Kavli Institute of Theoretical Physics
Cardiac Dynamics Meeting
July 25,2006

From Pulsus to Pulseless: The Saga of Cardiac Alternans

James N. Weiss, MD
David Geffen School of Medicine at UCLA
Los Angeles, CA

no relationships to disclose

Ludwig Traube

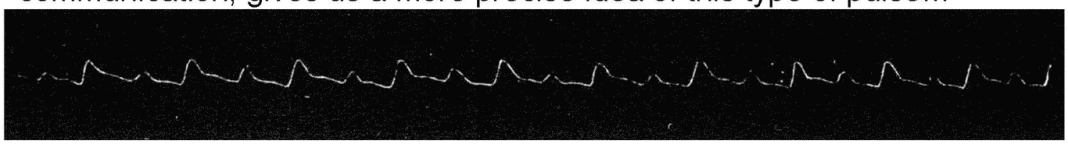
1818-1876

"Today, also, I maintain that the experiment is the 'sine qua non' of scientific pathology….Even therapeutics, I am convinced, will take a definite step forward when an attempt to is made in a systematic way to modify disease processes produced in animals by well-known drugs."

Translated from Traube L. Ein Fall von Pulsus Bigeminus nebst Bemerkungen tiber die Leberschwellungen bei Klappenfehlern und uber acute Leberatrophic. *Berl. Klin. Wcnschr.* **1872**;9:185-188.

"The following case, which came under my observation toward the close of last year, demonstrates a variation of the pulsus bigeminus: I designate it with the name of 'pulsus alternans'…..

The following curve taken by me with the aid of Marey's sphygmograph from the radial artery of a patient, which forms the starting point of this communication, gives us a more precise idea of this type of pulse…"



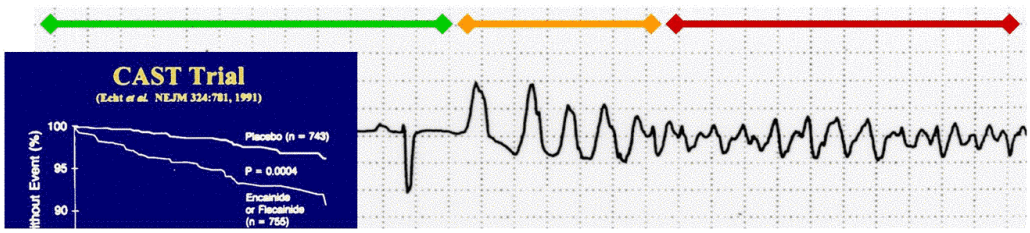
"H.W., laborer, forty-seven years old, who entered my service on October 16, 1871, had for years engaged in heavy labor, and was acknowledged an intemperate person….

On admission October 16, the following was noted: 'Patient complains of air hunger and pains in the epigastrium…'

I made the diagnosis of hypertrophy and dilatation of both ventricles….

Death occurred on December 27."

Sudden Cardiac Death (SCD)



Some facts to consider:

- Patients with cardiomyopathy have frequent PVC's
- 2 PVCs per minute = 1 million PVC's per year, yet SCD occurs on a time scale of months/years
- Programmed electrical stimulation with up to 3 premature extrastimuli rarely induces VT/VF in nonischemic heart failure patients
- Suppressing PVC's with AA drugs increases mortality
- **So what is so special about that one-in-a-million PVC that induces VT/VF and SCD in the diseased heart failure?**

It's not the PVC that is so special, it's the dynamic substrate that the PVC encounters!

Hypothesis: The really important cause of SCD is dynamic nature of the substrate that the PVC encounters, particularly **spatially discordant action potential duration (APD) alternans**

Part I: What is *spatially discordant* APD alternans, and how does it cause SCD?

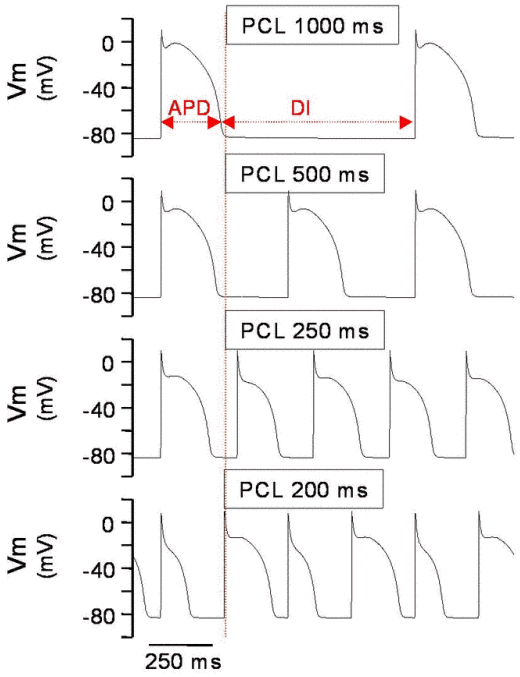
Part II: How do membrane voltage and Ca_i-cycling instabilities cause APD alternans, and why does heart failure exacerbate them?

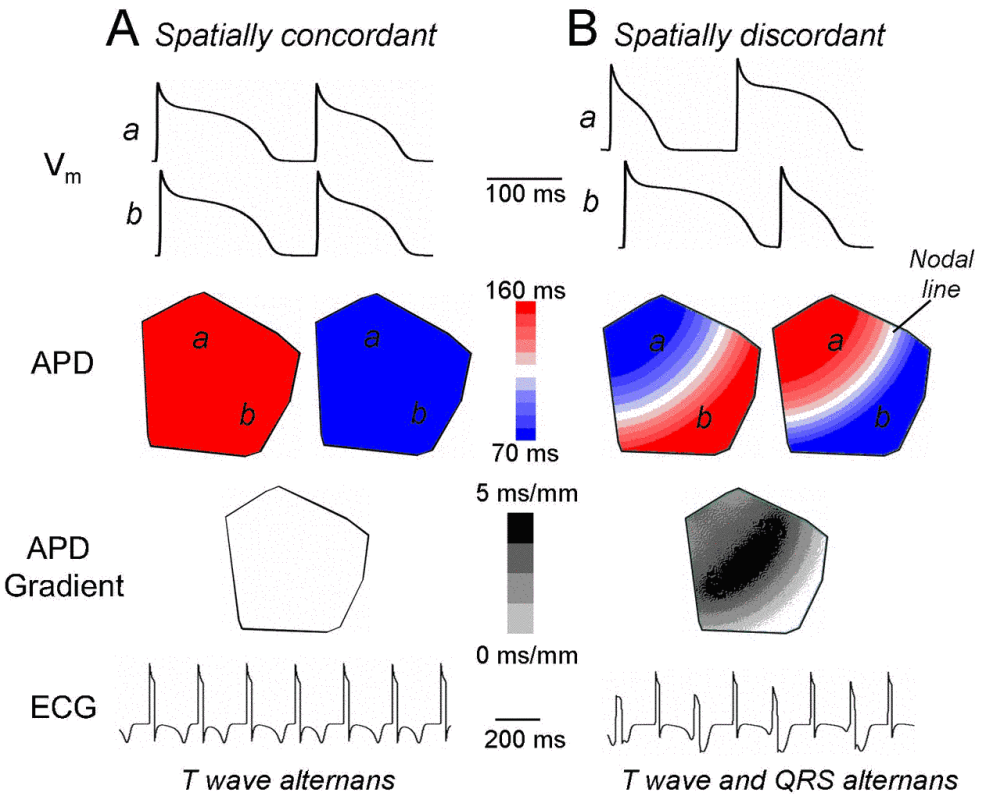
Part III: How are patterns of spatially discordant APD and Ca_i transient alternans influenced by the nature of bidirectional coupling between APD and Ca_i

