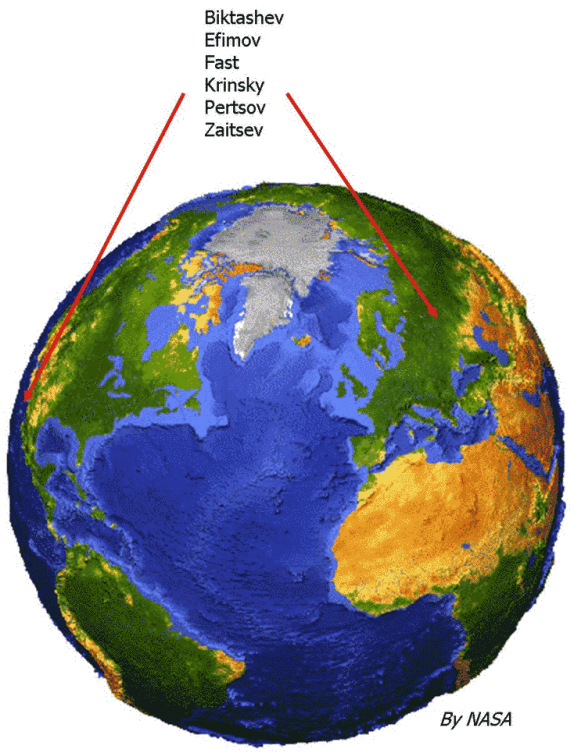
Evolution of Ventricular Fibrillation in the Ischemic Heart

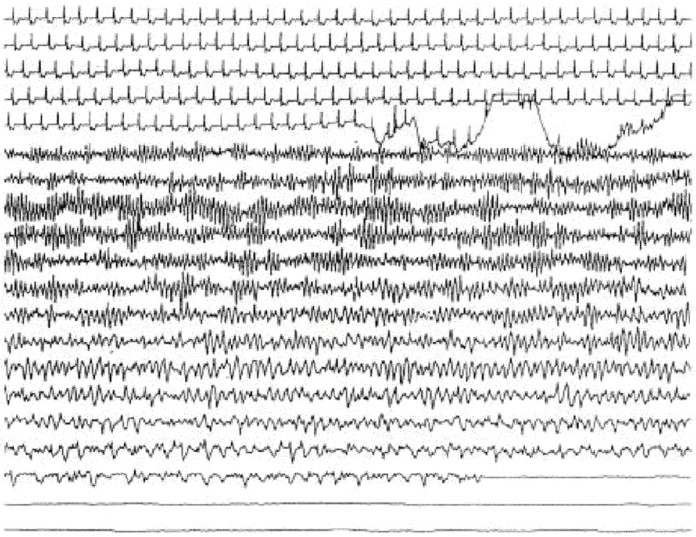
(a link between local periodicity, wavebreak and ECG)

Alexey V. Zaitsev, PhD

Nora Eccles Harrison Cardiovascular Research and Training Institute,
University of Utah, Salt Lake City



Evolution of Ventricular Fibrillation in a patient



Survival rate decreases by 10% per minute

From P-S Chen et al., 2003

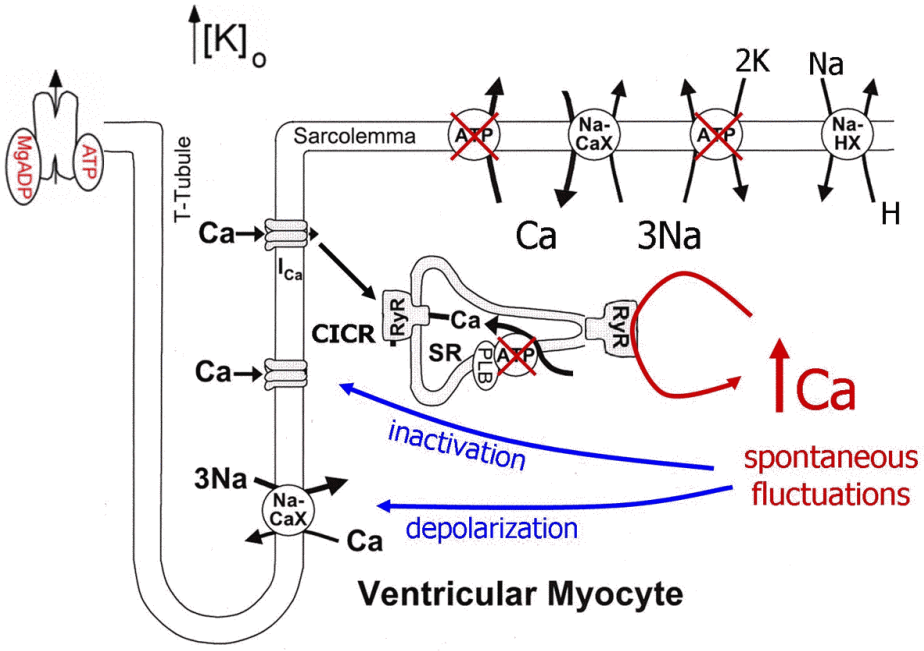
Overall survival rate for victims of out-of hospital cardiac arrest is ~5%

