Instituts thématiques

Inserm

Institut national de la santé et de la recherche médicale

PHYSIOLOGIE & MEDECINE EXPERIMENTALE COEUR MUSCLES MONTPELLIER

UNIVERSITÉ MONTPELLIER 2 SCIENCES ET TECHNIQUES

Université Montpellier 1

Ca^{2+}-dependent arrhythmia: rôle of RyR2 and mechanisms

S. Richard

EUROPEAN SOCIETY OF CARDIOLOGY

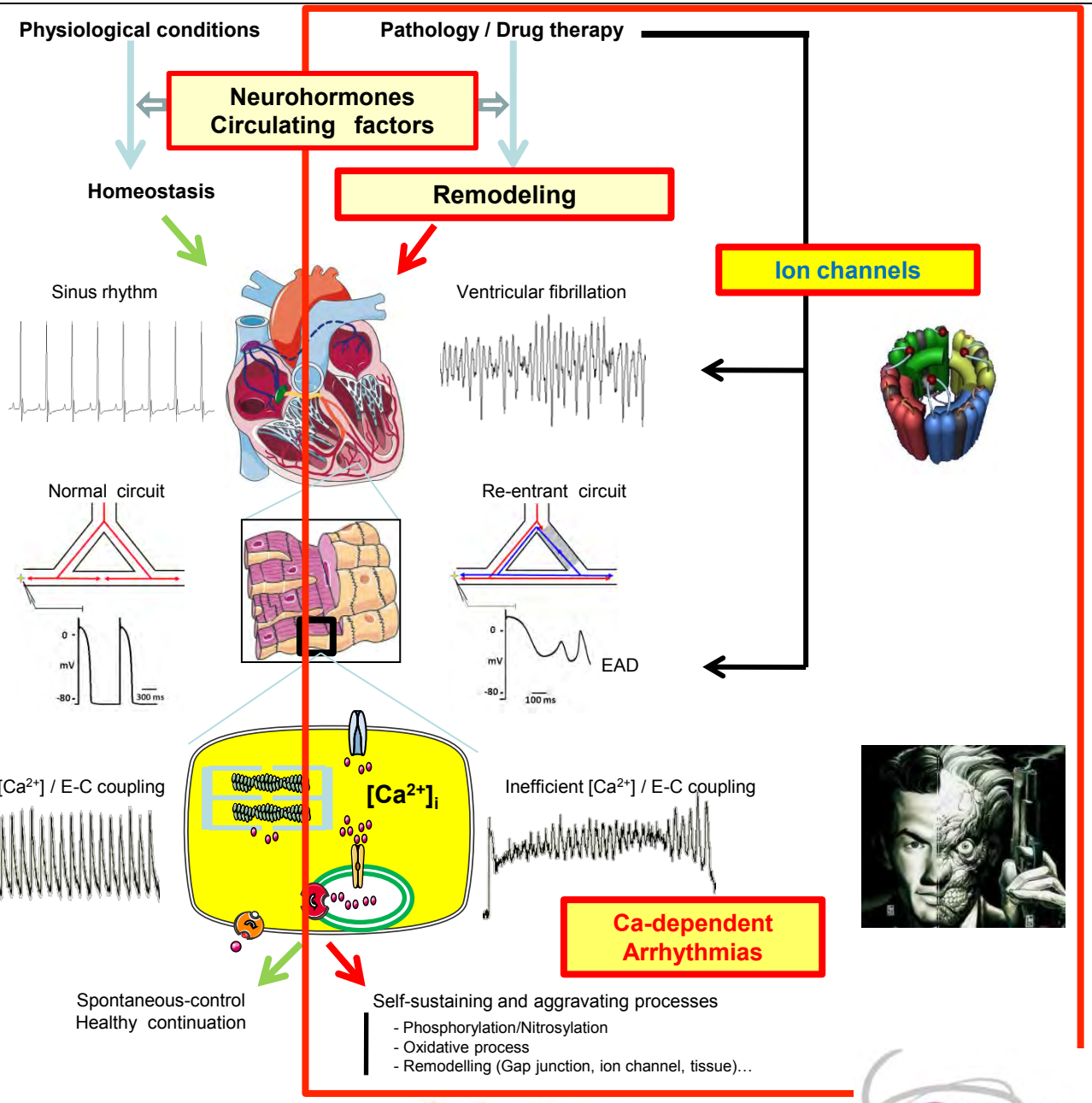
ESC Council on Basic Cardiovascular Science

Session VII B – Heart Failure and Arrythmogenesis

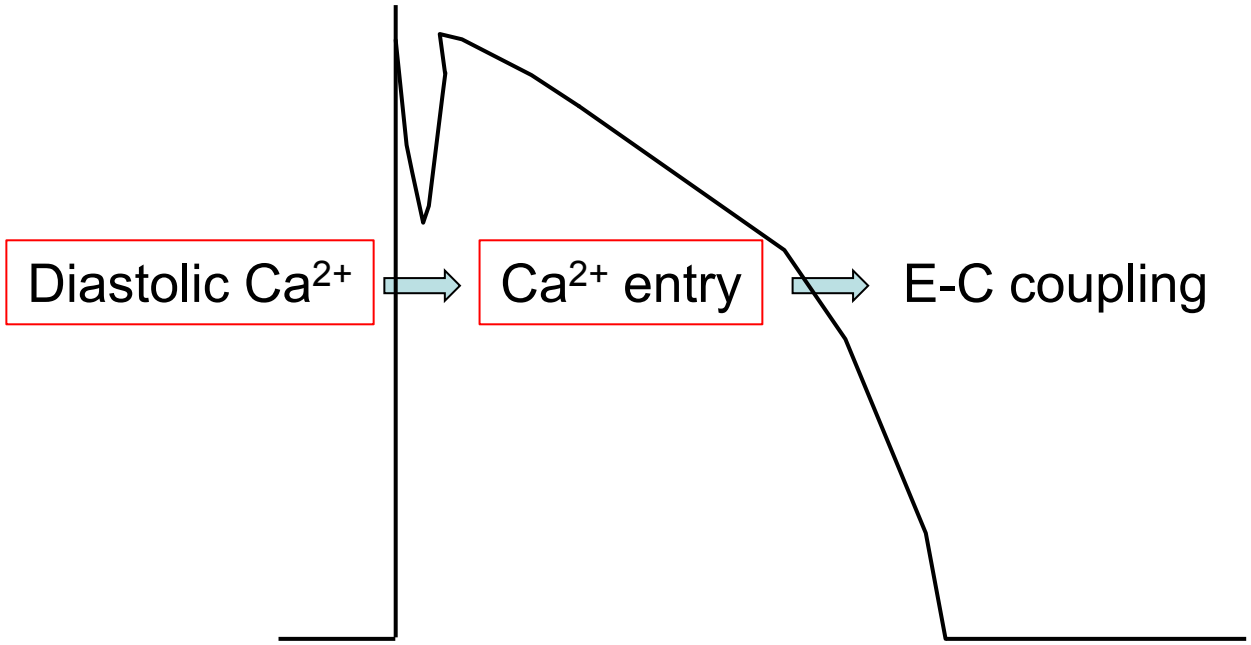
CBCS Summer School on Cardiovascular Sciences "From Basic Mechanisms to Clinical Application"

European Heart House / 12 – 16 June 2011

ESC Educational Courses


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)…

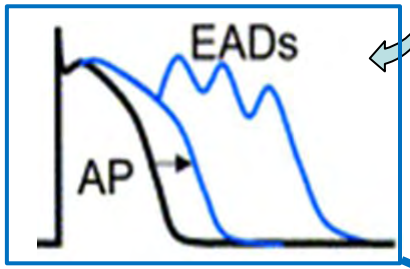
Ca^{2+}-dependent Arrhythmias in cardiomyocytes



Ca^{2+}-dependent Arrhythmias in cardiomyocytes: EADs

Sustained Depolarization

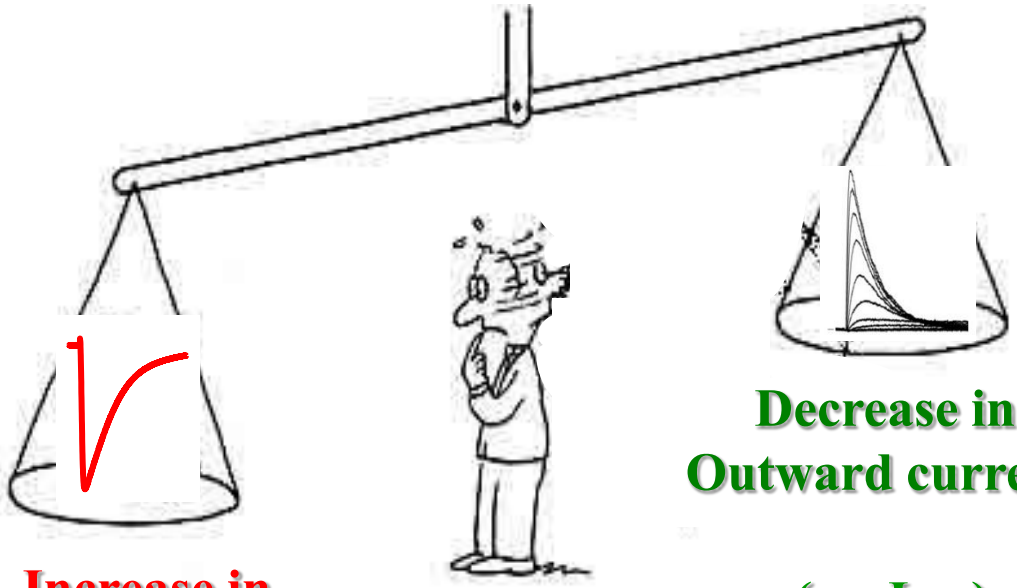
Diastolic Ca^{2+} → Ca^{2+} entry sustained → E-C coupling disorder



Arrhythmias

AP repolarization is critical for EADs

Pathology, Drugs, …

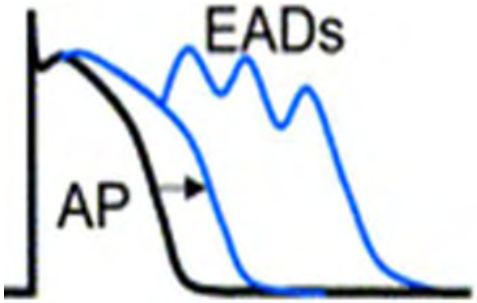


Increase in Inward currents

(*e.g* $I_{Na,Late}$)

Decrease in Outward currents

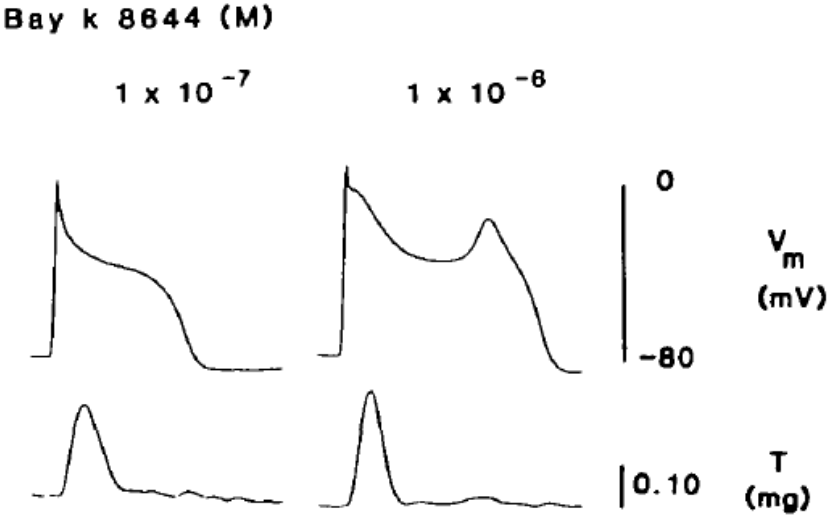
(*e.g* $I_{K...}$)



Role of Ca^{2+} entry in EADs: proof of concept

Early afterdepolarizations: mechanism of induction and block. A role for L-type Ca2+ current
CT January and JM Riddle
Circ. Res. 1989;64;977-990

A model for early afterdepolarizations: induction with the Ca2+ channel agonist Bay K 8644
CT January, JM Riddle and JJ Salata
Circ. Res. 1988;62;563-571



➡ **Role for window Ca^{2+} current**

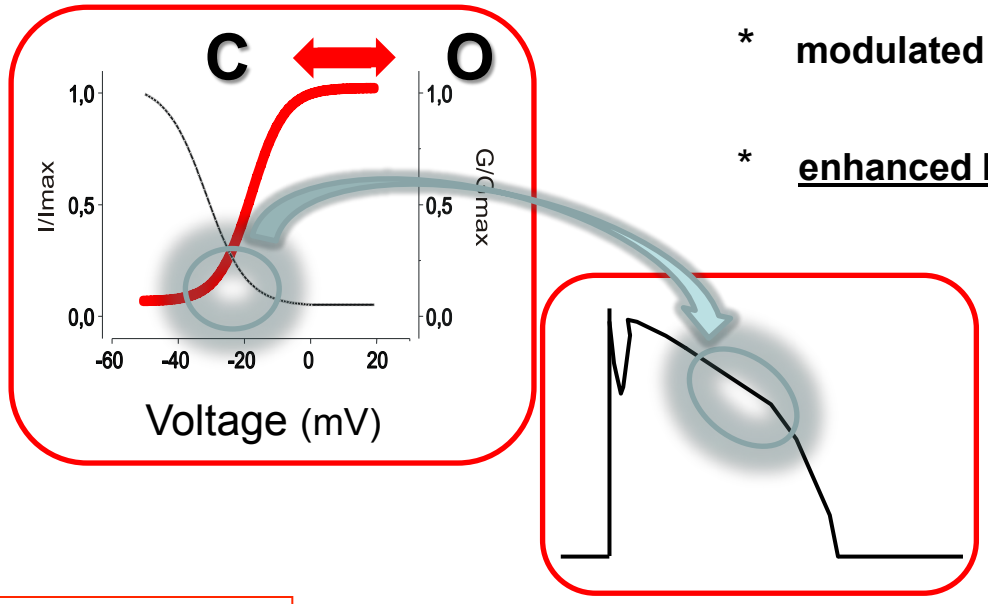
Modulation of I_{CaL} by Ca^{2+} release from the SR (in hypertrophy)

Window Ca2+ current and its modulation by Ca2+ release in hypertrophied cardiac myocytes from dogs with chronic atrioventricular block

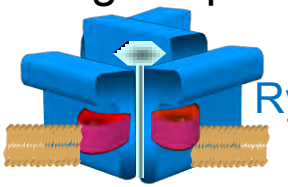
Gudrun Antoons, Paul G. A. Volders, Tania Stankovicova, Virginie Bito, Milan Stengl, Marc A. Vos and Karin R. Sipido

J. Physiol. 2007;579;147-160; originally published online Nov 30, 2006;

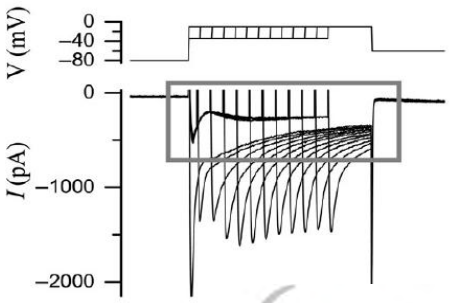
Larger Window I_{CaL}: Central role during AP plateau