Part I

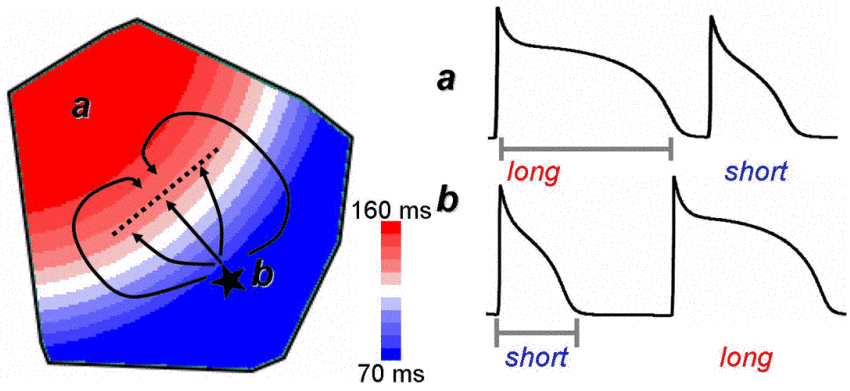
What is spatially discordant APD alternans, and why is it arrythmogenic?

APD (a surrogate for refractory period) and the Ca_i transient alternate at sufficiently fast heart rates





Spatially discordant APD alternans (repolarization alternans)



Action potential heterogeneity → Substrate for reentry

Pastore et al., Circulation, 1999

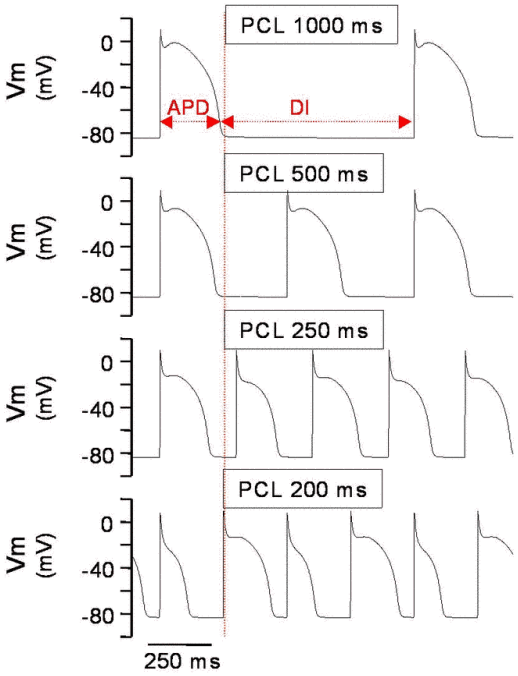
Summary

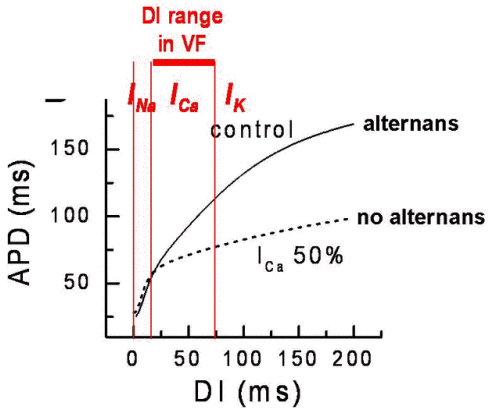
•Spatially disconcordant APD alternans creates marked dispersion of refractoriness by a purely dynamic patterning process, promoting the substrate for unidirectional conduction block and initiation of reentry by a PVC(s), or even by itself if the tissue is sufficiently heterogeneous.

Part II

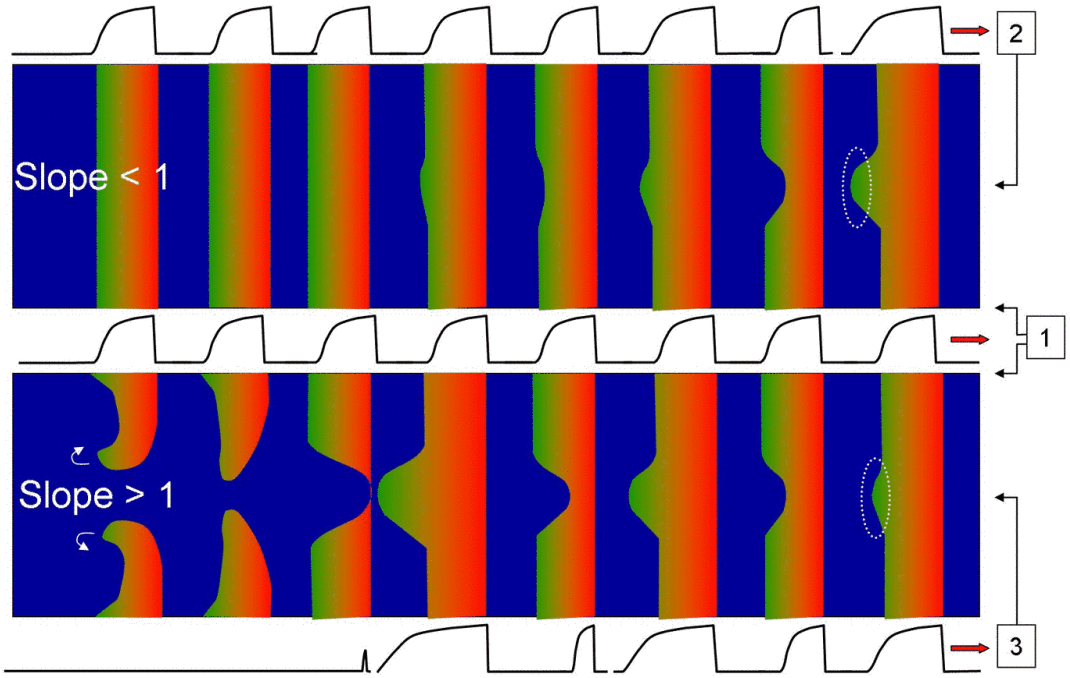
How do membrane voltage- and Ca_i-driven instabilities cause APD alternans, and why does heart failure exacerbate them?