Clinical Relevance

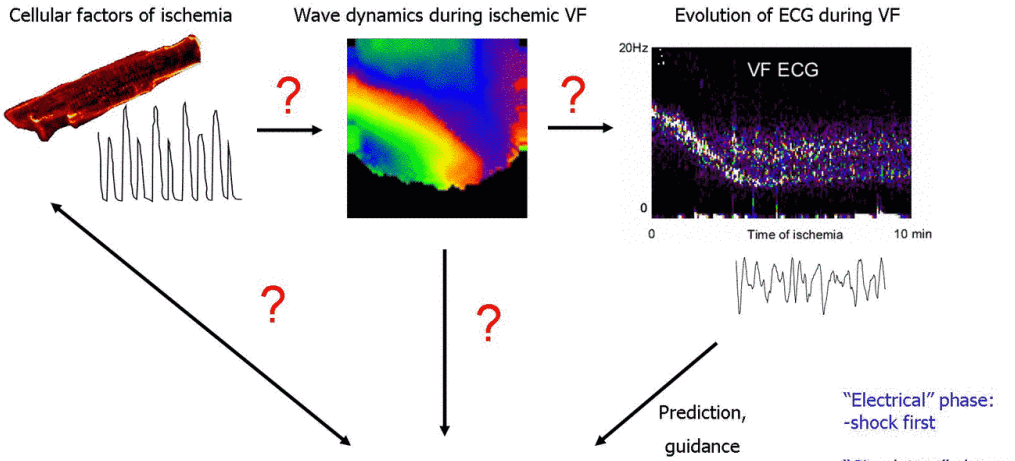
During the time course of VF, there is a parallel decrease in organization of ECG and the chance of successful defibrillation (Menegazzi et al., 2004)

Understanding of *how* and *why* the behavior of electrical waves changes with time after VF onset may help to explain the rapid deterioration of defibrillation efficacy and and ultimately improve treatment of VF

Cellular effects of ischemia



VF evolution: unresolved issues



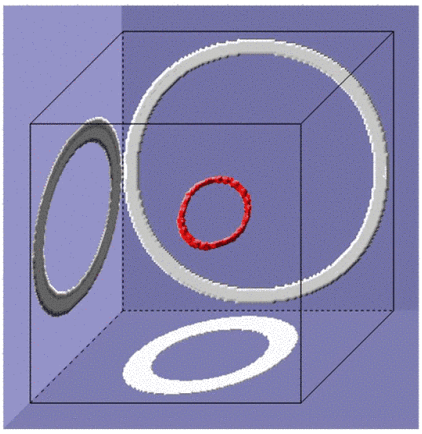
CPR, defibrillation, survival

Part I: HOW?

Part II: WHY?

Part I: HOW?

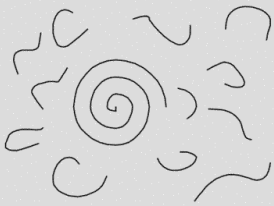
Ventricular Fibrillation – tornadoes in the heart?



Courtesy Dr. Pertsov

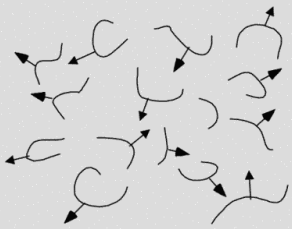
The 100 years long debate:

- "Mother rotor"



- Single periodic source of waves
- Wavelets are an epi-phenomenon

- "Multiple wavelets"