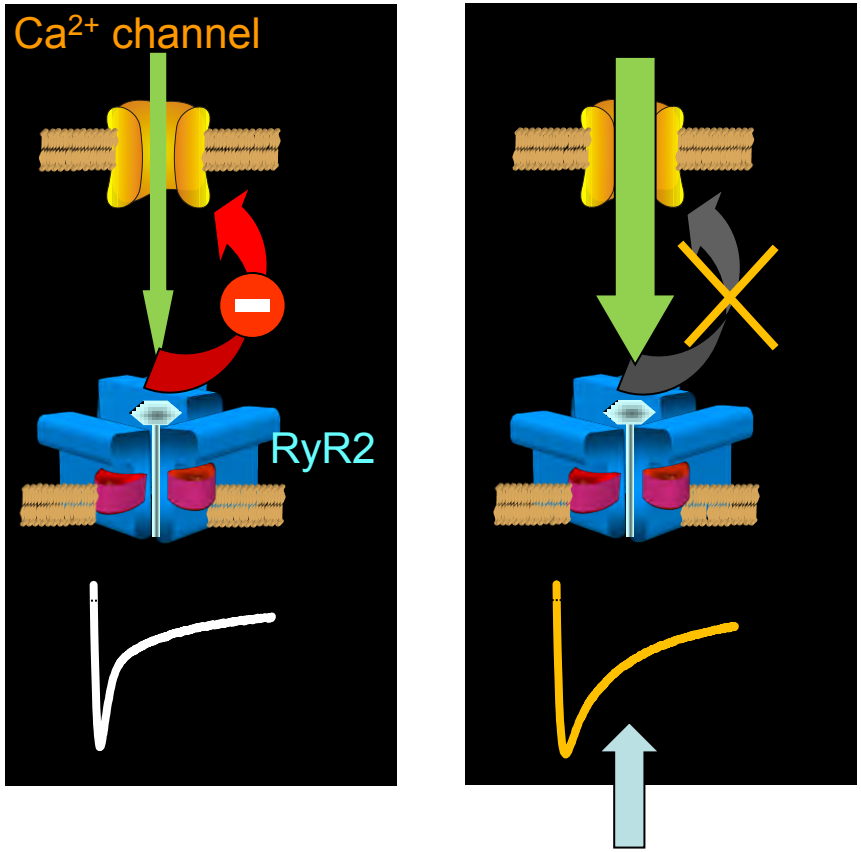
* **modulated by SR Ca^{2+} release**



* **<u>enhanced by β-AR stimulation</u> (increased Ca^{2+} release)**



Ca^{2+}-dependent inactivation of I_{CaL} and SR Ca^{2+} release



Ca^{2+} buffer (BAPTA)
SR Ca^{2+} depletion (thapsigargin)
RyR inhibition (Ryanodine)

Less SR Ca^{2+} release

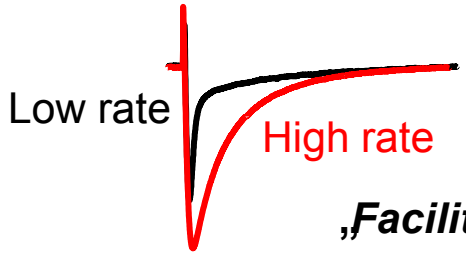
Less Inactivation of I_{CaL}

More Ca^{2+} entry
(depolarising inward current)

Dynamic regulation of AP Duration

'beat-to-beat basis'

(pacing rate)



‚Facilitation'

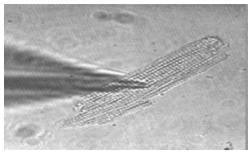
Richard et al., 2006, Prog Biophys & Mol Biol.

Pacing-dep. AP prolongation and EADs (in HF; rodents)

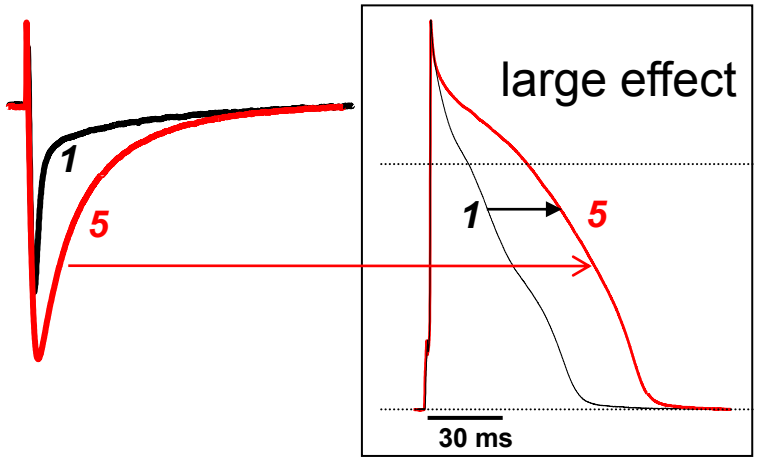
Cardiomyocytes hypertrophic status after myocardial infarction determines distinct types of arrhythmia: Role of the ryanodine receptor

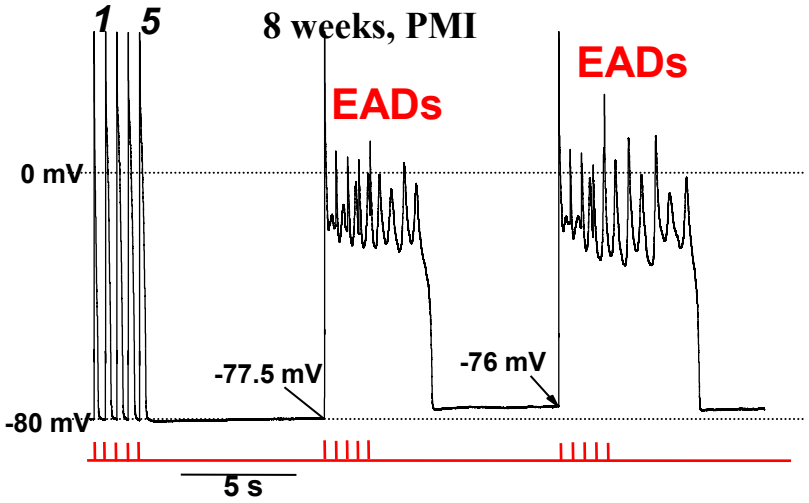
Jérémy Fauconnier[a,1], Jean-Luc Pasquié[a,b,1], Patrice Bideaux[a,1], Alain Lacampagne[a,1], Sylvain Richard[a,*]

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



Less SR Ca release during systole





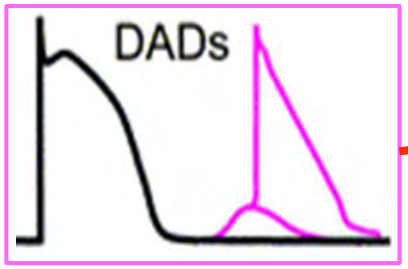
Ca^{2+}-dependent Arrhythmias in cardiomyocytes: DADs

Diastolic Ca^{2+} ⟹

E-C coupling

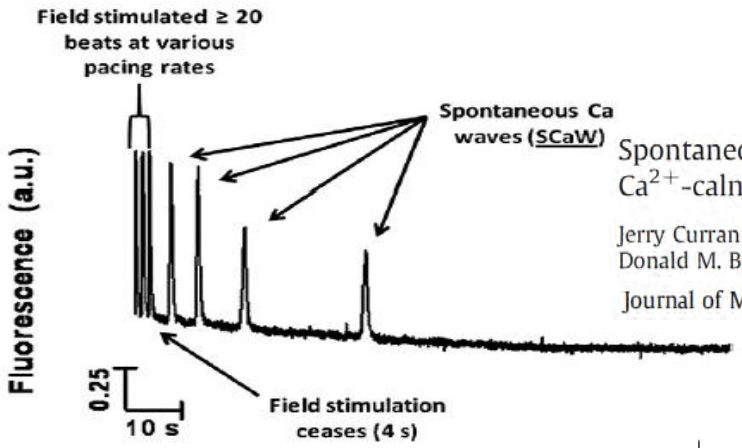
Ca^{2+} waves

I_{ti} (NCX)



Arrhythmias

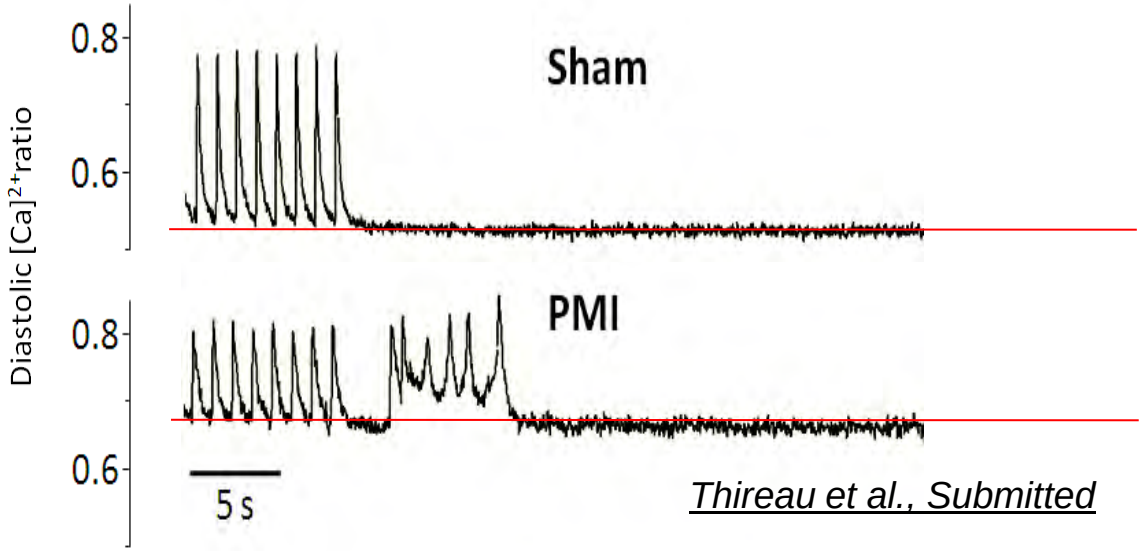
Spontaneous Ca^{2+} waves/transients in cardiomyocytes



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

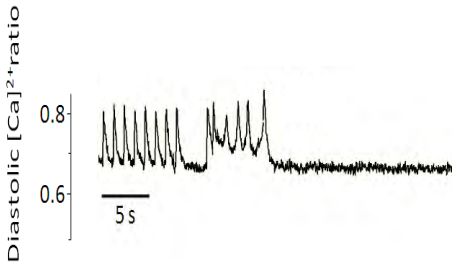
Jerry Curran [a], Kathy Hayes Brown [a], Demetrio J. Santiago [a], Steve Pogwizd [b], Donald M. Bers [c], Thomas R. Shannon [a,*]

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



Thireau et al., Submitted

Spontaneous Ca^{2+} waves/transients in cardiomyocytes



1) CPVT

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

2) CO

(heart with normal function ;
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3) *Duchenne Muscular Dystrophy (mdx)*

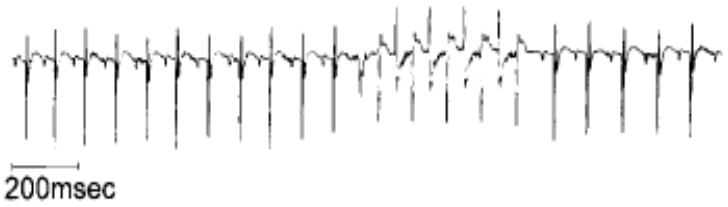
(progressive cardiomyopathy;
fatal cardiac arrhythmias)

4) Heart Failure

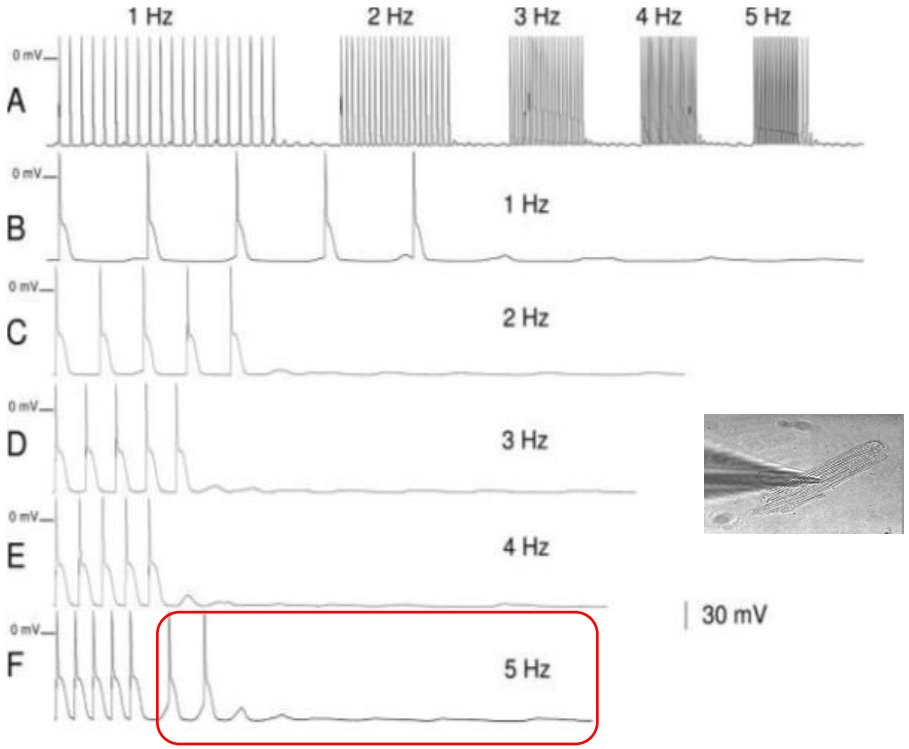
Arrhythmia in CPVT

SG. Priori, C. Napolitano

RyR2 **R4496C**



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



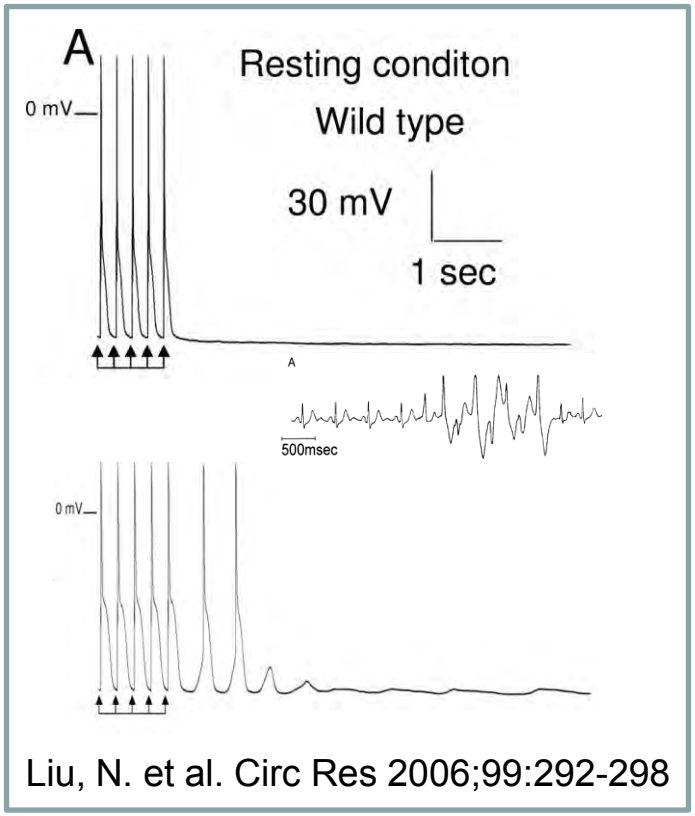
Arrhythmogenesis in Catecholaminergic Polymorphic Ventricular Tachycardia