Voltage-driven APD alternans: The role of APD restitution slope



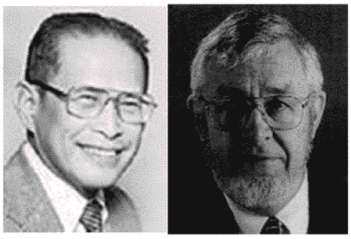


Dynamic wavebreak due to steep APD restitution slope



JOURNAL OF APPLIED PHYSIOLOGY
Vol. 25, No. 2, August 1968. *Printed in U.S.A.*

A graphic method for the study of alternation in cardiac action potentials



Jesus Nolasco, MD Roger W. Dahlen PhD

J. B. NOLASCO AND ROGER W. DAHLEN
Department of Physiology, New Jersey College of Medicine and Dentistry, Jersey City, New Jersey

NOLASCO, J. B., AND ROGER W. DAHLEN. *A graphic method for the study of alternation in cardiac action potentials.* J. Appl. Physiol. 25(2): 191–196. 1968.—The cardiac action-potential duration (A) is influenced by the preceding diastolic interval (D_0) and inversely affects the next diastolic interval (D_1). Action potentials were recorded through microelectrodes impaled into frog ventricular muscle strips driven electrically to produce alternation. The graph of $A = f(D_0)$ during the steady state was plotted and the relationship $D_1 = f(A)$ was drawn. The point of intersection of these two curves describes the action-potential duration and diastolic interval in the steady state. When stimulus frequency is altered, the plots of action potentials immediately following the rate change deviated from the steady-state curve. The action-potential behavior in this nonsteady state was explicable by a functional curve, the slope of which determined the occurrence of alternans. Transient alternation appeared and lasted longer as this slope increased and at a driving rate where the slope was +1, persistent alternans occurred. The existence of more than one amplitude of alternation at a given rate was also deduced from the graphs and demonstrated experimentally.

behavior of the action potentials which follow different degrees of acceleration was charted and from the charts, postulates defining the conditions leading to alternans were formulated.

In this communication we aim to explain the theoretical basis for the graphic model, including the model's construction and operation, and to present the postulates, the experimental observations supporting these postulates, and some perspectives about cardiac alternation suggested by this approach.

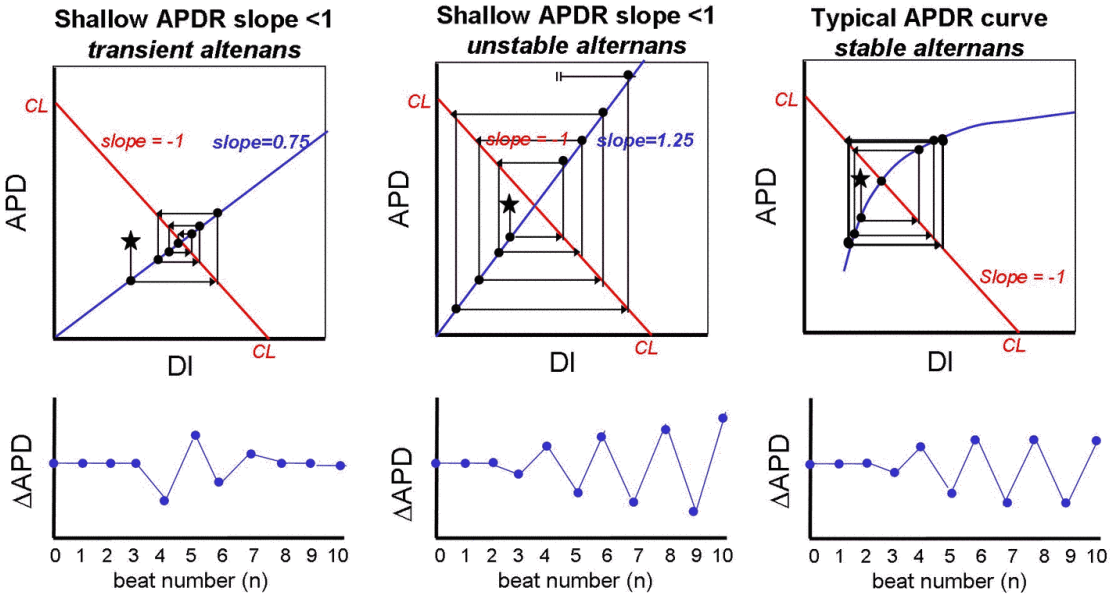
ANALOGY TO AN ELECTRICAL FEEDBACK SYSTEM AND IDENTITY OF TRANSFER FUNCTIONS

In a simple electrical negative feedback system where an independent signal (X) is a part of the input (I) and following amplification (G) a fraction (F) of the output (O) is fed back to the input, the equations defining the relationship between I and O as elements in the feedback loop may be used to solve for the steady-state value of O at any given value of X (19). The transfer functions $O = G(I)$ and $I = X - F(O)$ may be plotted on common coordinates and the intersection of the graphs provides a simultaneous solution for the two equations

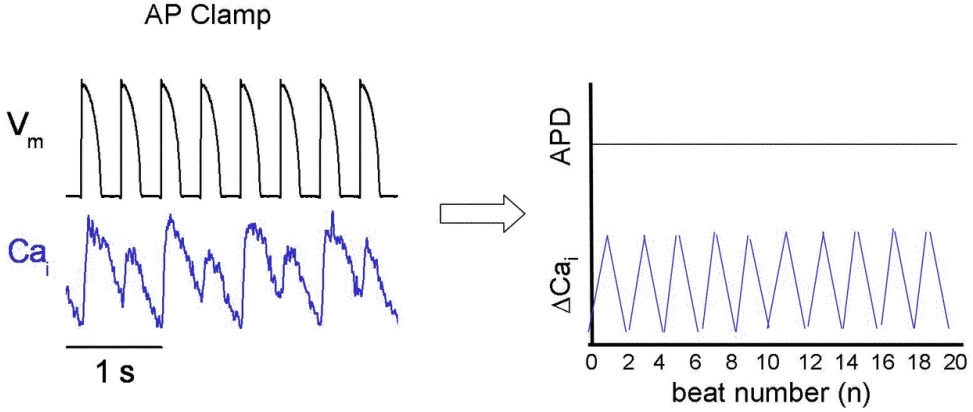
Graphical method to predict APD alternans

