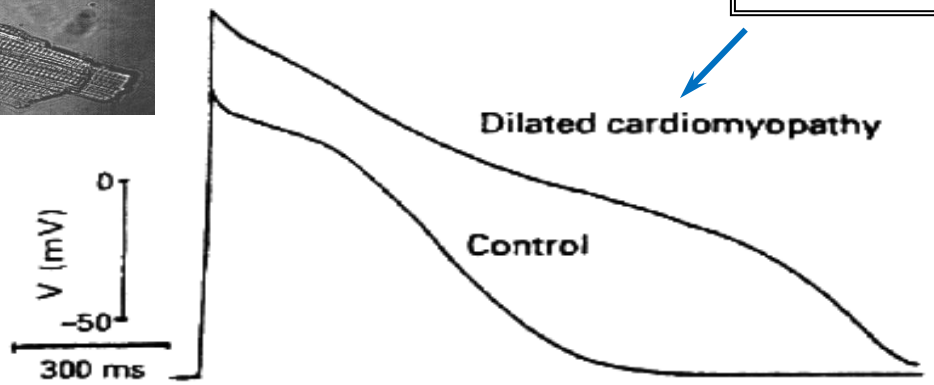
4) Heart Failure

Ca^{2+} handling disorders are critical in HF

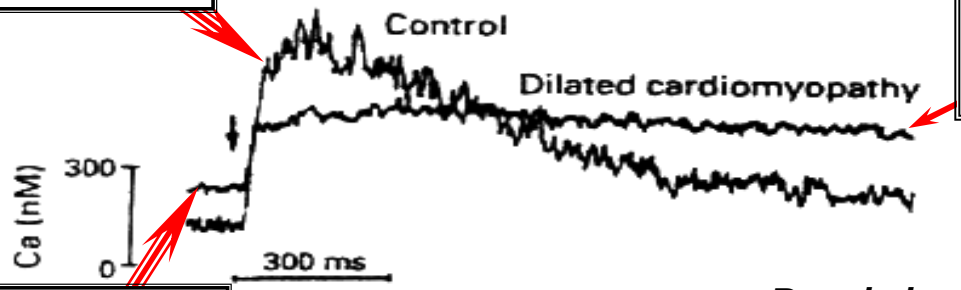


Ca^{2+} entry



Resting $[Ca^{2+}]_i$

Decreased systolic Ca^{2+}



Prolongation of Ca^{2+} transients

Elevated diastolic Ca^{2+}

Beuckelmann et al., Circulation, 1992

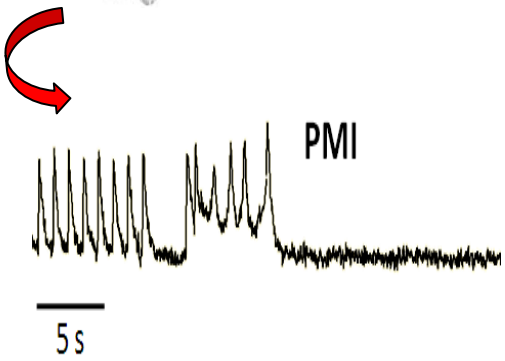
Abnormal RyR2 openings during diastole promote Ca^{2+} waves and spontaneous AP

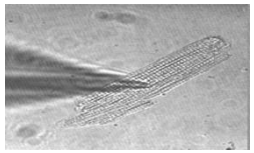
Cardiomyocytes hypertrophic status after myocardial infarction determines distinct types of arrhythmia: Role of the ryanodine receptor