Insights From a RyR2 R4496C Knock-In Mouse Model

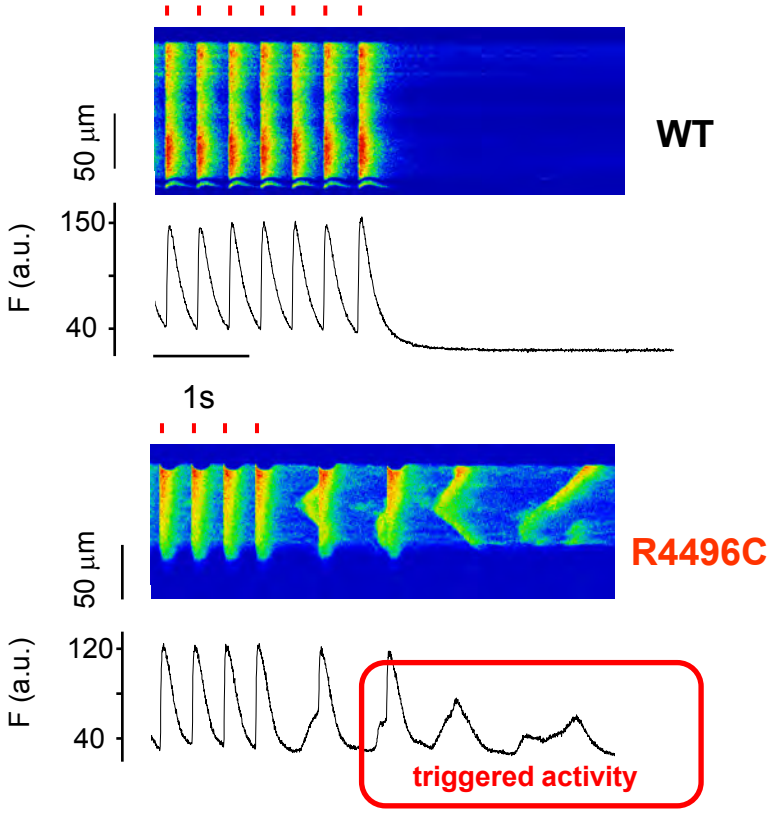
Nian Liu, Barbara Colombi, Mirella Memmi, Spyros Zissimopoulos, Nicoletta Rizzi, Sara Negri, Marcello Imbriani, Carlo Napolitano, F. Anthony Lai, Silvia G. Priori

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

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



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

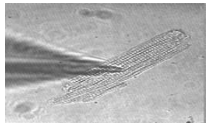


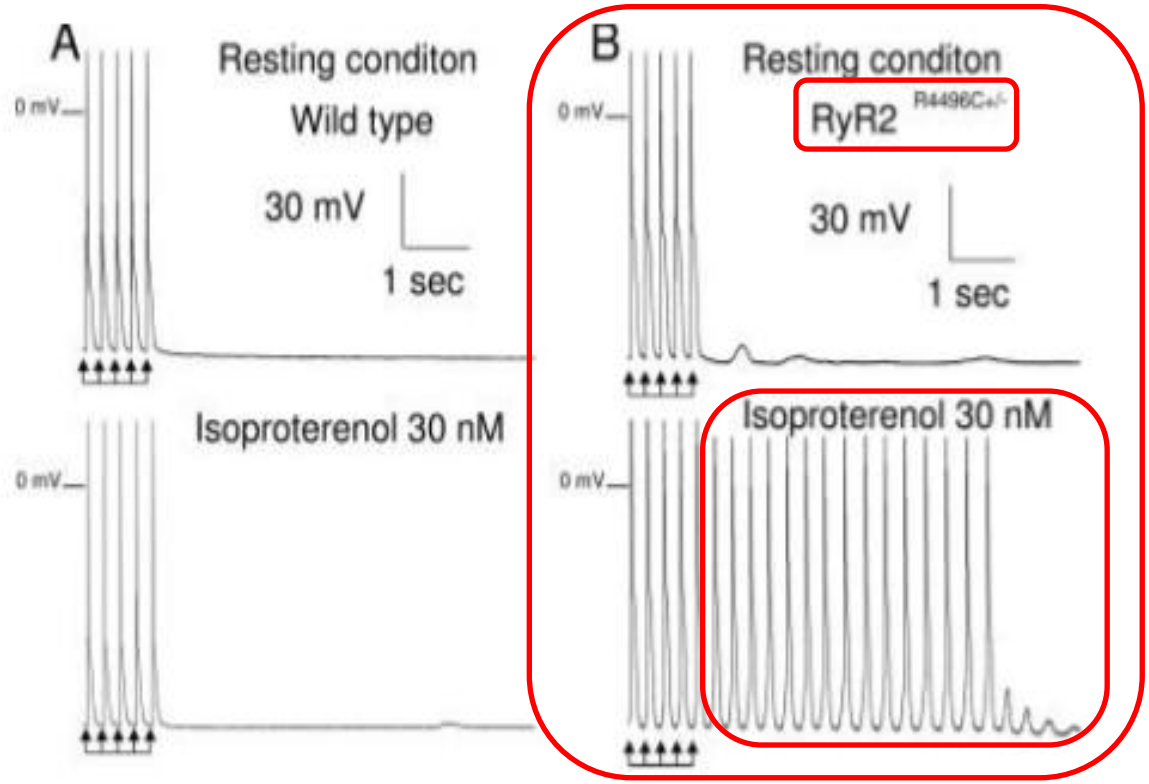
Increased Ca^{2+} Sensitivity of the Ryanodine Receptor Mutant $RyR2^{R4496C}$ Underlies Catecholaminergic Polymorphic Ventricular Tachycardia

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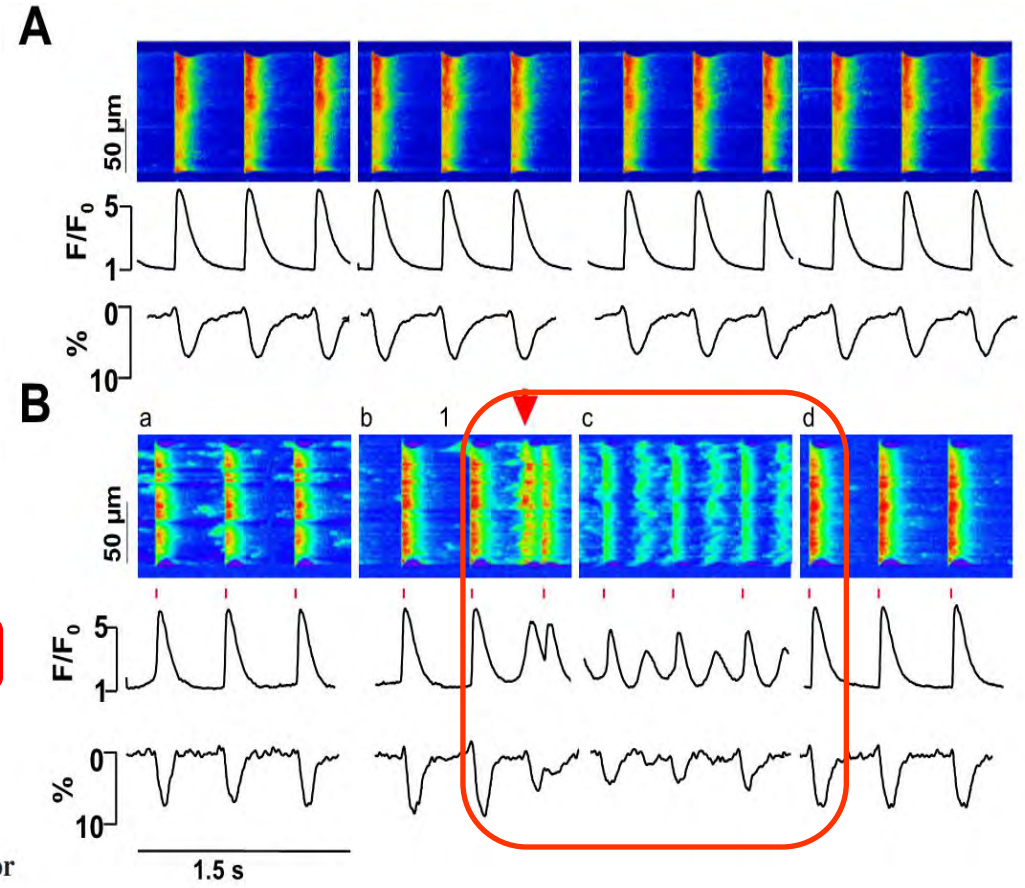
(*Circ Res*. 2006;99:292-298.)

… more spontaneous Ca^{2+} waves with isoproterenol

WT + 1 µM Iso

$RyR^{24496C+/-}$ + 1 µM Iso



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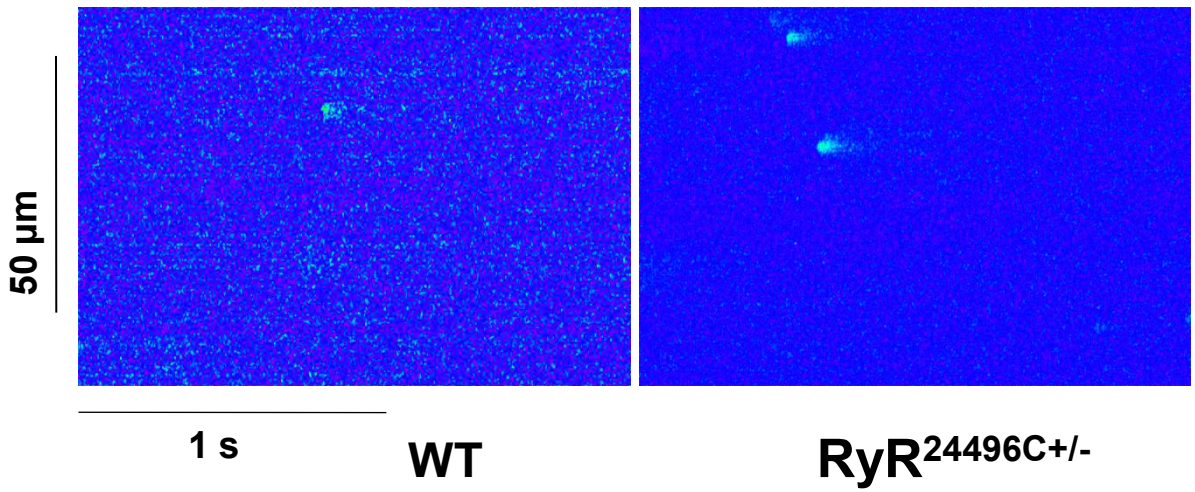
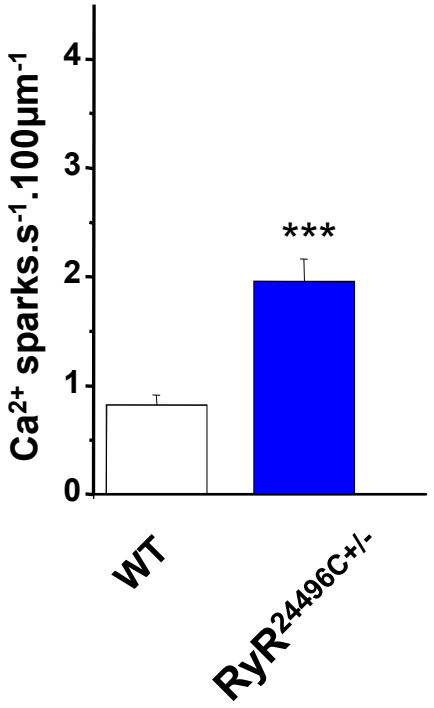
Circ Res. 2009;104:201-209.

Spontaneous RyR2 activity is increased





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Spontaneous Ca^{2+} waves/transients in cardiomyocytes

1) CPVT

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

2) CO

(heart with normal function ;
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3) Duchenne Muscular Dystrophy

(mdx)

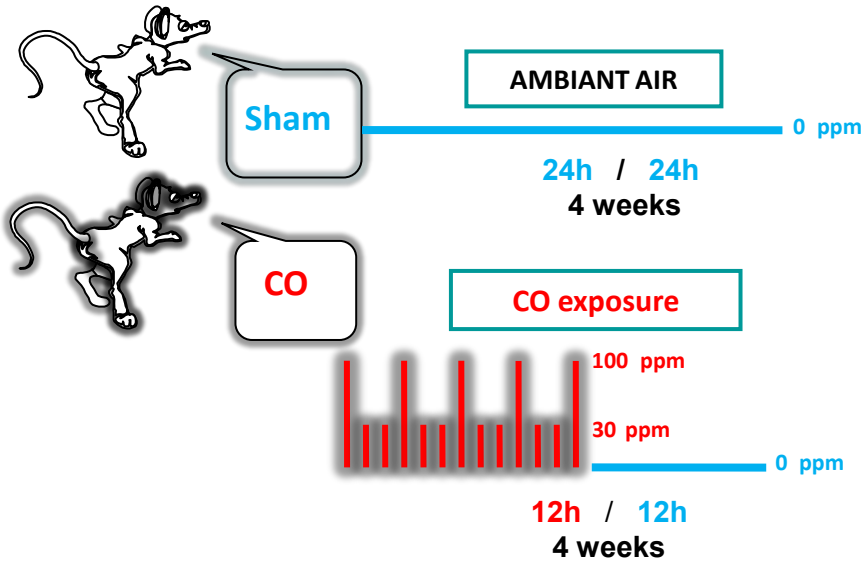
(progressive cardiomyopathy;
fatal cardiac arrhythmias)

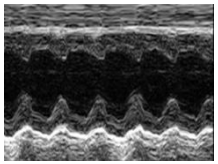
4) Heart Failure

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 exposure altered heart morphology (hypertrophy, LV interstitial and perivascular fibrosis) but weak effects on *in vivo* cardiac function

No change in cardiomyocyte size

BUT...

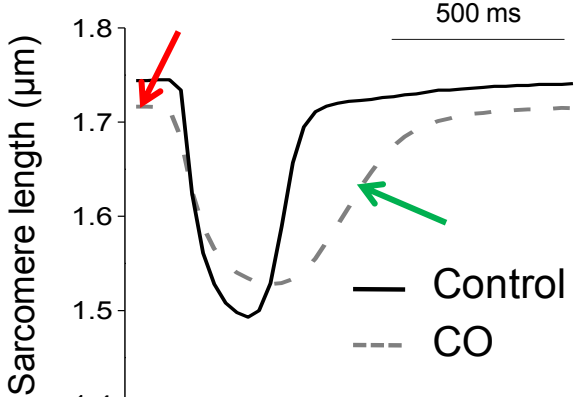
TABLE 1. EFFECTS OF CHRONIC CARBON MONOXIDE EXPOSURE ON CARDIOVASCULAR FUNCTION AND CARDIAC MORPHOLOGY *IN VIVO*

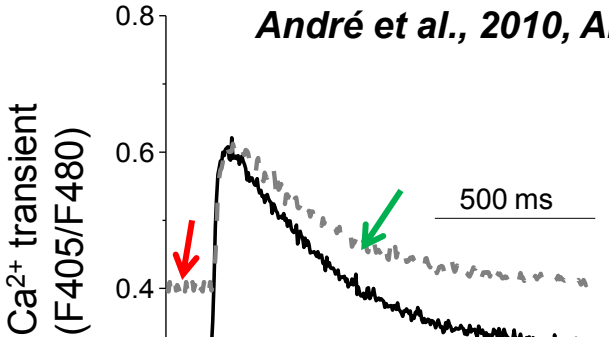
	Control ($n = 12$)	CO ($n = 16$)
Morphological data		
Body wt, g	514 ± 9	511 ± 5
Heart wt/100 g body wt, mg/100 g	259 ± 4	276 ± 6*
LV/100 g body wt, mg/100 g	204 ± 5	219 ± 4*
Fibrosis, % of total area	1.96 ± 0.29	3.72 ± 0.4*
Echocardiographic data		
LVEdD, mm	9.46 ± 0.14	9.61 ± 0.21
LVEsD, mm	5.76 ± 0.17	6.30 ± 0.16*
Anterior wall thickness, mm	1.02 ± 0.04	1.06 ± 0.06
Posterior wall thickness, mm	1.16 ± 0.11	1.29 ± 0.19*
LV shortening fraction, %	39.22 ± 1.18	34.35 ± 1.11*
Posterior wall end-systolic strain, %	98 ± 7	78 ± 9*
E/A-wave velocity ratio	1.89 ± 0.33	1.98 ± 0.34
Hemodynamic data		
Systolic arterial pressure, mm Hg	120 ± 10	121 ± 4
Diastolic arterial pressure, mm Hg	93 ± 9	96 ± 4
Mean arterial pressure, mm Hg	102 ± 10	105 ± 5
LV developed pressure, mm Hg	104 ± 5	106 ± 5
LV dP/dt max, mm Hg/s	5018 ± 326	4781 ± 255
LV dP/dt min, mm Hg/s	−4700 ± 285	−4676 ± 287
LV tau, s	8.22 ± 0.27	8.31 ± 0.16

Definition of abbreviations: CO = carbon monoxide; LV = left ventricular; LVEdD = left ventricular end-diastolic diameter; LVEsD = left ventricular end-systolic diameter; LV dP/dt max = maximal first derivative of left ventricular pressure; LV dP/dt min = minimal first derivative of left ventricular pressure; LV tau = time constant of left ventricular pressure decay; *$P < 0.05$ vs. control.