Definitions:
APD = action potential duration
DI = diastolic interval
CL = cycle length

Equations:
$CL = APD_n + DI_n$
$APD_n = CL - DI_n$
$APD_{n+1} = f(DI_n)$



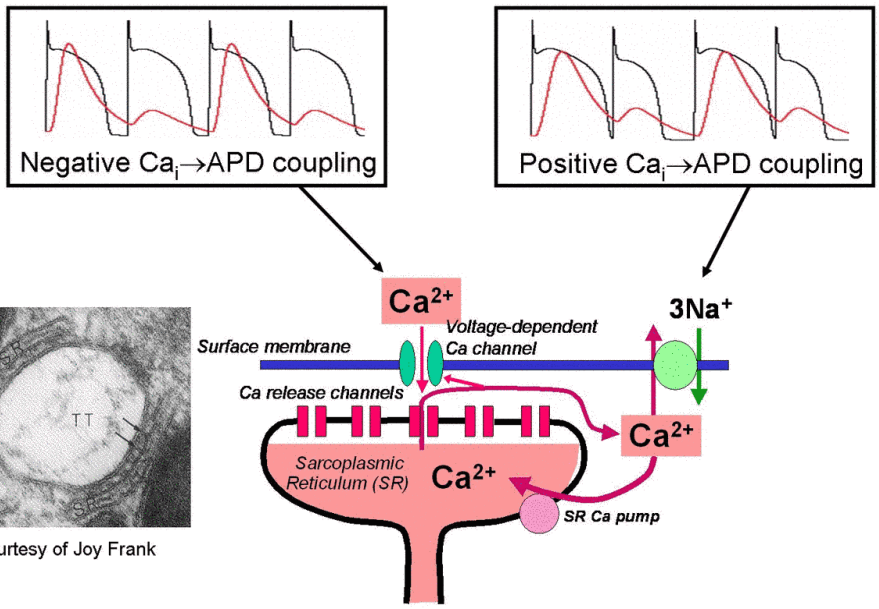
Primary Ca_i alternans



Isolated rabbit ventricular myocyte (35°C, perforated patch) paced at CL 210 ms

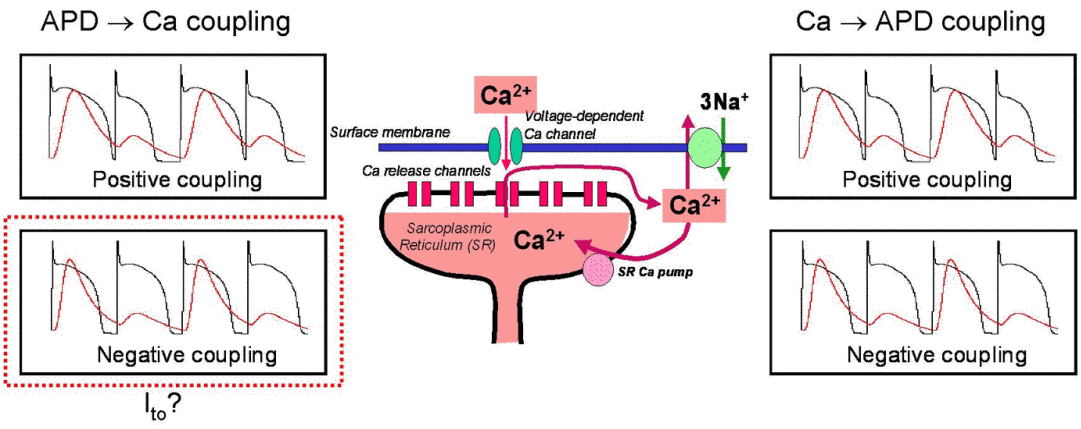
(E Chudin et al *Biophys J* 77:2930-2941, 1999)

Intracellular Ca alternans causes APD alternans

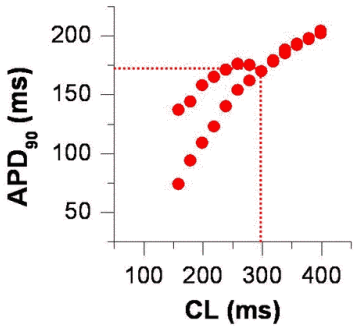


Courtesy of Joy Frank

APD and Ca are bi-directionally coupled: Instabilities in either or both can cause APD alternans

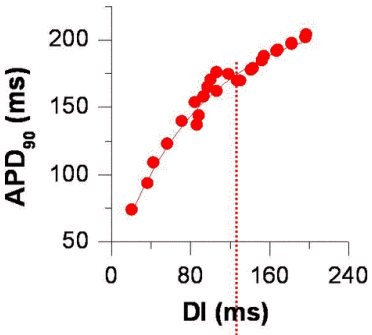


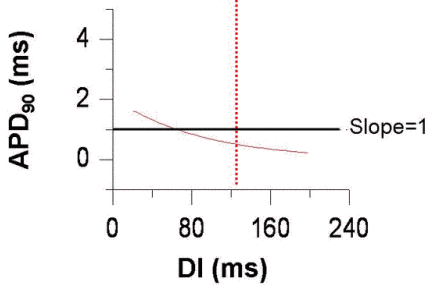
Onset of APD alternans does not correlate with APDR slope >1