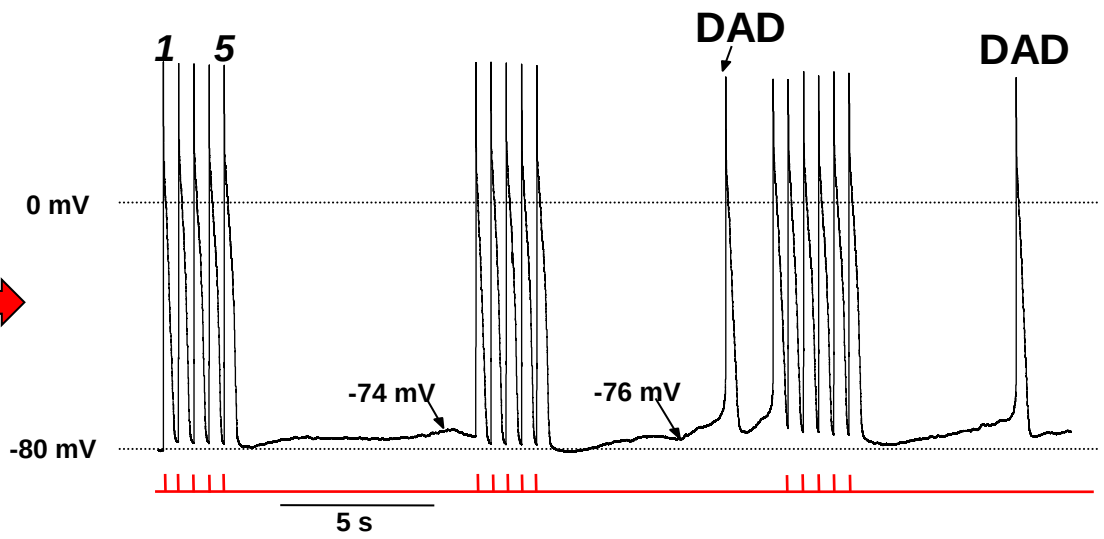
Jérémy Fauconnier[a,1], Jean-Luc Pasquié[a,b,1], Patrice Bideaux[a,1], Alain Lacampagne[a,1], Sylvain Richard[a,*]

Progress in Biophysics and Molecular Biology 103 (2010) 71–80

SR Ca^{2+} leak via RyR2



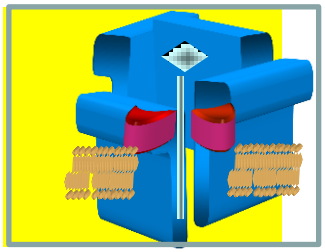




Cellular Mechanisms translating RyR2 dysfunction into electrical abnormalities?

RyR2 dysfunction

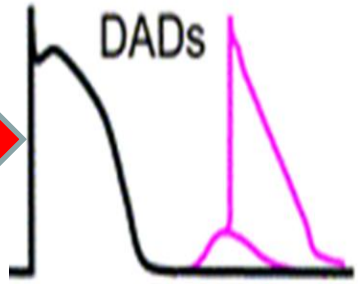
Arrhythmia / SCD



Abnormal Ca^{2+} release

?