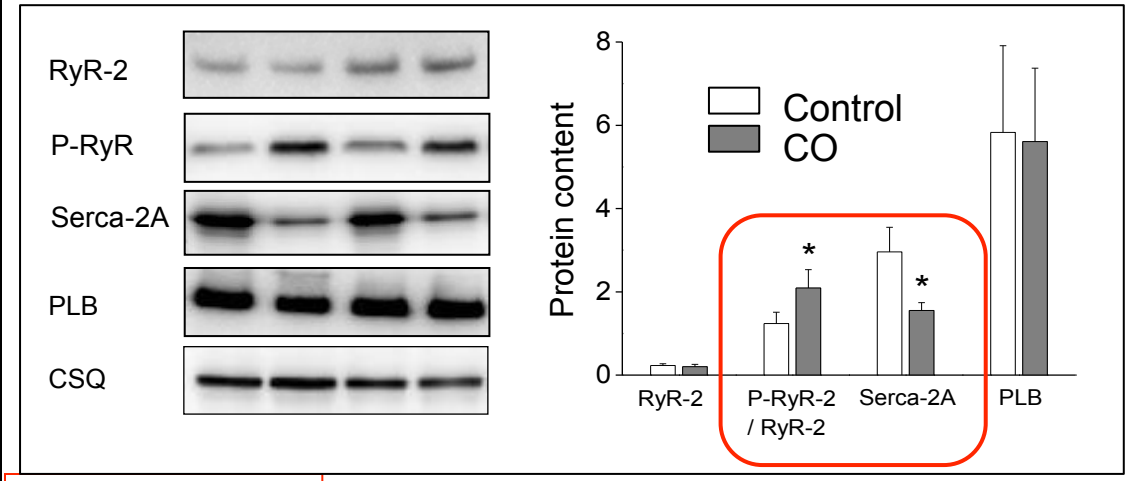
André et al., 2010, Am J Respir Crit Care Med

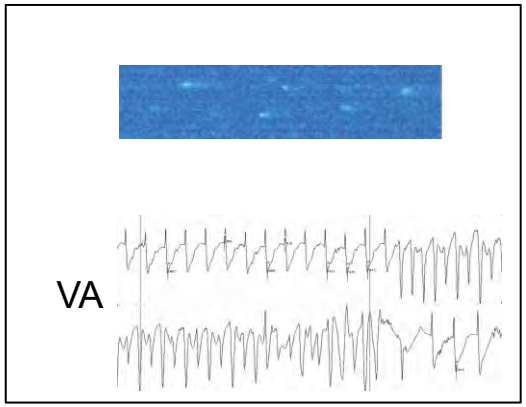
Chronic CO alters cell contraction and Ca^{2+} transients (both RyR2 and SERCA involved)



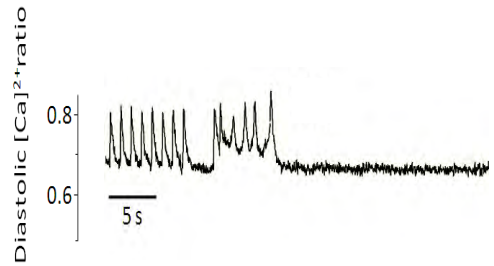


André et al., 2010, Am J Respir Crit Care Med





Spontaneous Ca^{2+} waves/transients in cardiomyocytes



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3) Duchenne Muscular Dystrophy (mdx)

(progressive cardiomyopathy;
fatal cardiac arrhythmias)

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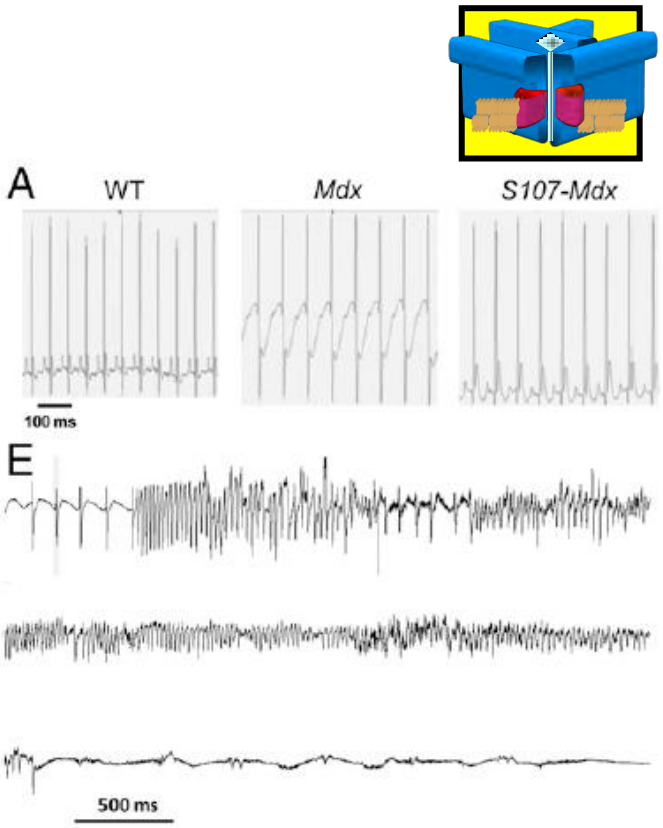
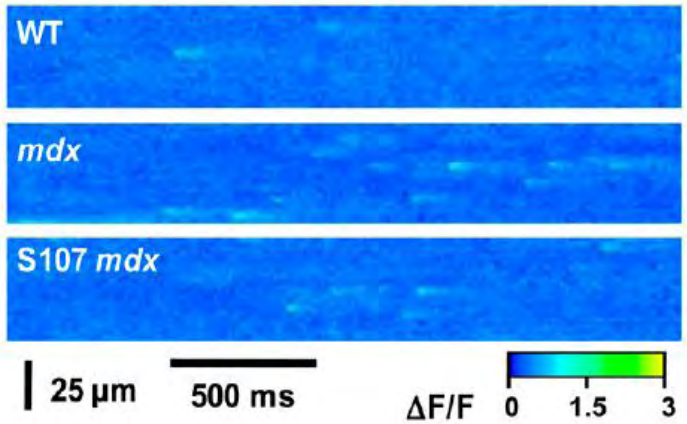
Leaky RyR2 trigger ventricular arrhythmias in Duchenne muscular dystrophy

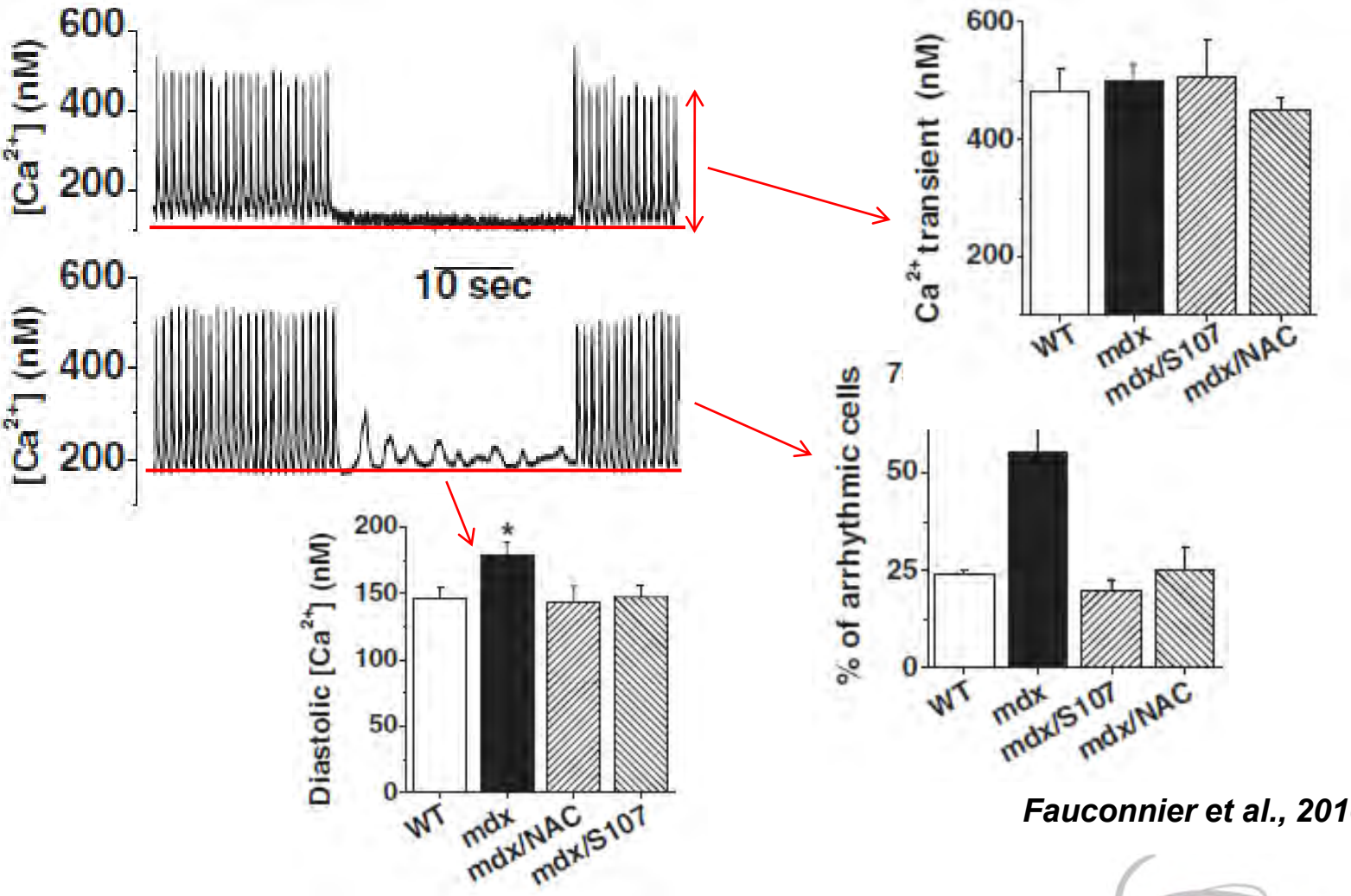
Jérémy Fauconnier[a,b,1], Jérôme Thireau[a,1], Steven Reiken[c], Cécile Cassan[a,b], Sylvain Richard[a,b], Stefan Matecki[b,d], Andrew R. Marks[c], and Alain Lacampagne[a,b,2]

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



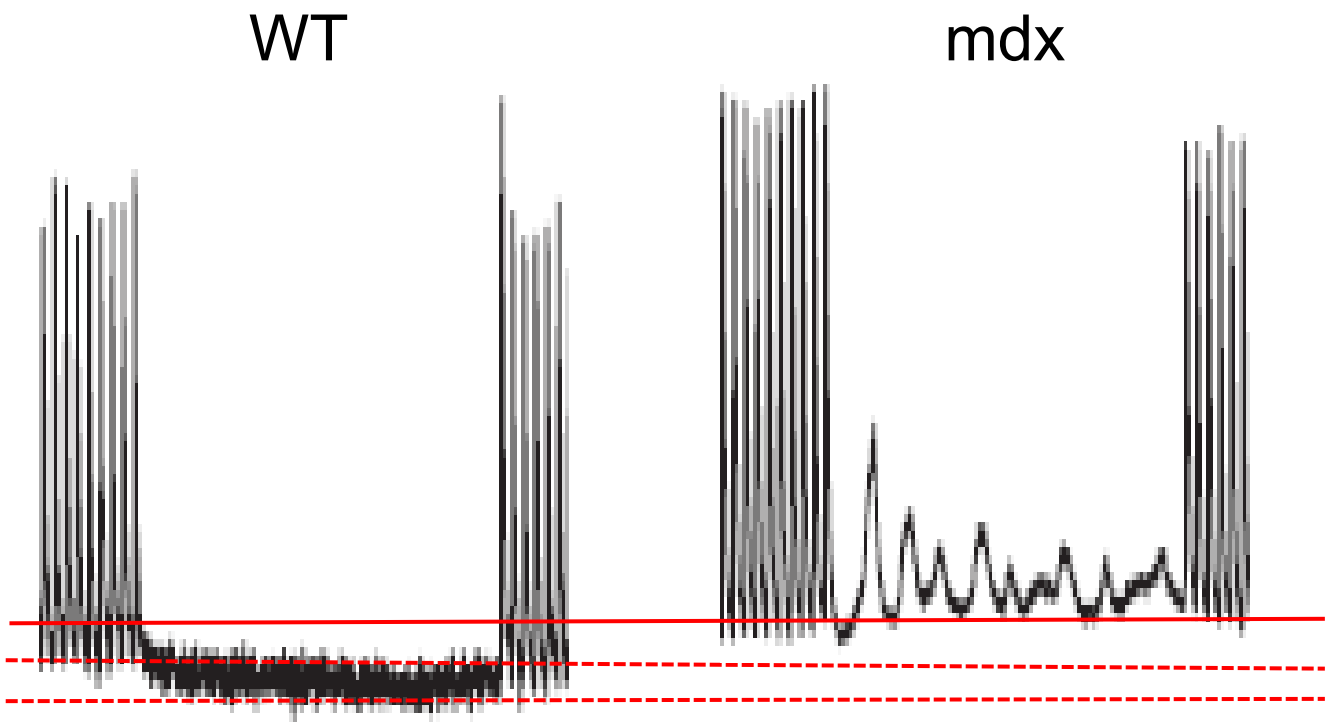


Diastolic Ca^{2+} and spontaneous Ca^{2+} waves in *mdx* mice



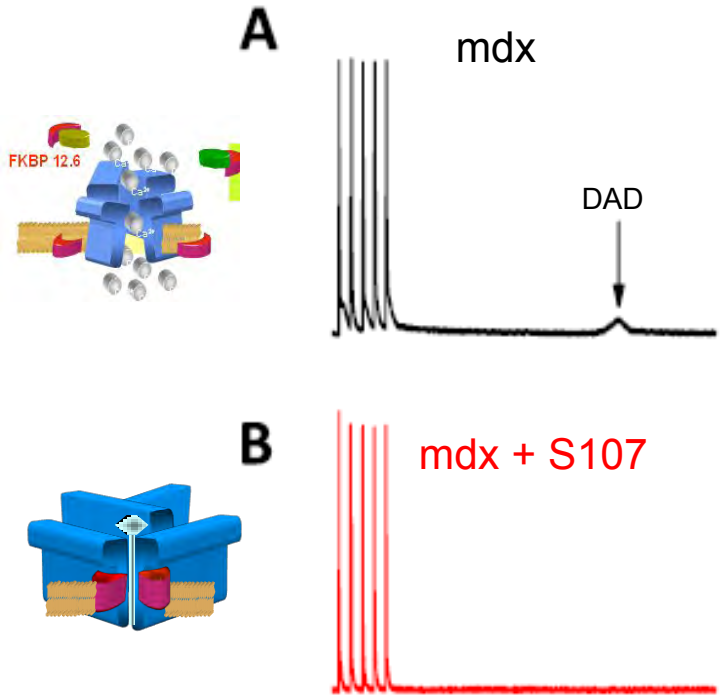
Fauconnier et al., 2010, PNAS

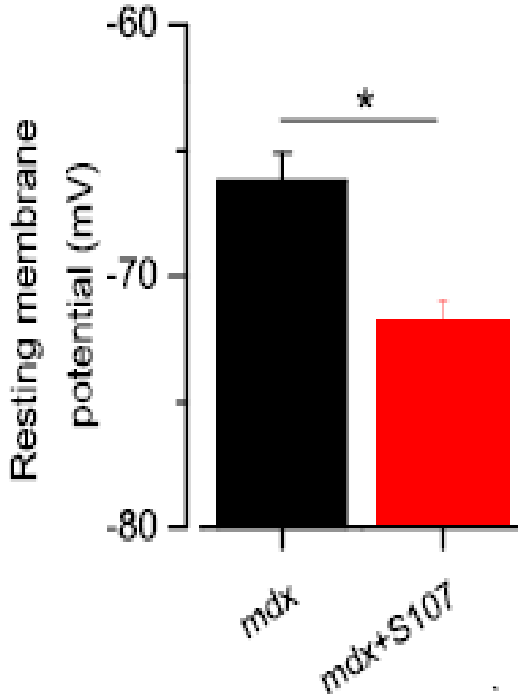
High diastolic Ca^{2+} and Ca^{2+} waves