Rabbit ventricular myocyte, perforated patch at 35_oC

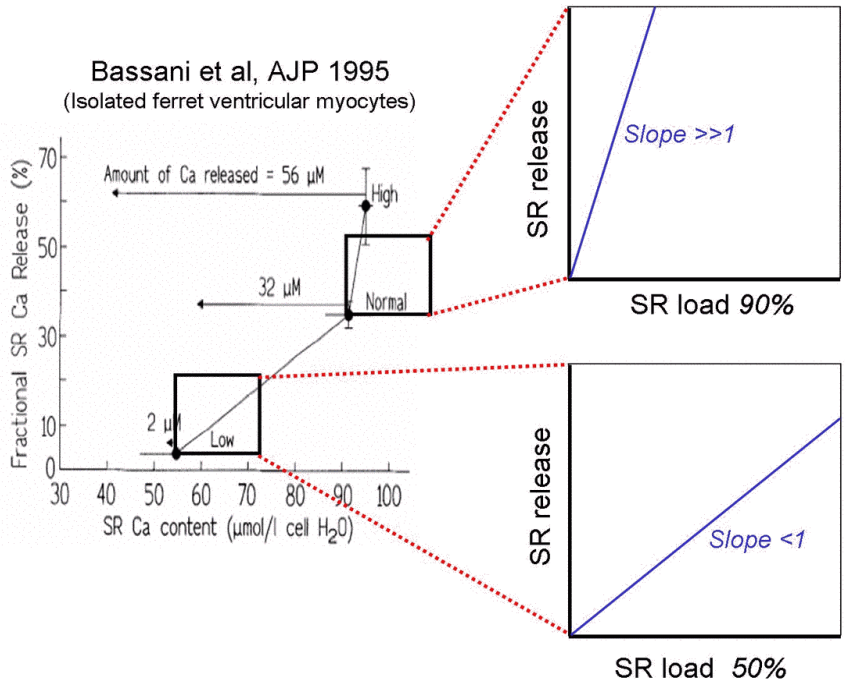
(J Goldhaber et al, *Circ. Res.* 96:459, 2005)





Fractional Ca release from the SR load is SR-load dependent

Bassani et al, AJP 1995
(Isolated ferret ventricular myocytes)



Graphical analysis of SR Ca cycling dynamics

(in tribute to Nolasco & Dahlen)

Definitions:

l = *SR load*
r = *SR release*
m = *slope of SR release vs load*
u = *SR Ca reuptake fraction*
t = *total Ca*

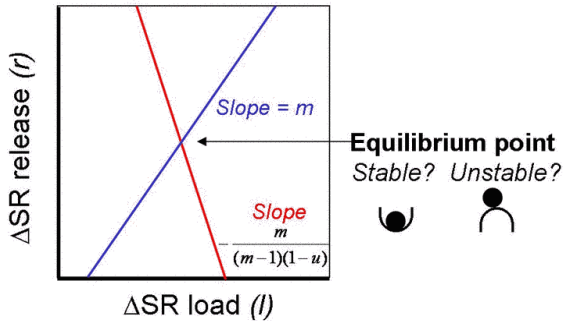
Equations:

$$\Delta r_n = m\Delta l_n$$ ← *Straight line, slope = m*

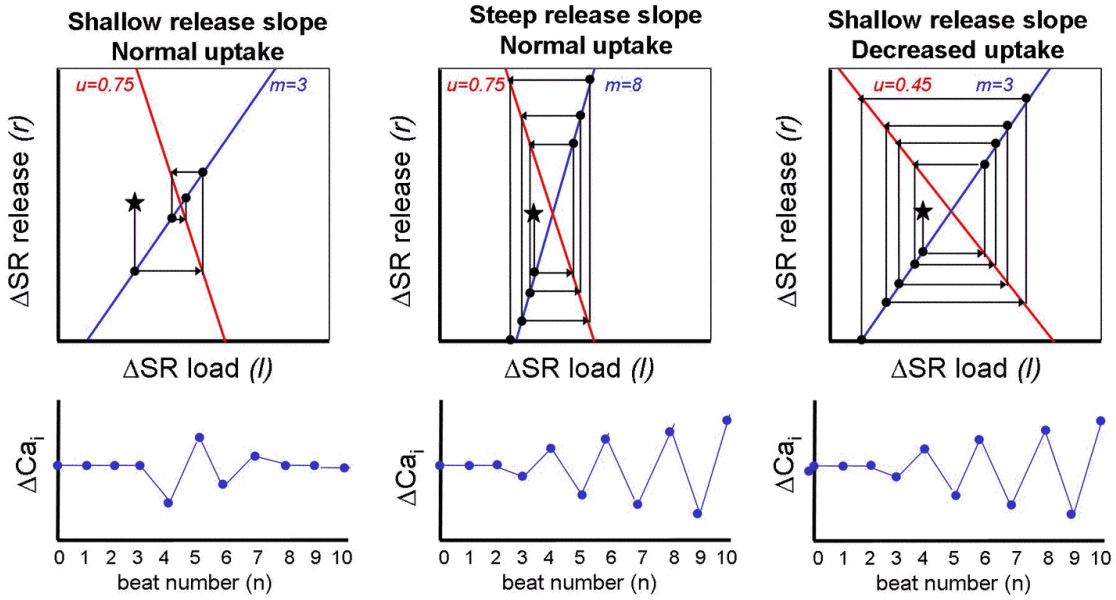
$$l_{n+1} = l_n - r_n + u(t - l_n + r_n)$$

(Amount left in SR) (Amount in cytoplasm)

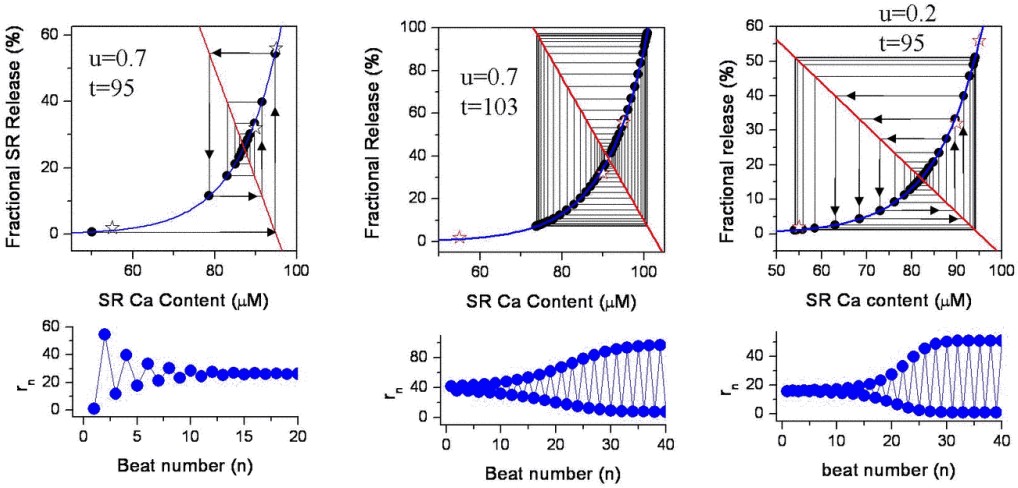
$$\Delta r_n = -\frac{m}{(m-1)(1-u)}\Delta l_{n+1}$$ ← *Straight line slope* $-\frac{m}{(m-1)(1-u)}$