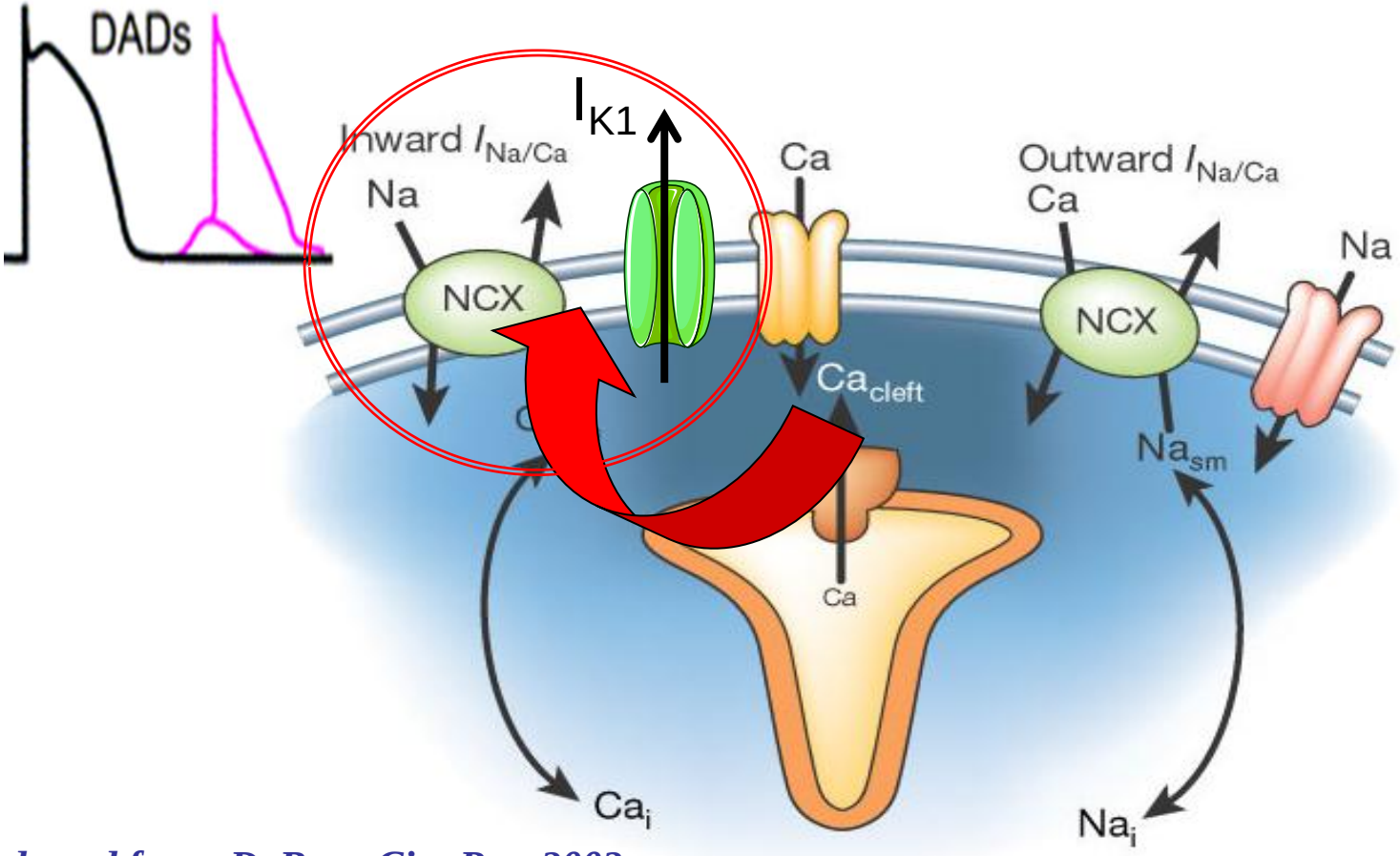
Ca^{2+}-dependent ionic currents



Molecular mechanisms

Cellular mechanisms

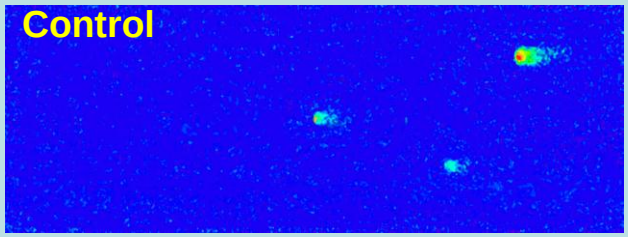
Sub-cellular Mechanisms converting RyR2 dysfunction into electrical abnormalities

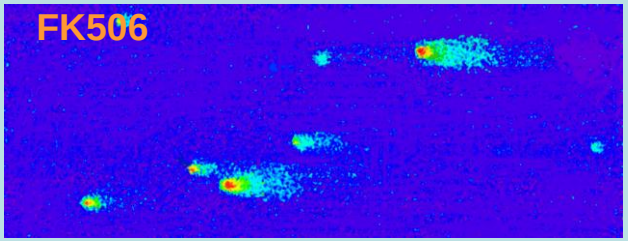


Adapted from D. Bers, Circ Res, 2002

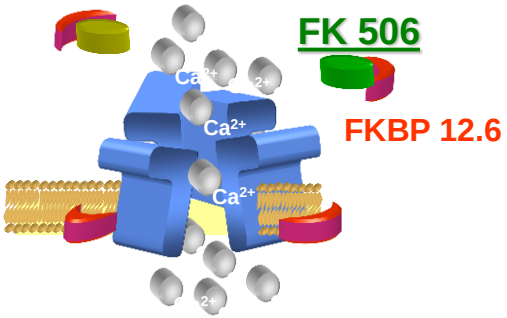
FK506 blocks I_{K1} by promoting RyR2 leakage