Fauconnier et al., 2010, PNAS

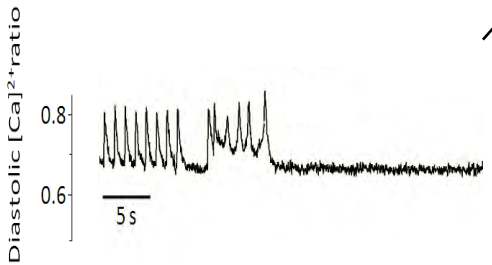
„Rycal"S107 suppresses DADs





Fauconnier et al., 2010, PNAS

Spontaneous Ca^{2+} waves/transients in cardiomyocytes



1) CPVT

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

2) CO

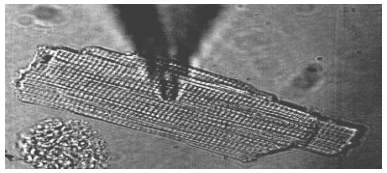
(heart with normal function ;
alterations of Ca^{2+} signaling)

3) *Duchenne Muscular Dystrophy (mdx)*

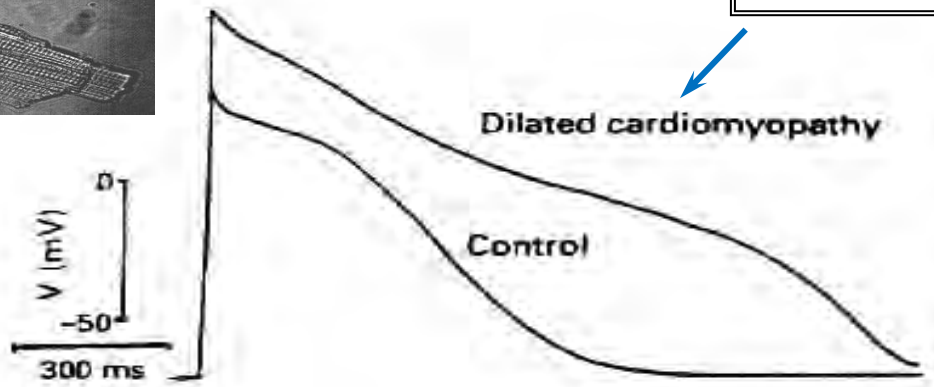
(progressive cardiomyopathy;
fatal cardiac arrhythmias)

4) Heart Failure

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

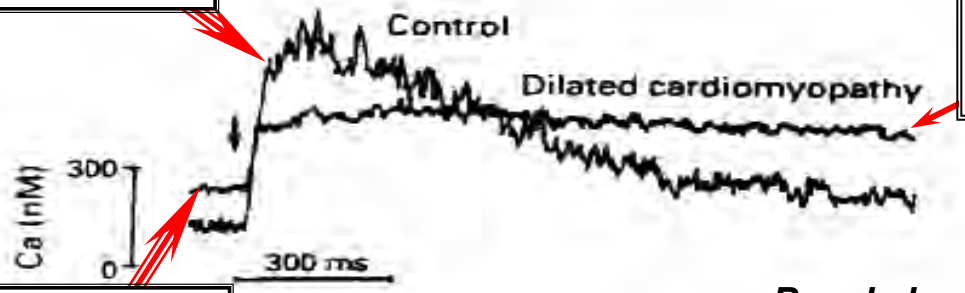


Ca^{2+} entry



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

Decreased systolic Ca^{2+}

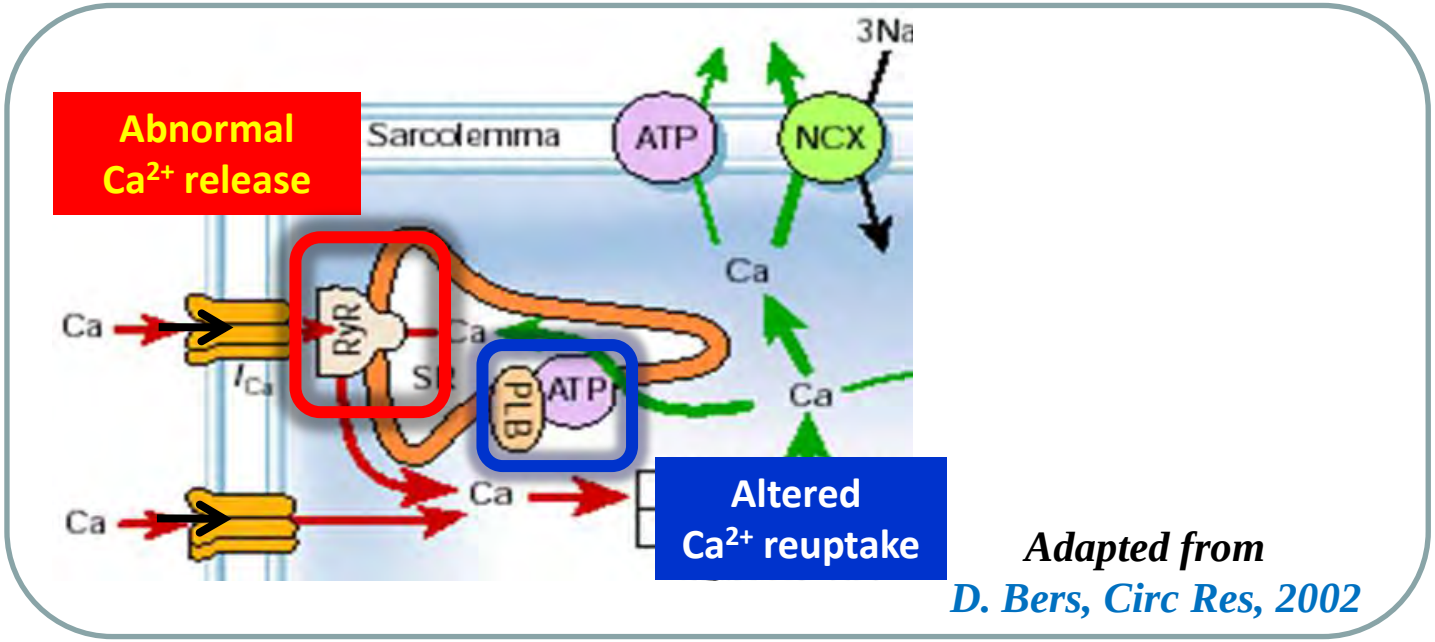


Prolongation of Ca^{2+} transients

Elevated diastolic Ca^{2+}

Beuckelmann et al., Circulation, 1992

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



Adapted from
D. Bers, Circ Res, 2002

« SERCA inhibition increases the chance of spontaneous SR Ca^{2+} release via RyR2 at a given SR content »

Interplay between SERCA and sarcolemmal Ca^{2+} efflux pathways controls spontaneous release of Ca^{2+} from the sarcoplasmic reticulum in rat ventricular myocytes

S. C. O'Neill, L. Miller, R. Hinch and D. A. Eisner

J Physiol 559.1 (2004) pp 121–128

Leaky RyR2 in Ca^{2+}-dependent arrhythmia in HF

Sarcoplasmic Reticulum Ca2+ and Heart Failure: Roles of Diastolic Leak and Ca 2+ Transport
Donald M. Bers, David A. Eisner and Héctor H. Valdivia
Circ. Res. 2003;93;487-490

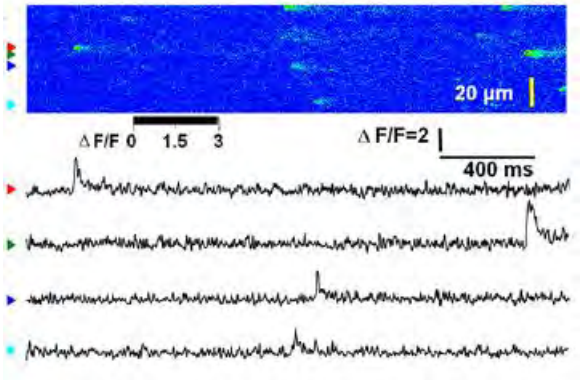
Enhanced Ryanodine Receptor-Mediated Calcium Leak Determines Reduced Sarcoplasmic Reticulum Calcium Content in Chronic Canine Heart Failure
Andriy Belevych,*† Zuzana Kubalova,¶ Dmitry Terentyev,*† Robert L. Hamlin,‡ Cynthia A. Carnes,*§ and Sandor Györke*†
Biophysical Journal Volume 93 December 2007 4083–4092

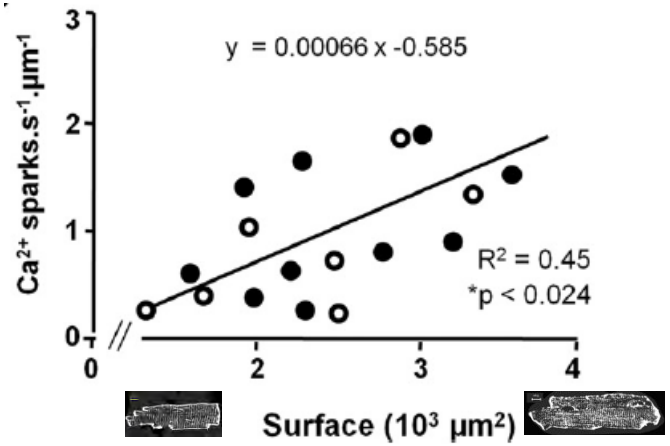
Abnormal intrastore calcium signaling in chronic heart failure
Zuzana Kubalova*, Dmitry Terentyev*, Serge Viatchenko-Karpinski*, Yoshinori Nishijima†, Inna Györke*, Radmila Terentyeva*, Daise N. Q. da Cuñha†, Arun Sridhar‡, David S. Feldman*§, Robert L. Hamlin†, Cynthia A. Carnes*¶, and Sandor Györke*¶‖
PNAS | September 27, 2005 | vol. 102 | no. 39

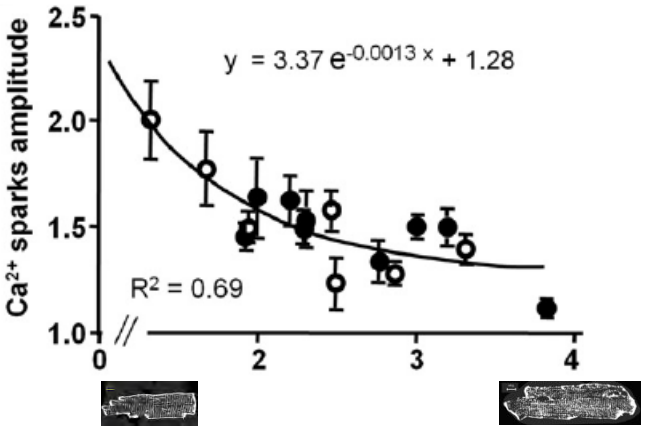
Elevated Sarcoplasmic Reticulum Ca2+ Leak in Intact Ventricular Myocytes From Rabbits in Heart Failure
Thomas R. Shannon, Steven M. Pogwizd and Donald M. Bers
Circ. Res. 2003;93;592-594; originally published online Aug 28, 2003;

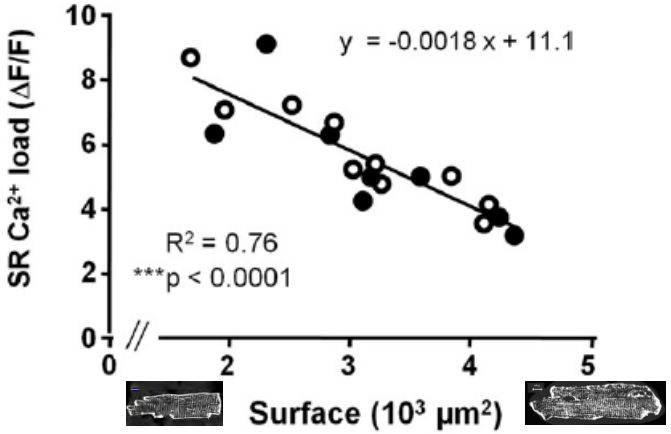
PKA Phosphorylation Dissociates FKBP12.6 from the Calcium Release Channel (Ryanodine Receptor): Defective Regulation in Failing Hearts
Steven O. Marx,*†‖ Steven Reiken,*†‖ Yuji Hisamatsu,*† Thotalla Jayaraman,*† Daniel Burkhoff,*† Nora Rosemblit,*† and Andrew R. Marks*†‡§
Cell, Vol. 101, 365–376, May 12, 2000,

Cellular hypertrophy, Ca^{2+} sparks and SR Ca^{2+} load









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,*]

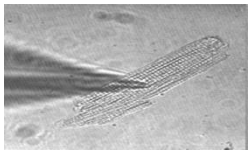
Progress in Biophysics and Molecular Biology 103 (2010) 71–80

Pacing-dependent AP prolongation and EADs (in HF)

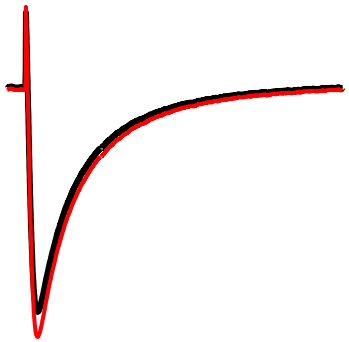
Cardiomyocytes hypertrophic status after myocardial infarction determines distinct types of arrhythmia: Role of the ryanodine receptor

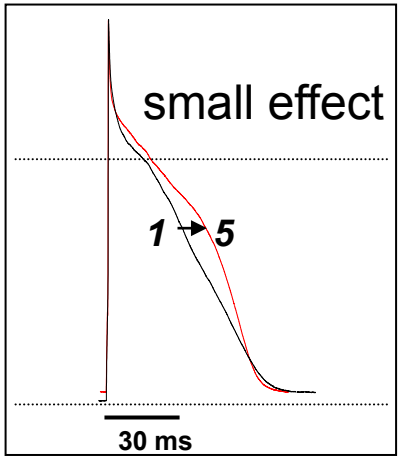
Jérémy Fauconnier [a,1], Jean-Luc Pasquié [a,b,1], Patrice Bideaux [a,1], Alain Lacampagne [a,1], Sylvain Richard [a,*]

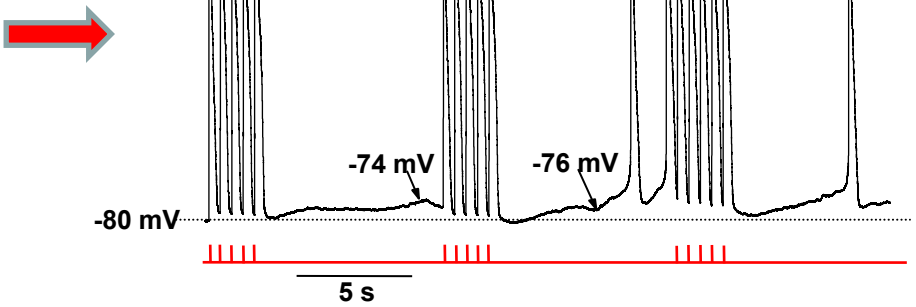
Progress in Biophysics and Molecular Biology 103 (2010) 71–80