Cobweb diagrams to predict Ca_i transient alternans

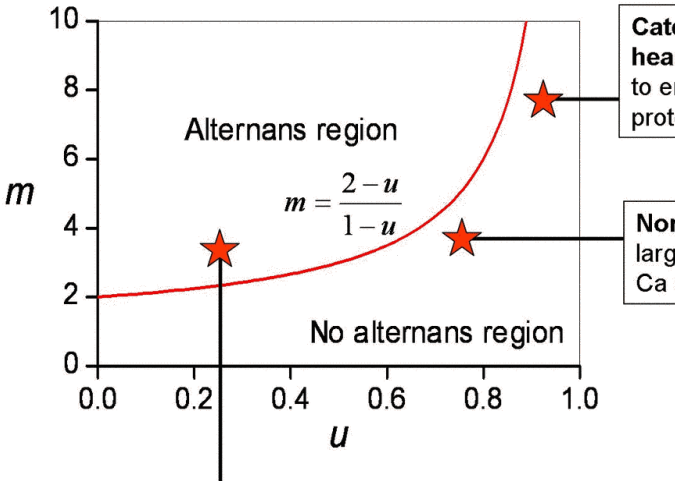


Graphical simulations of Ca_i transient alternans using a realistic (nonlinear) SR Ca release curve



(Courtesy of Zhilin Qu)

Stability Analysis



Catecholamine-stimulated normal heart: *m* increases, but so does *u* due to enhanced SERCA pump activity, protecting against Ca alternans

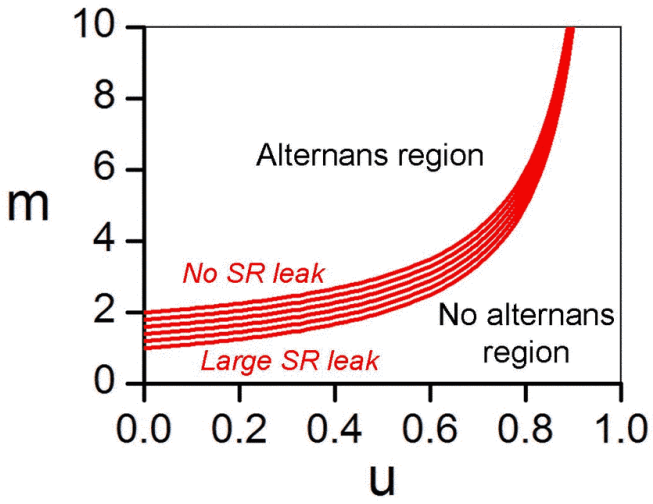
Normal heart (*u*>0.7), requires large *m* (i.e Ca overload) to cause Ca alternans

Failing heart/acute ischemia: may have normal or increased *m*, but SERCA downregulation (in heart failure) or acute inhibition (ischemia) lower the threshold for Ca alternans

Role of SR leakiness (due to hyperphosphorylation of RyR from chronic β-adrenergic stimulation)

New Stability Equation: $m = \frac{1+(1-u)(1-p)}{1-u}$

p = fractional SR leak



Summary

- Voltage-driven APD alternans is promoted by steep APD restitution slope >1 (if no short-term memory is present)

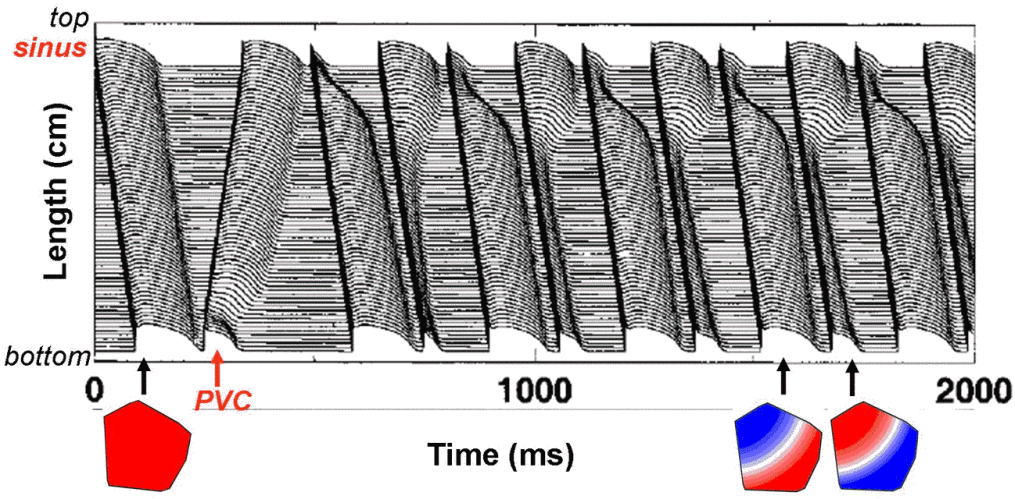
- Ca_i-driven alternans is promoted by
  - Steep SR Ca release vs load relationship (*m* factor), which increases as SR Ca load increases
  - Impaired SR Ca reuptake (*u* factor) due to SERCA depression
  - Increased SR leakiness (*p* factor) due to RyR hyperphosphorylation

- We hypothesize that
  - Acute β-adrenergic stimulation protects against Ca_i-driven alternans by simultaneously increasing SR uptake via increased SERCA activity
  - Chronic β-adrenergic stimulation in heart failure promotes Ca_i-driven alternans by downregulating SERCA pump activity and enhancing SR leak

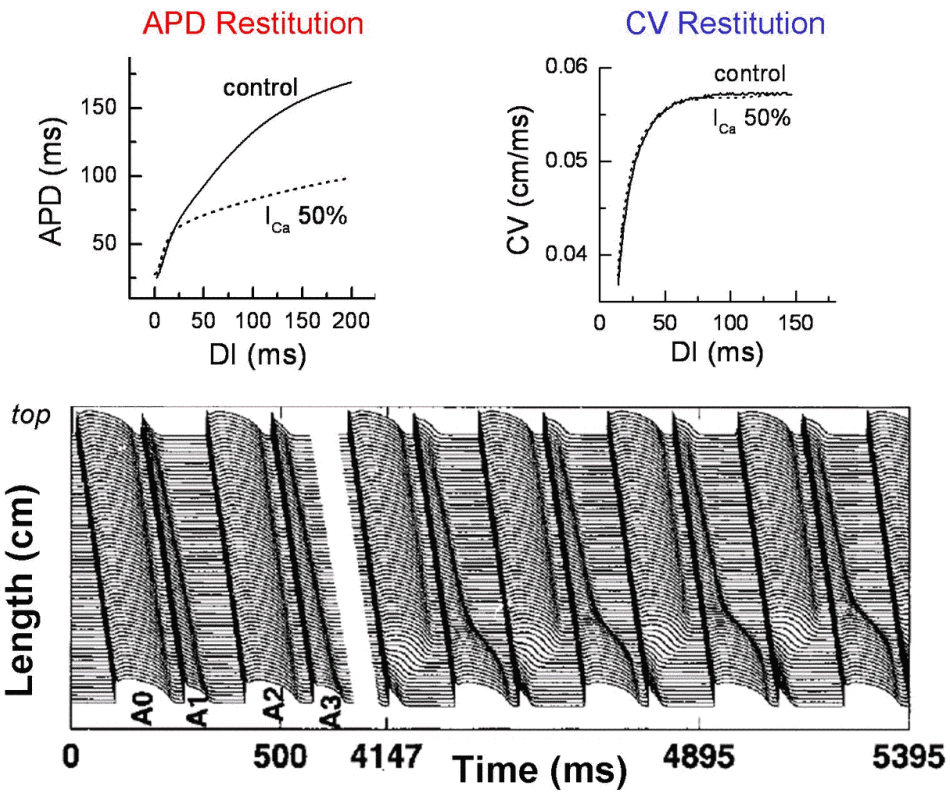
Conditions for Spatially Discordant Alternans