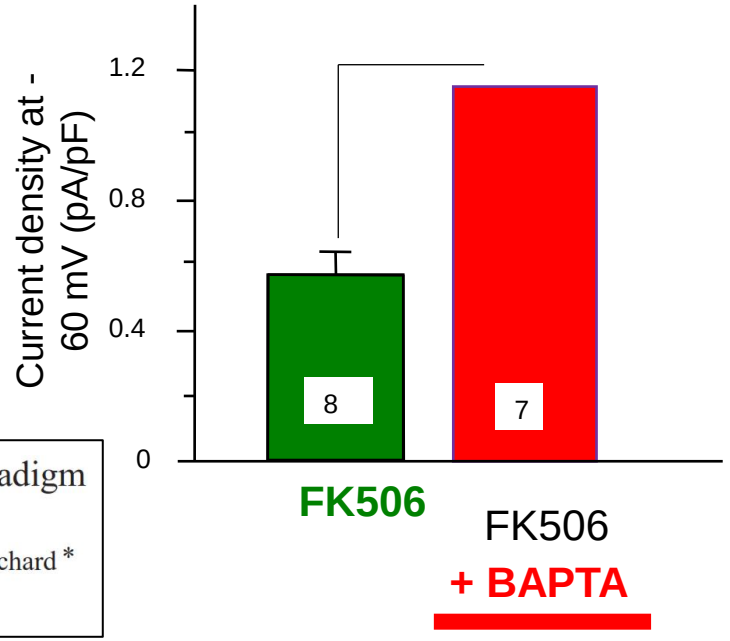
Normal





Gomez et al., 2005, Am. J. Physiol.





Ca^{2+}-dependent reduction of I_{K1} in rat ventricular cells: A novel paradigm for arrhythmia in heart failure?

Jérémy Fauconnier, Alain Lacampagne, Jean-Michel Rauzier, Guy Vassort, Sylvain Richard *

Cardiovascular Research 68 (2005) 204 – 212

Normalization of RyR2 activity: therapeutic avenue?

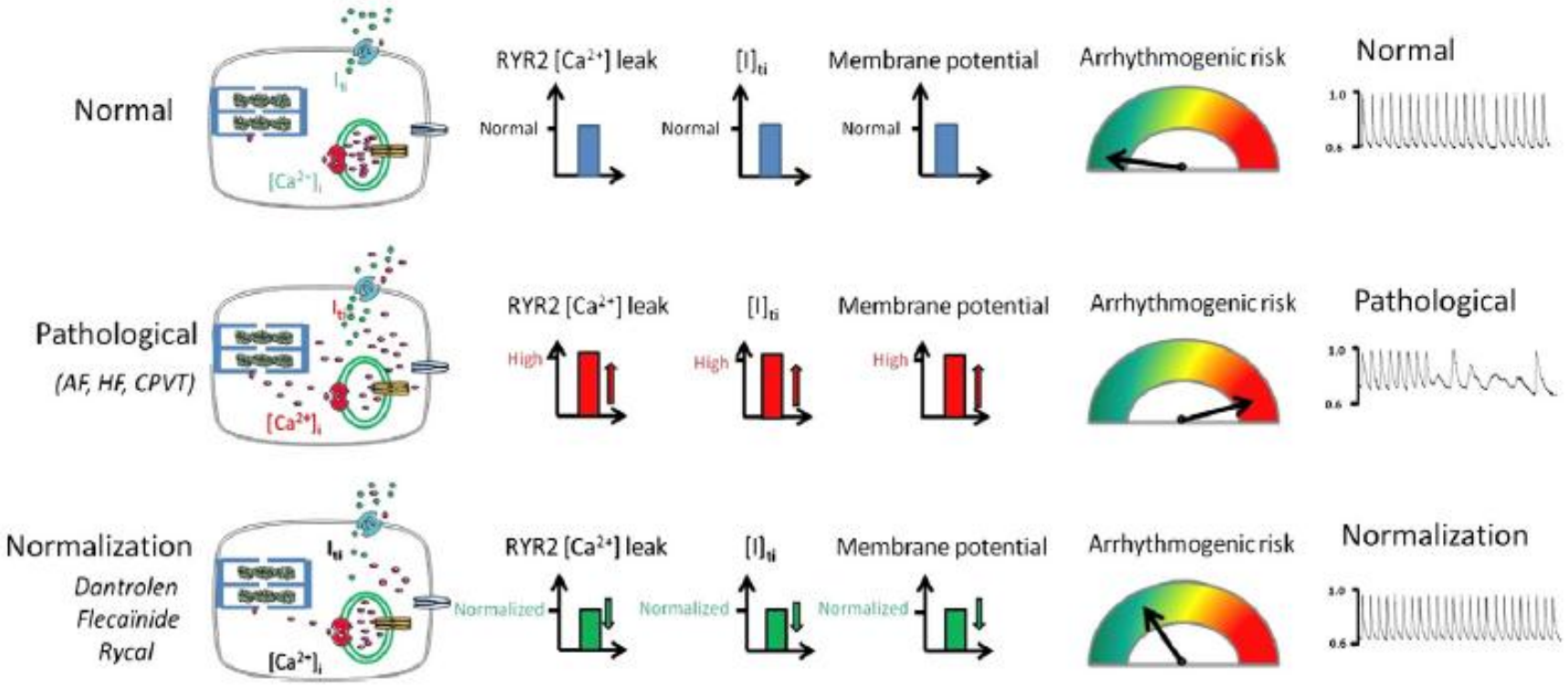
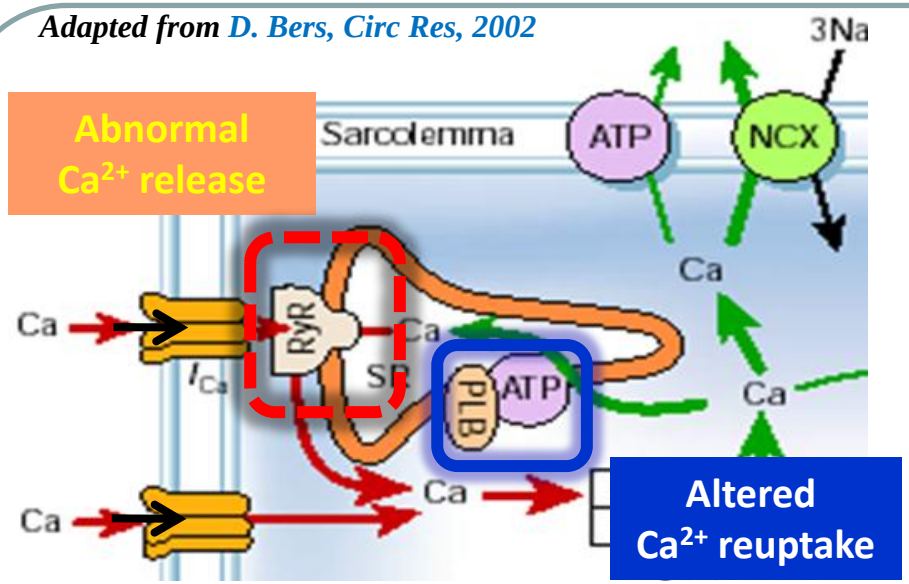