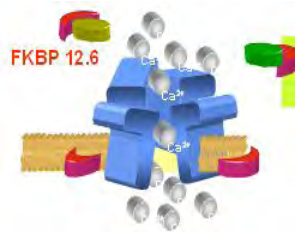


SR Ca^{2+} leak via RyR2







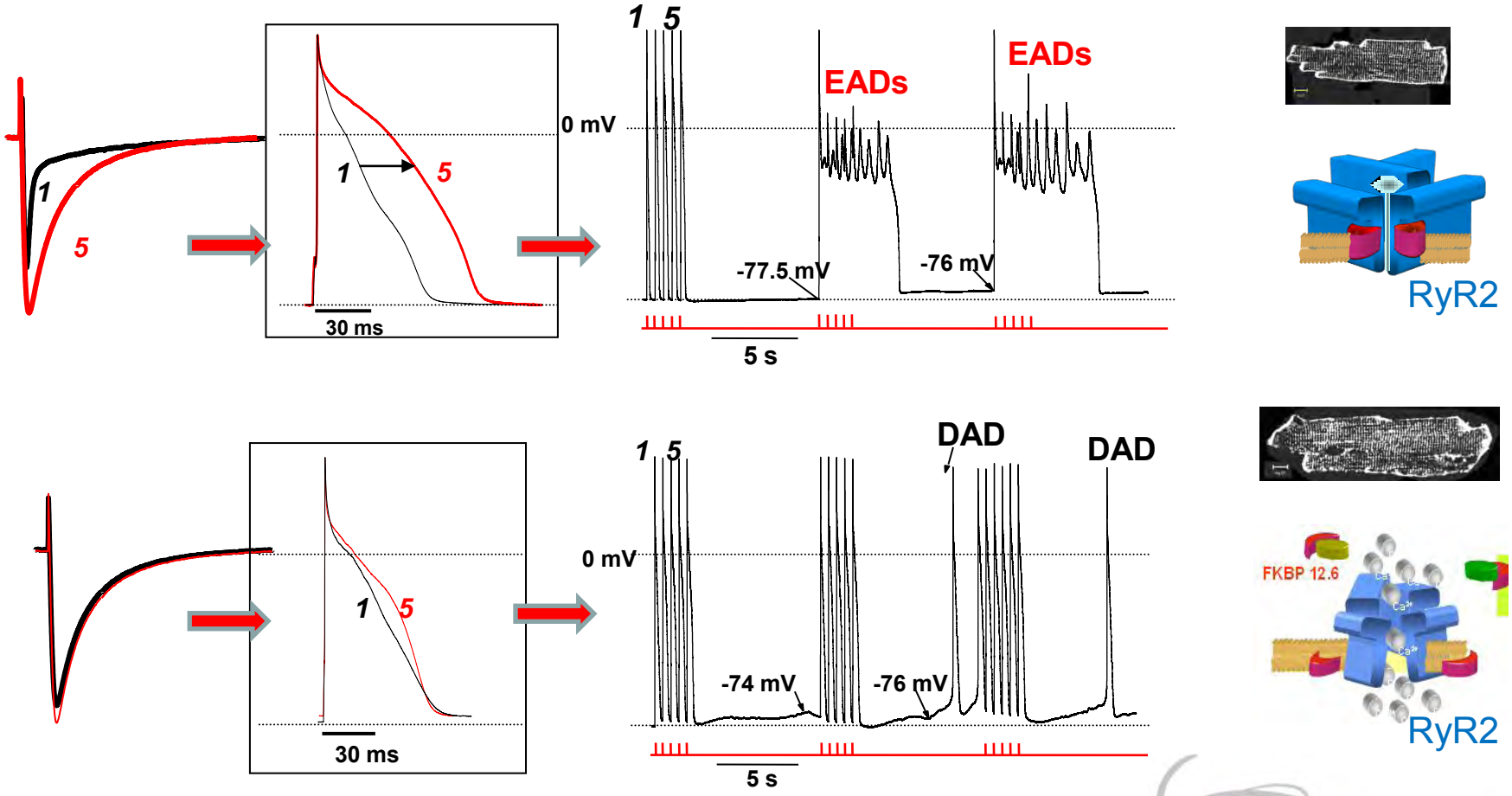


Abnormal RyR2 openings during diastole promote arrhythmias

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



Ca^{2+}-dependent Arrhythmias

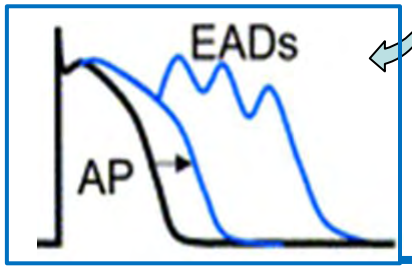
Sustained Depolarization

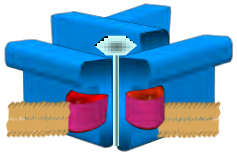
Diastolic Ca^{2+} → Ca^{2+} entry → E-C coupling

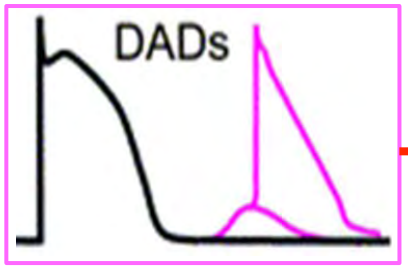
Ca^{2+} re-entry

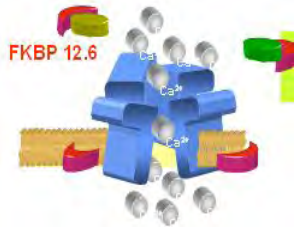
Ca^{2+} waves

I_{ti} (NCX)







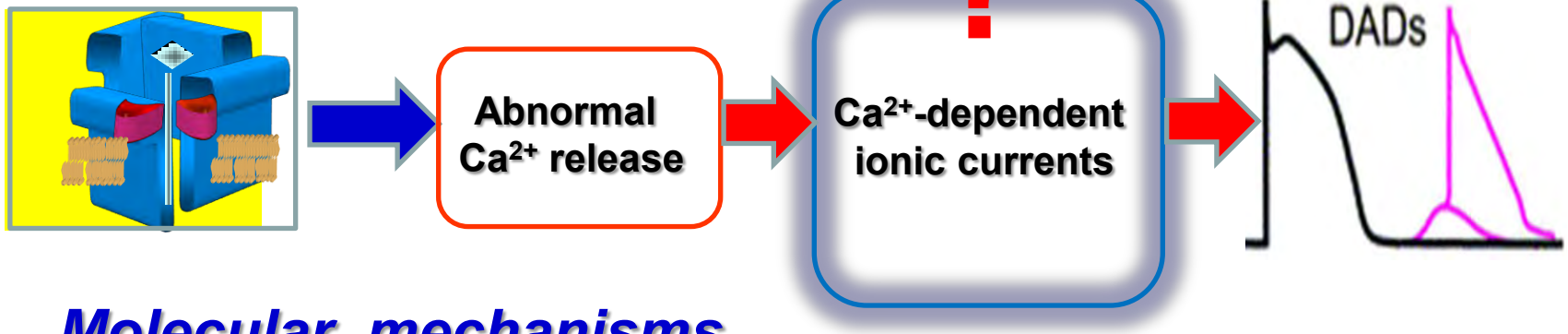


Ca^{2+} → Arrhythmias

Cellular Mechanisms translating RyR2 dysfunction into electrical abnormalities?

RyR2 dysfunction

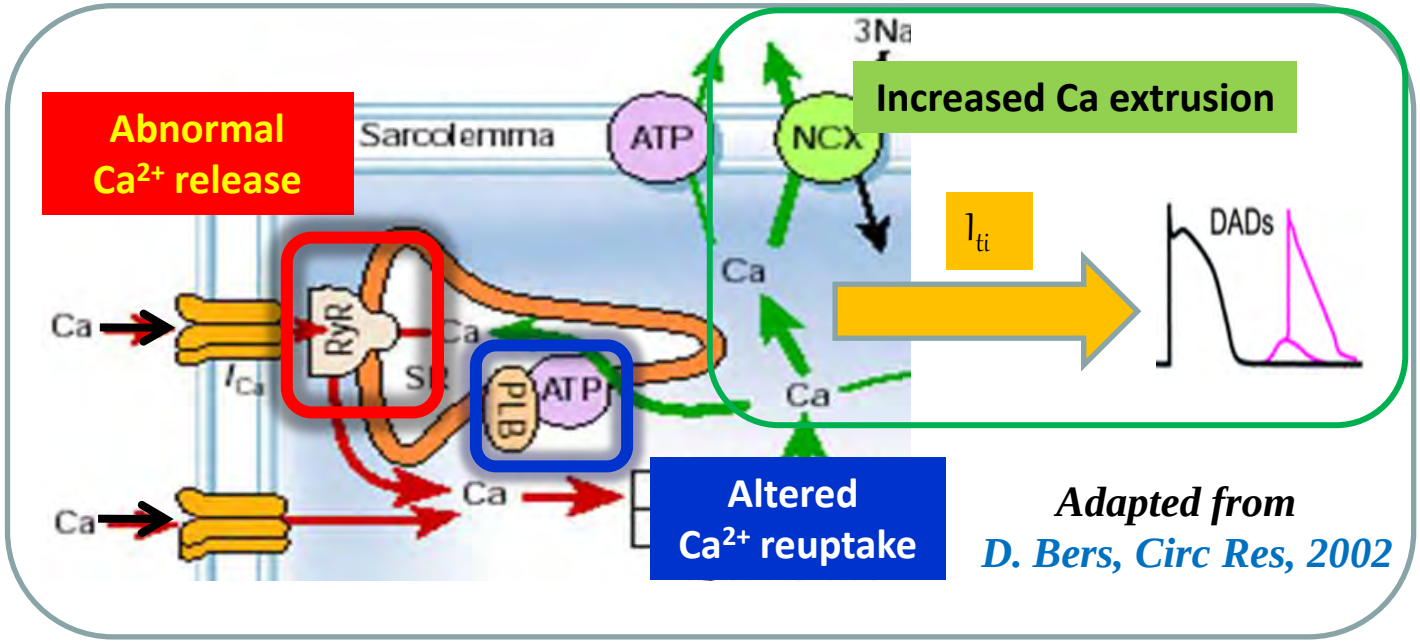
Arrhythmia / SCD



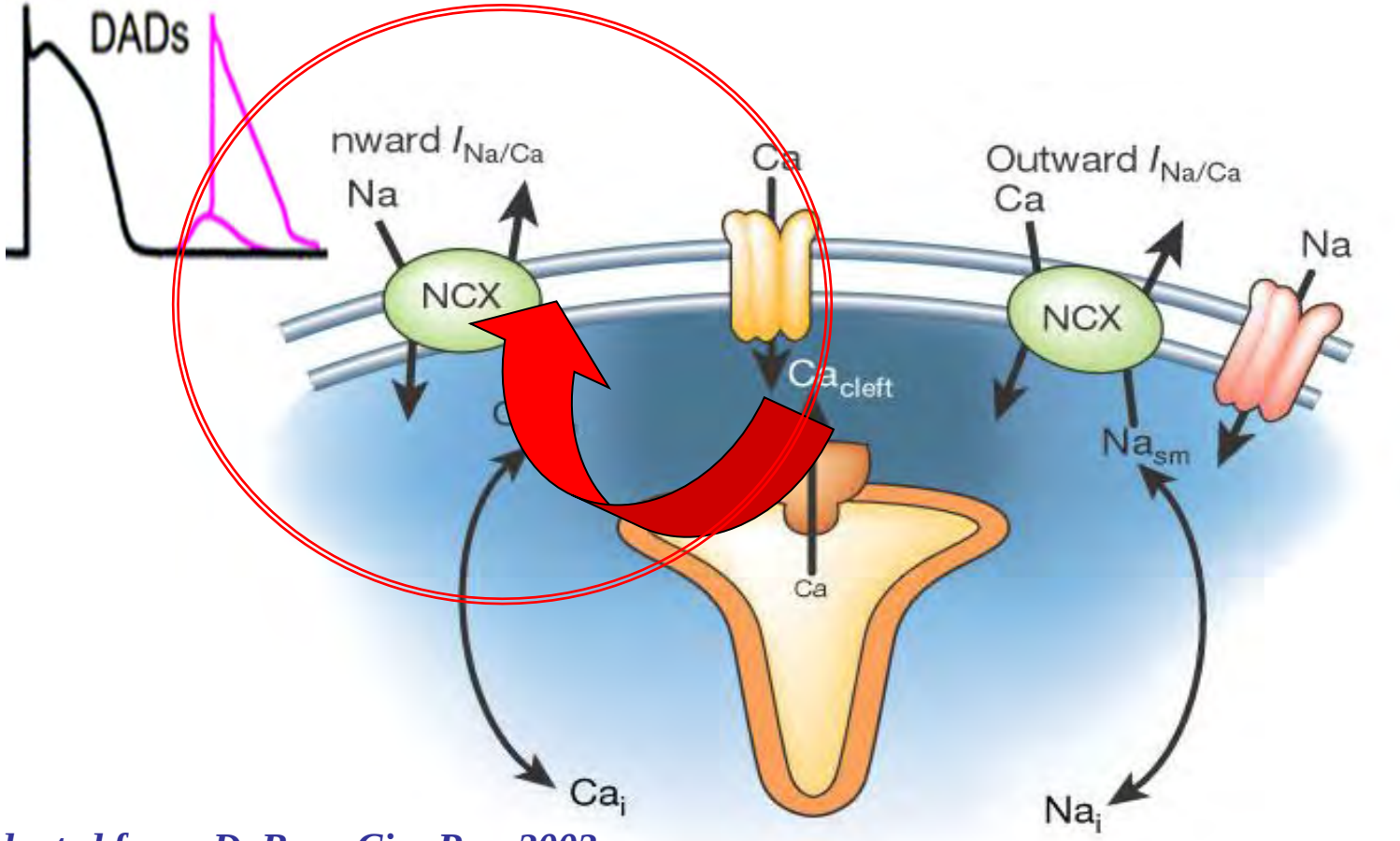
Molecular mechanisms

Cellular mechanisms

Translation of Ca^{2+} waves into arrhythmia : role of I_{TI}



Sub-cellular Mechanisms converting RyR2 dysfunction into electrical abnormalities



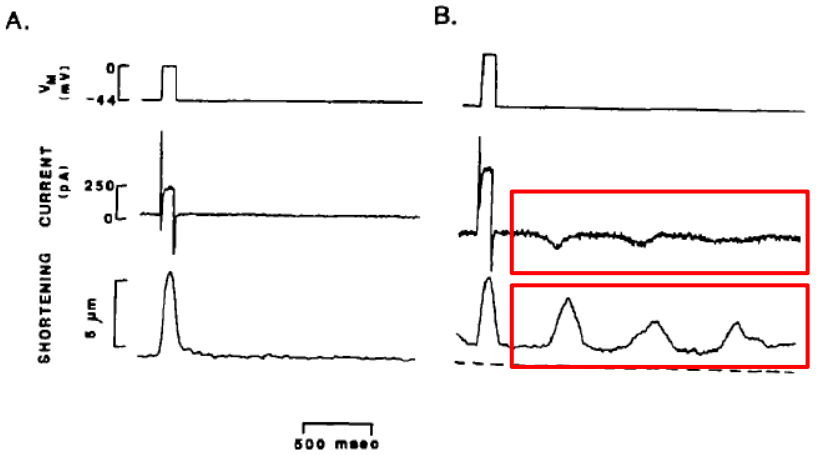
Adapted from D. Bers, Circ Res, 2002

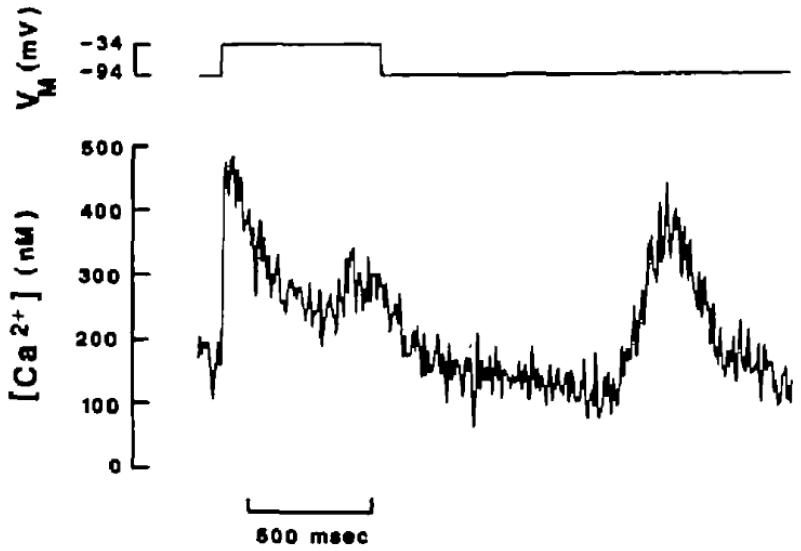
Ca^{2+} waves produce I_{TI} in conditions of Ca^{2+} overload