1. A mechanism producing APD alternans at the cellular level
   - Voltage-mediated – steep APD restitution
   - Ca-mediated – instability in intracellular Ca_i cycling
2. A mechanism creating spatial inhomogeneity
   - CV restitution
   - Premature beat at a different site in homogeneous tissue, or at the same or a different site in heterogeneous tissue
   - Negative Ca $\rightarrow$ V coupling

Induction of spatially discordant APD alternans by a PVC in a simulated 1D cable



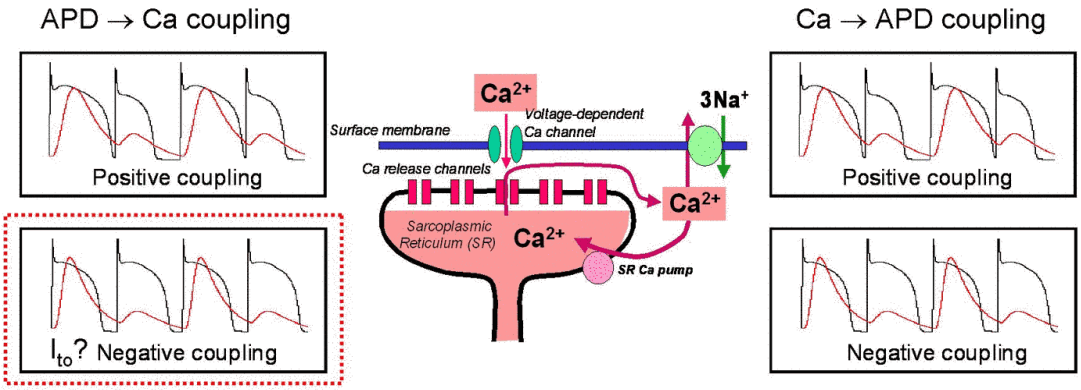
from Watanabe et al JCE, 2002



Part III

How are patterns of spatially discordant APD and Ca_i transient alternans influenced by the nature of bidirectional coupling between APD and Ca_i?

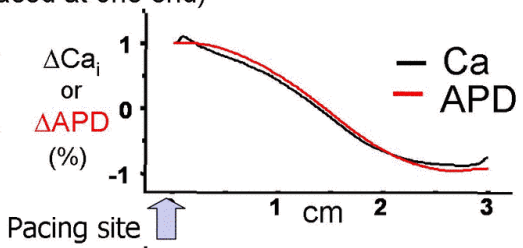
Bi-directional coupling between APD and Ca_i



Spatial APD and Ca_i alternans in a 1D cable of cells

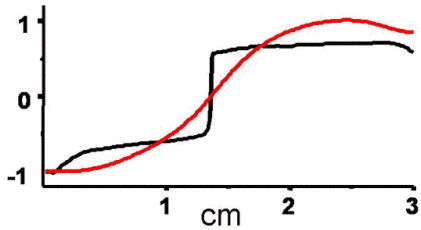
(paced at one end)

Voltage-driven alternans
(Positive APD→Ca coupling)

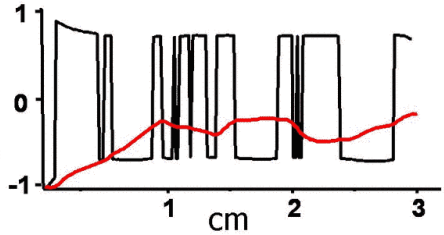


Pacing site

Ca_i-driven alternans
(Positive Ca→APD coupling)



Ca_i-driven alternans
(Negative Ca→APD coupling)



- CV restitution plays no role
- Dynamically patterns emerge via a novel mechanism that depends sensitively on the coupling
- Ca alternans pattern does not coincide with APD alternans pattern

Y Shiferaw, D Sato, A Garfinkel, Z Qu, JN Weiss, A. Karma. Spatially discordant alternans in cardiac tissue: the role of Ca cycling. *Heart Rhythm* 2(Suppl):S58, 2005.

Explanation

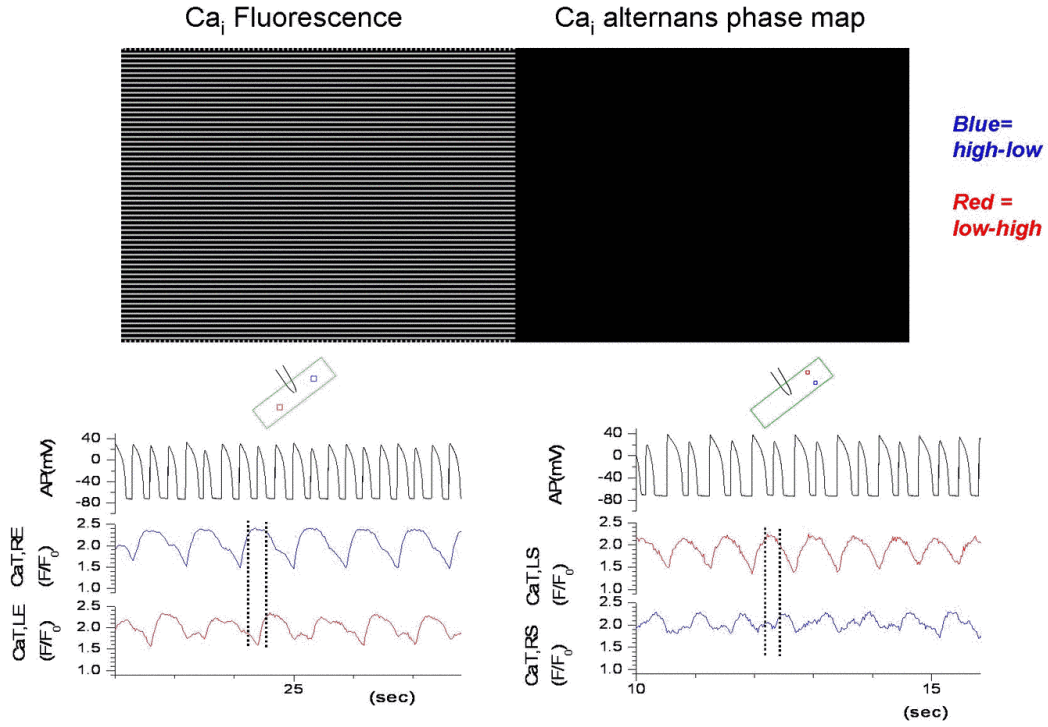
• The cell's APD controls its Ca_i transient amplitude by the usual graded Ca-induced Ca release mechanism, and is not significantly influenced by the Ca_i transient of adjacent cells *due to the slow rate of Ca_i diffusion between cells*