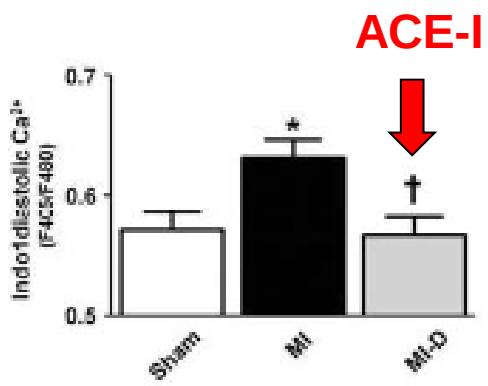
Fig. 4. Blockers and stabilizers of RyR2 prevent arrhythmia. Under normal conditions, RyR2 rarely opens in diastole. Spontaneous opening leads to leaky RyR2 in various pathophysiological situations, generating aberrant Ca^{2+} sparks and Ca^{2+} waves that activate inward depolarising I_{ti} currents via NCX, that in turn generate DADs and arrhythmia. Compounds that block or stabilize the RyR2-FKBP12.6 interaction (Rycals) prevent Ca^{2+} leakage and arrhythmogenic risk.

New drugs vs. old concepts: A fresh look at antiarrhythmics
Jérôme Thireau [a], Jean-Luc Pasquié [a], Eric Martel [b], Jean-Yves Le Guennec [a], Sylvain Richard [a,*]
Pharmacology & Therapeutics 132 (2011) 125–145

SERCA2a, Ca^{2+} overload and upstream Therapy (HF)

Adapted from D. Bers, Circ Res, 2002

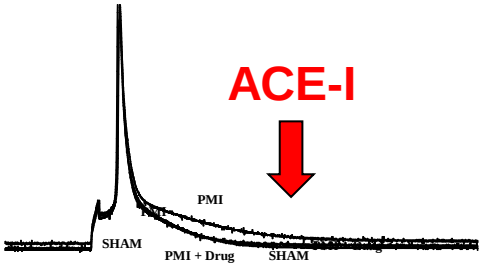




ACE Inhibition Prevents Diastolic Ca^{2+} Overload and Loss of Myofilament Ca^{2+} Sensitivity after Myocardial Infarction

S. Zalvidea[1,2], L. André[1], X. Loyer[3], C. Cassan[1], Y. Sainte-Marie[4], J. Thireau[1], I. Sjaastad[2], C. Heymes[4], J.-L. Pasquié[1], O. Cazorla[1], F. Aimond[1] and S. Richard[*,1]

Current Molecular Medicine 2012, *12*, 206-217



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