Cellular origins of the transient inward current in cardiac myocytes. Role of fluctuations and waves of elevated intracellular calcium

JR Berlin, MB Cannell and WJ Lederer

Circ. Res. 1989;65;115-126



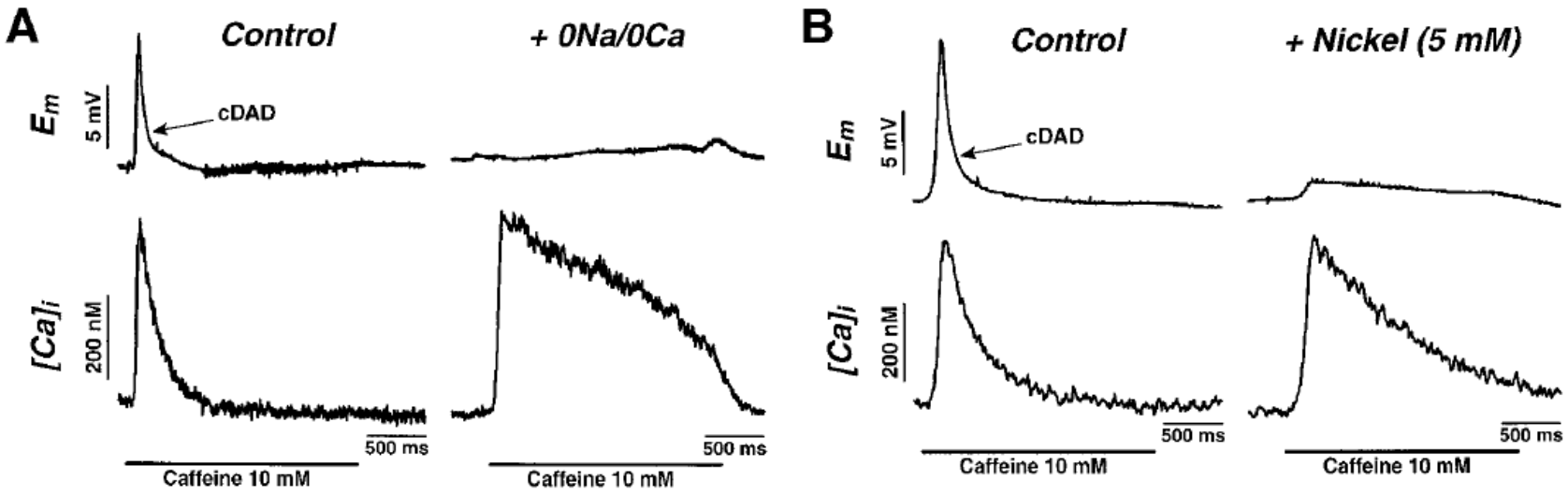


SR Ca^{2+} release can generate DADs via NCX

Sarcoplasmic Reticulum Ca2+ Release Causes Myocyte Depolarization : Underlying Mechanism and Threshold for Triggered Action Potentials

Klaus Schlotthauer and Donald M. Bers

Circ. Res. 2000;87;774-780



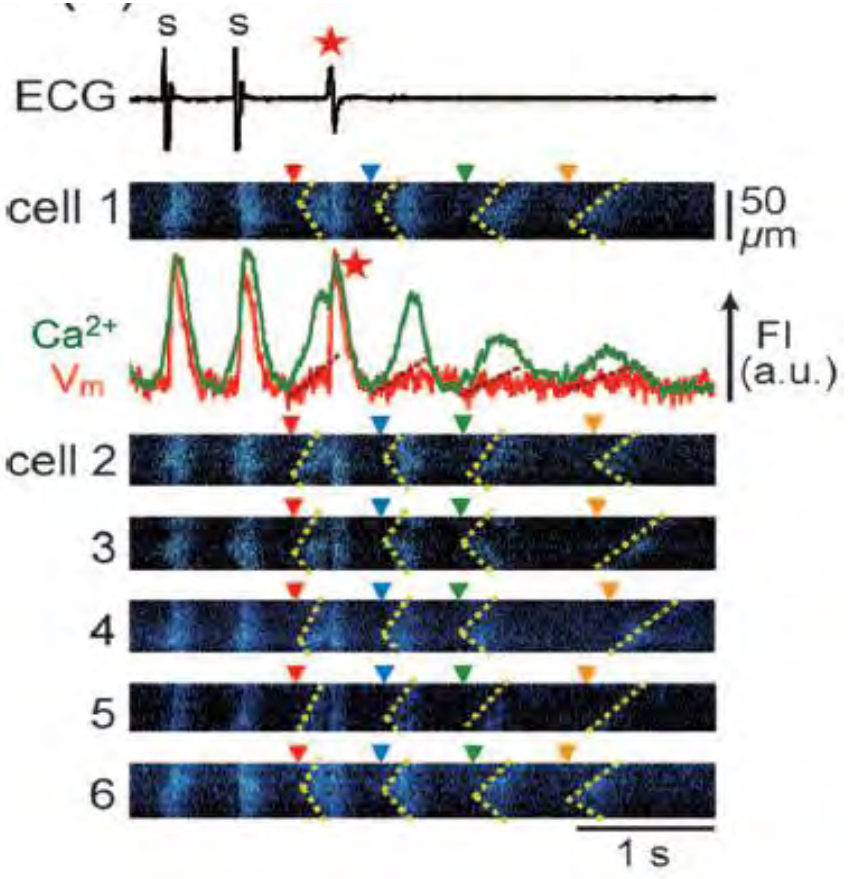
Ca^{2+} waves produce arrhtyhmia via NCX

Burst Emergence of Intracellular Ca^{2+} Waves Evokes Arrhythmogenic Oscillatory Depolarization via the Na^{+}–Ca^{2+} Exchanger

Simultaneous Confocal Recording of Membrane Potential and Intracellular Ca^{2+} in the Heart

Katsuji Fujiwara,* Hideo Tanaka,* Hiroki Mani, Takuo Nakagami, Tetsuro Takamatsu

(*Circ Res*. 2008;103:509-518.)



Stabilization of cardiac ryanodine receptor prevents intracellular calcium leak and arrhythmias

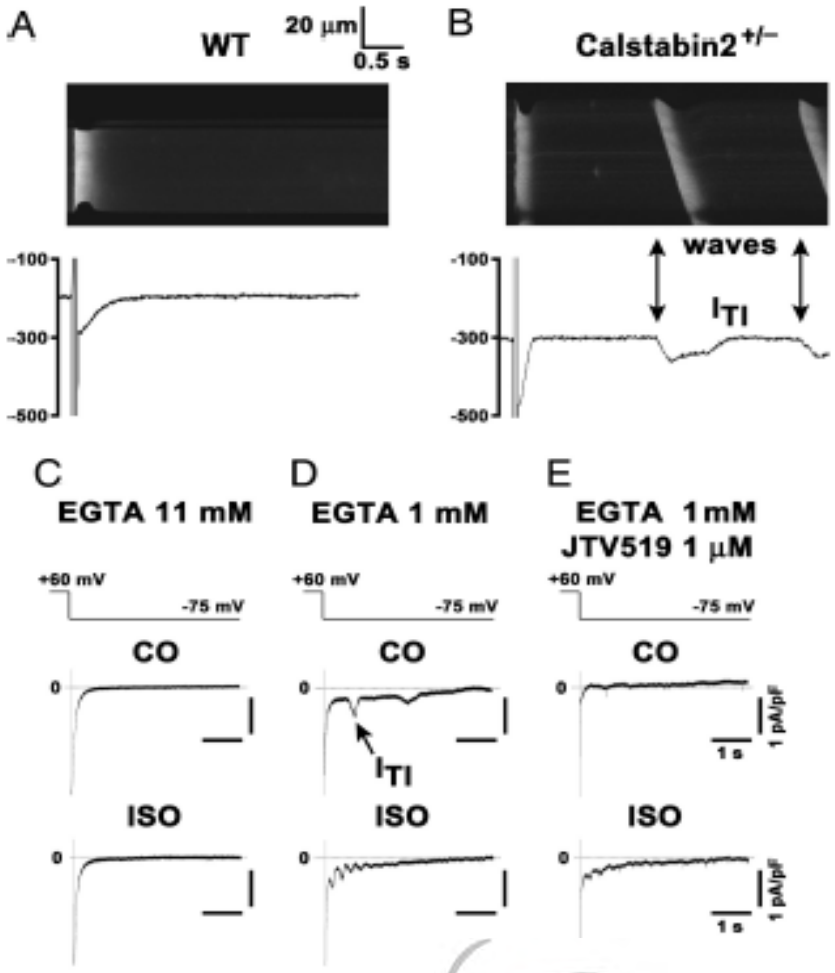
Stephan E. Lehnart*, Cecile Terrenoire†, Steven Reiken*, Xander H. T. Wehrens*, Long-Sheng Song‡, Erik J. Tillman*, Salvatore Mancarella*, James Coromilas§, W. J. Lederer‡¶, Robert S. Kass†, and Andrew R. Marks*§‖

| PNAS | May 16, 2006 | vol. 103 | no. 20

Inhibition of I_{TI} *in* haploinsufficient *calstabin-2 cardiomyocytes by JTV519 (Rycal).*

(A,B) Confocal Ca^{2+} line scan images (1 μM isoproterenol: ISO).
After a depolarization–repolarization step, the *ICa tail* current rapidly activated a homogeneous intracellular [Ca2]i transient followed by a long electrically stable resting phase.

(C) Typical current recorded at 75 mV after a preconditioning depolarization train under control conditions (CO) or after 4 min of 1 M ISO in cells dialyzed with 11 or 1 mM EGTA *(D) or 1 mM* EGTA and 1MJTV519 pretreatment *(E).*

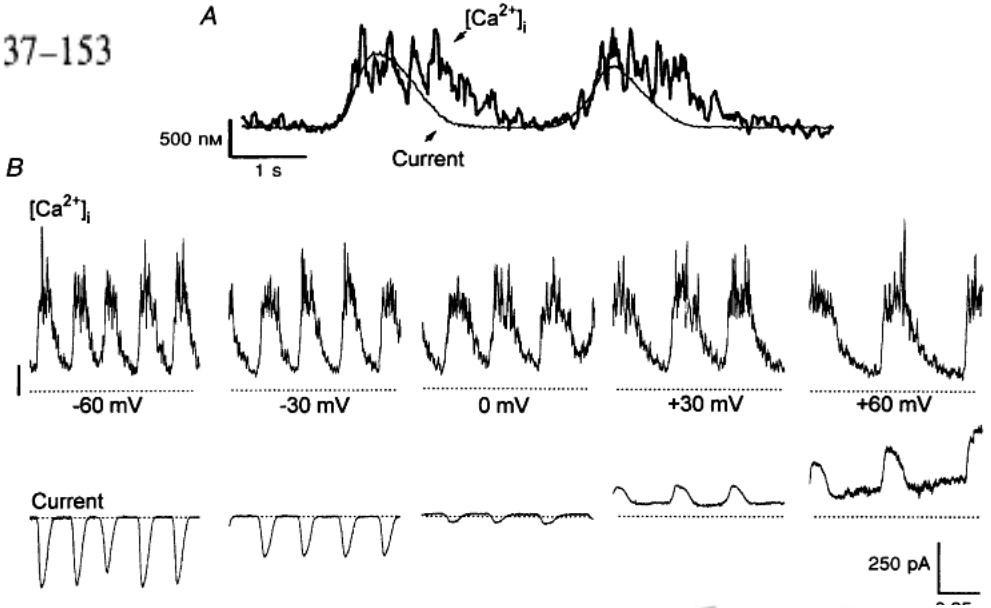


Ca^{2+}-activated Cl currents may generate ITI [and produce arrhtyhmia (?)]

CALCIUM-ACTIVATED TRANSIENT MEMBRANE CURRENTS ARE CARRIED MAINLY BY CHLORIDE IONS IN ISOLATED ATRIAL, VENTRICULAR AND PURKINJE CELLS OF RABBIT HEART

GYULA SZIGETI, ZOLTÁN RUSZNÁK, LÁSZLÓ KOVÁCS AND ZOLTÁN PAPP*

Experimental Physiology (1998), **83**, 137–153

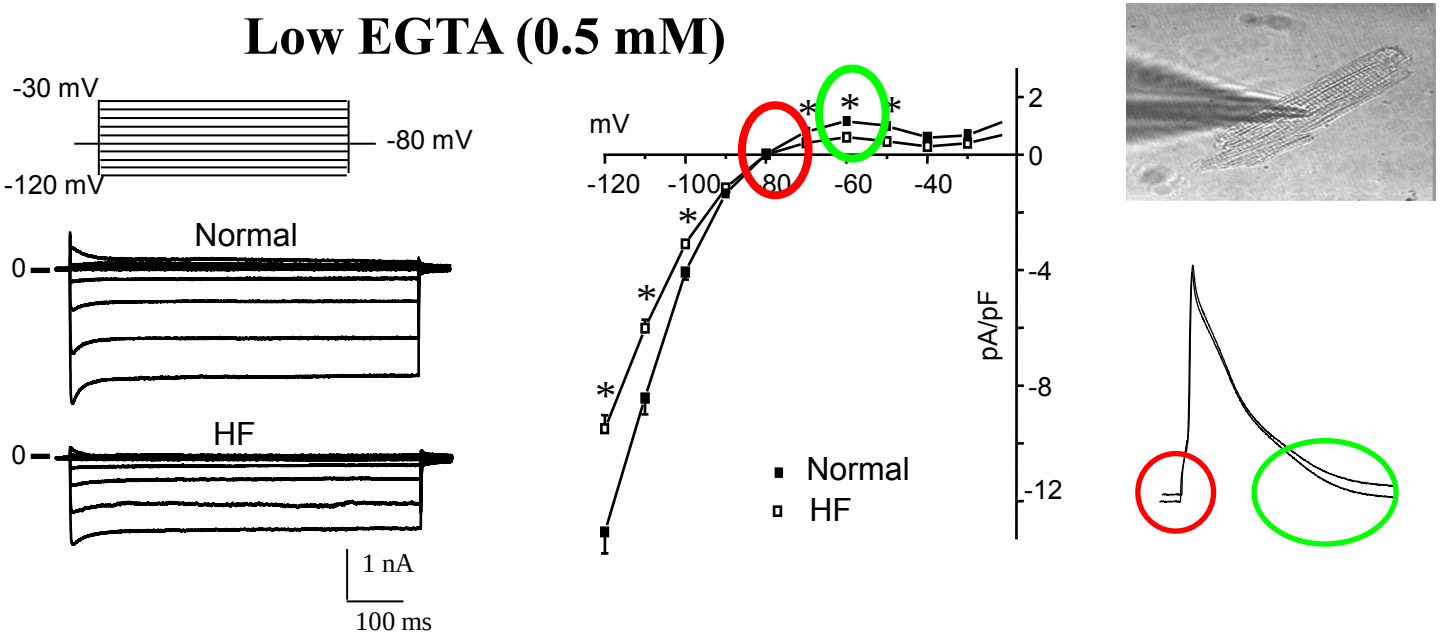


I_{K1} may be another cause : I_{K1} is decreased in HF Rats

Changes in expression level of I_{K1} channels (Kir2.X) unlikely

Kääb *et al*. Circulation. 1998 . Wang *et al.* Circulation. 1998 .