• However, a cell's Ca_i transient cannot control its APD, because APD is also influenced strongly by the APD of adjacent cells, *i.e. voltage diffuses rapidly over a space constant of several millimeters*

• Thus Ca_i can change its alternans phase over very short, even subcellular distances

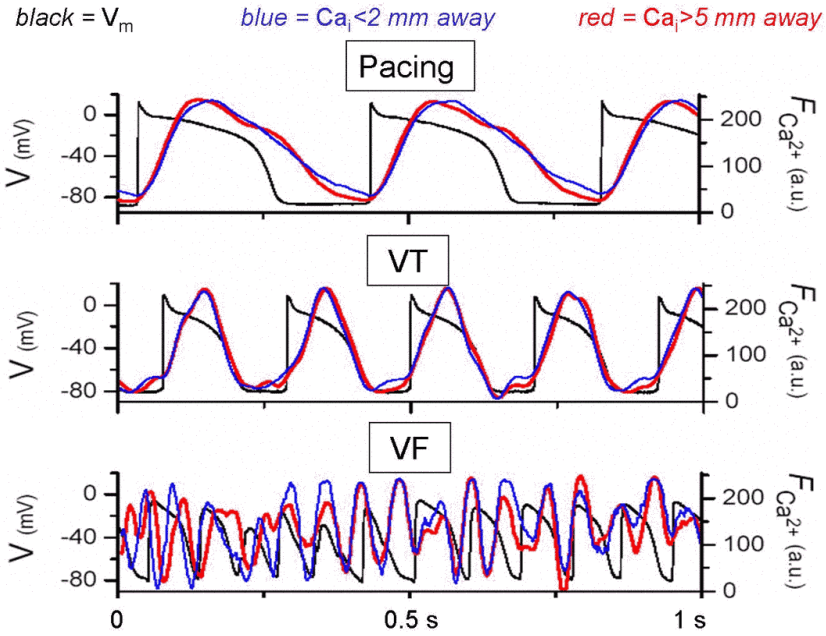
• However, APD cannot concomitantly change its alternans phase over a short distance, because of electronic effects of the APD of adjacent cells

Complex APD-Ca_i Behavior in the Single Myocyte



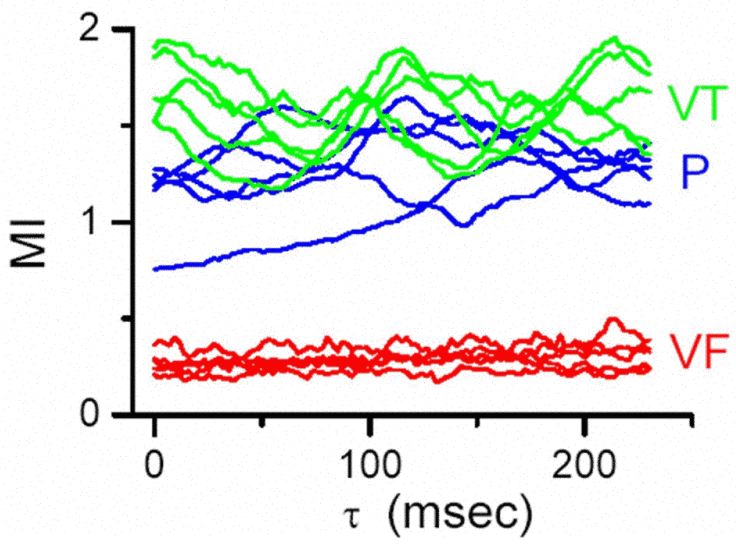
Rabbit ventricular myocyte, perforated patch, 23^{0}C (Experiment by Lai-Hua Xie, PhD)

Simultaneous microelectrode V_m and optical Ca_i (F_{Ca}) during pacing, VT and VF in porcine RV



Omichi et al, Intracellular Ca dynamics in ventricular fibrillation, *Am J Physiol,* 286:H1836-H1844, 2004

Mutual information (MI) between Ca_i and V_m is lower during VF than during VT or pacing (P)



Omichi et al, Intracellular Ca dynamics in ventricular fibrillation, *Am J Physiol,* 286:H1836-H1844, 2004

Summary

• Spatially discordant APD alternans provides a direct substrate for wavebreak to initiate reentry, as well as greatly enhancing the likelihood that a PVC (e.g. DAD) induces reentry

• In normal heart, APD alternans can be driven by steep APD restitution slope, Ca_i dynamics, or both. The Ca_i dynamics typically cause the initial instability as heart rate increases.

• Heart failure exacerbates the Ca_i cycling instability driving APD alternans, promoting APD alternans at even normal heart rates, seen clinically as pulsus alternans and T wave alternans.

• Interactions between APD and Ca_i instabilities produce rich variety of dynamics at both the cellular and tissue levels.

What is it that makes that one-in-a-million PVC so special?

~~PVC Hypothesis?~~

PVC Paradox

Dynamic Substrate Hypothesis

Acknowledgements

Mathematical Modeling

Alan Garfinkel, PhD
Zhilin Qu,PhD
Yohannes Shiferaw, PhD
Boris Kogan, PhD
Alain Karma, PhD (Northeastern U)
Daisuke Sato, PhD

Tissue Studies

Peng-Sheng Chen, MD
Hrayr Karagueuzian, PhD
Shien-Fong (Marc) Lin, PhD
Michael Fishbein, MD
Miguel Valderrabano, MD

Molecular and Cellular Studies

James Weiss, MD
Scott John, PhD
Aman Mahajan, MD
Riccardo Olcese, PhD
Lai-Hua Xie, PhD