8 weeks, PMI



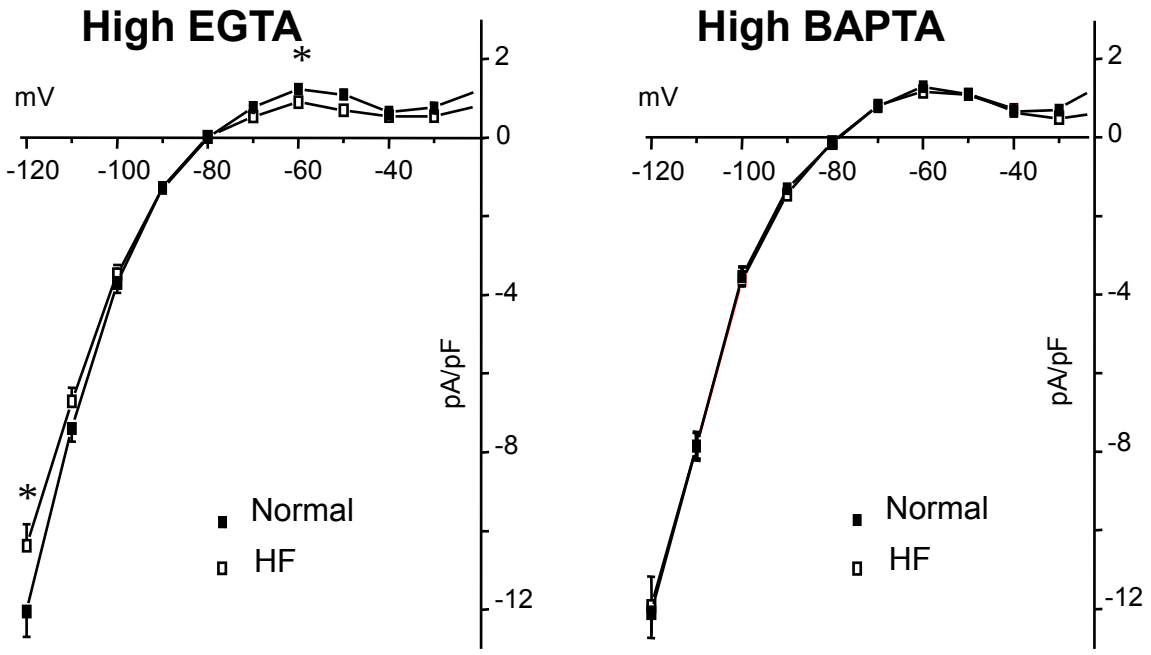
Ca^{2+}-dependent reduction of I_{K1} in rat ventricular cells: A novel paradigm for arrhythmia in heart failure?

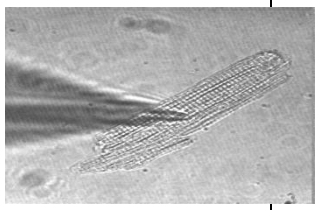
Jérémy Fauconnier, Alain Lacampagne, Jean-Michel Rauzier, Guy Vassort, Sylvain Richard *

Cardiovascular Research 68 (2005) 204 – 212

Effect of HF on I_{K1} involves Intracellular Ca^{2+}

Attenuated or prevented by Ca^{2+} buffers





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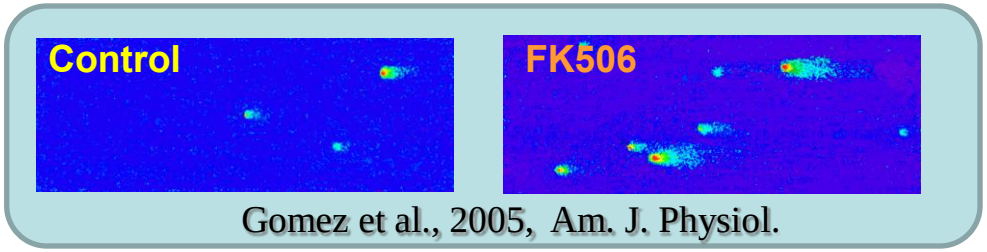
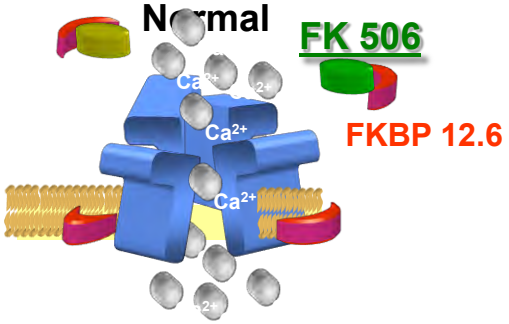
Jérémy Fauconnier, Alain Lacampagne, Jean-Michel Rauzier, Guy Vassort, Sylvain Richard *

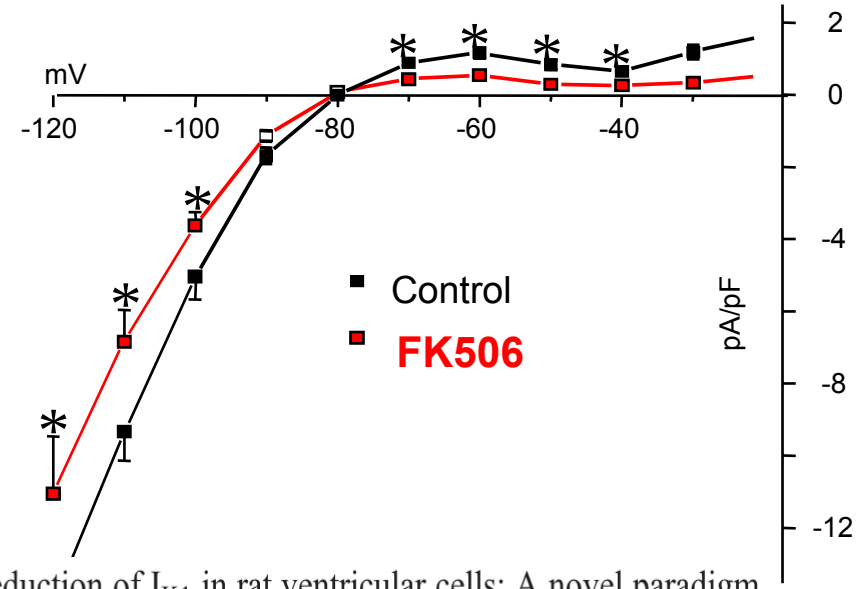
Cardiovascular Research 68 (2005) 204 – 212

FK506 reproduces effect of HF on I_{K1} in Normal cells



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





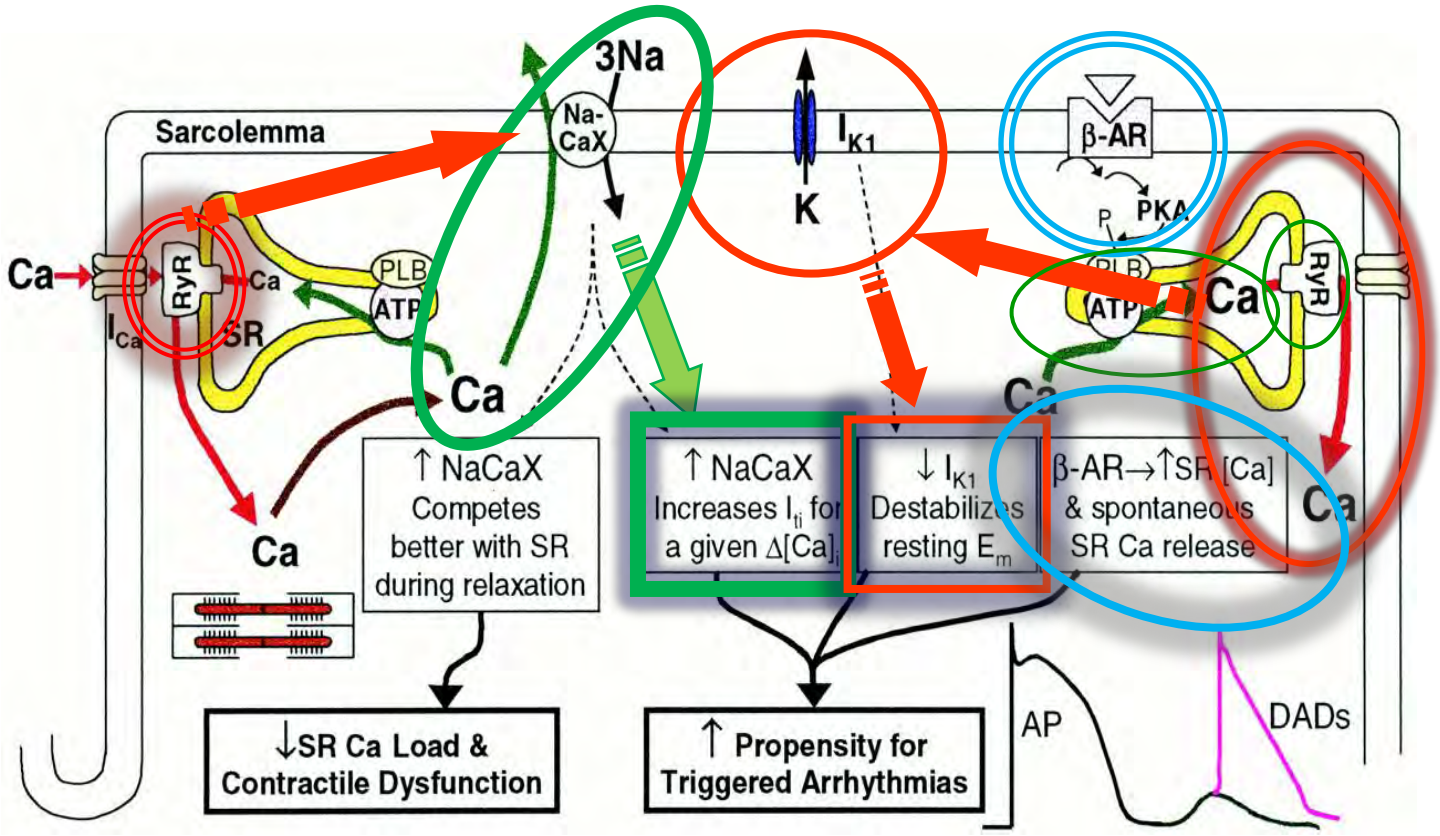
Ca^{2+}-dependent reduction of I_{K1} in rat ventricular cells: A novel paradigm for arrhythmia in heart failure?

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

Cardiovascular Research 68 (2005) 204 – 212

The *"Arrhythmia connection"* in HF

Up-regulated NaCaX, decreased I_{K1}, preserved β-Adrenergic responsiveness enhance triggered *arrhythmias*



Adapted From Pogwizd, S.M. et al. Circ Res 2001;88:1159-1167.

Normalization of RyR2 activity: therapeutic avenue?

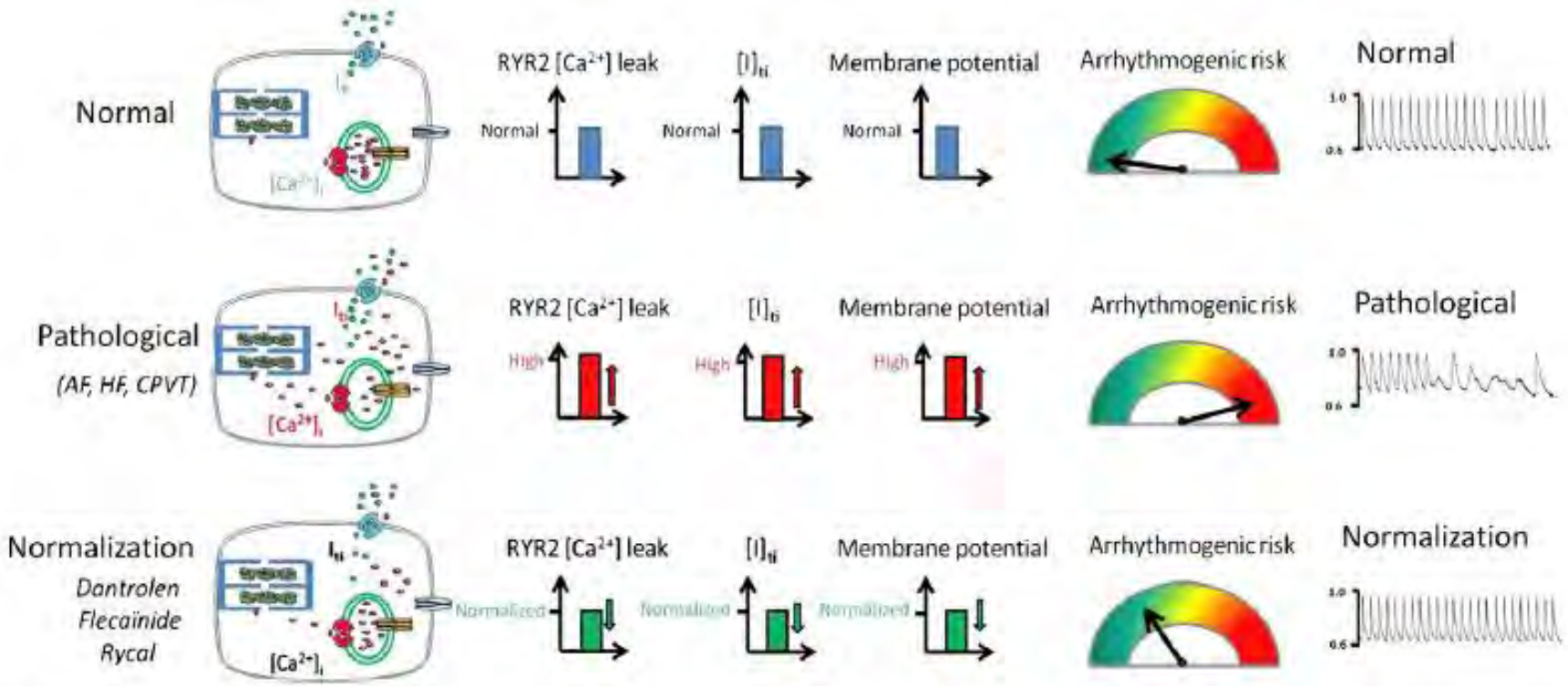


Fig. 4. Blockers and stabilizers of RyR2 prevent arrhythmia. Under normal conditions, RyR2 rarely opens in diastole. Spontaneous opening leads to leaky RyR2 in various pathophysiological situations, generating aberrant Ca^{2+} sparks and Ca^{2+} waves that activate inward depolarising I_{ti} currents 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

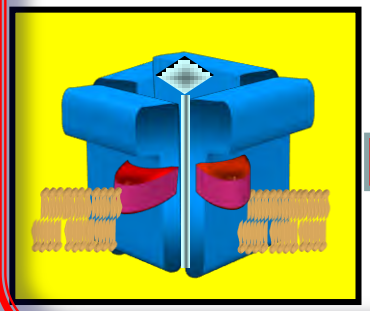
Jérôme Thireau [a], Jean-Luc Pasquié [a], Eric Martel [b], Jean-Yves Le Guennec [a], Sylvain Richard [a,*]

Pharmacology & Therapeutics xxx (2011) xxx–xxx

Are "Rycals" the panacea against arrhythmias and HF?

(2) HF (multiple defects)
= Sealing RyR2 enough? Prevent HF Remodeling also ?

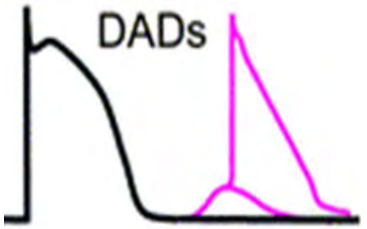
RyR2 dysfunction



Abnormal Ca^{2+} release

Ca^{2+}-dependent ionic currents

Arrhythmia / SCD



(1)

CPVT (isolated defect)
= Sealing the RyR2 in diastole

PHYSIOLOGIE & MEDECINE EXPERIMENTALE COEUR MUSCLES MONTPELLIER *

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Thank You

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