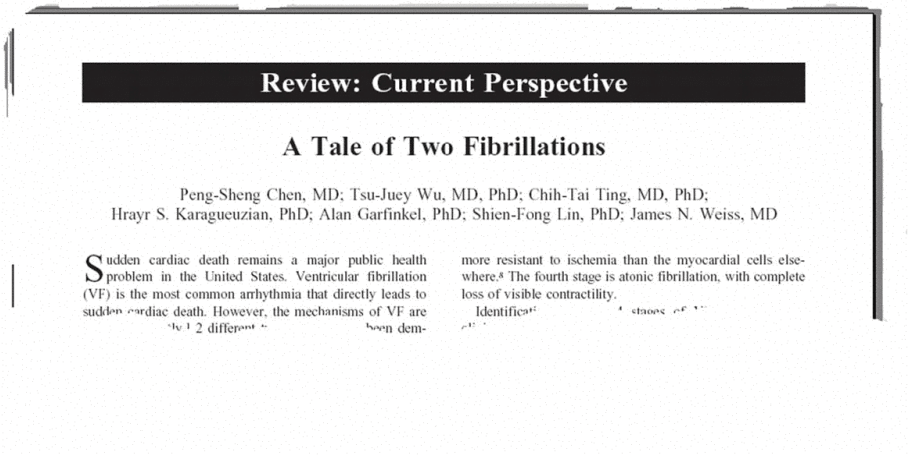


-Wavelets are the engine of the rhythm
- no periodicity

In either case, the focus has been on the mechanism of wavebreak.

A hypothesis:

VF evolution is a transition from "type I VF" to "type II VF"



Review: Current Perspective

A Tale of Two Fibrillations

Peng-Sheng Chen, MD; Tsu-Juey Wu, MD, PhD; Chih-Tai Ting, MD, PhD; Hrayr S. Karagueuzian, PhD; Alan Garfinkel, PhD; Shien-Fong Lin, PhD; James N. Weiss, MD

Sudden cardiac death remains a major public health problem in the United States. Ventricular fibrillation (VF) is the most common arrhythmia that directly leads to sudden cardiac death. However, the mechanisms of VF are [illegible] 2 different [illegible] been demonstrated. [illegible] more resistant to ischemia than the myocardial cells elsewhere.[illegible] The fourth stage is atonic fibrillation, with complete loss of visible contractility.

Identificat[illegible] stages of [illegible]

A hypothesis:

VF evolution is due to a transition from "fast VF" to "slow VF"

- Two types of VF were found in isolated perfused rabbit heart (Wu et al., 2002)
  - ***Type I (fast) VF*** is is associated with a steep APD restitution, flat CV restitution, and multiple wandering wavelets.
  - ***Type II (slow) VF*** is associated with flat APD restitution, broad CV restitution, decreased excitability, and spatiotemporal periodicity in activation maps.
- The two types of VF can occur in the same heart *through changes in VF over time due to ischemia*

Types of Ventricular Fibrillation: 1, 2, 4, 5, or 300,000?

RAYMOND E. IDEKER, M.D., PH.D.,*,†,‡ JACK ROGERS, PH.D.,†,‡ and JIAN HUANG, M.D.†

From the Departments of *Physiology and Biophysics, †Medicine, and ‡ Biomedical Engineering, University of Alabama at Birmingham, Birmingham, Alabama, USA

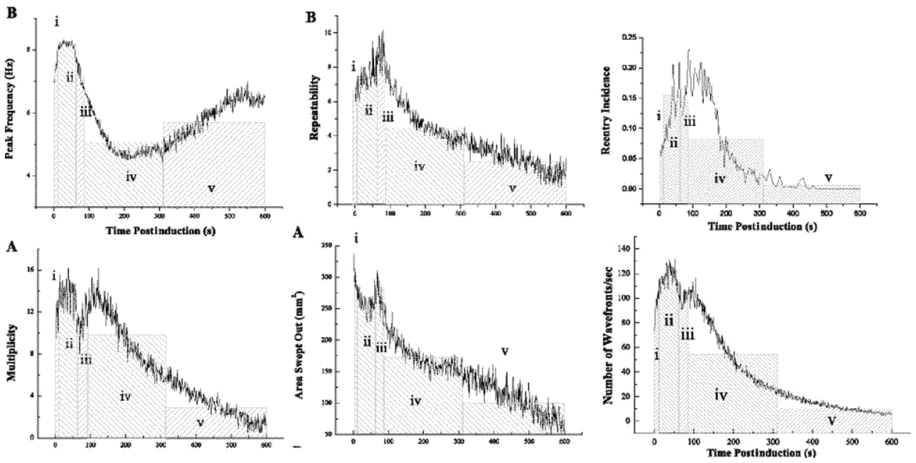
Editorial Comment

Ventricular fibrillation (VF) has been considered to be caused by totally disorganized electrical activity,[1] but evidence accumulating for over half a century suggests different ...s and types of organization exist during VF. As VF ...it progresses through di... stages. Wi...

...of the APD restitution curve decreased in the ischemic region consistent with type II VF, whereas the slope increased in the nonischemic region, consistent with type I VF. They also found that the incidence of conduction block was increased in all portions of the mapped myocardium after occlusion, i.e., in the ischemic zone, in the ... border zone encompassing ...

... How many types of instabilities are there? Because no two hearts are exactly alike, one answer is that each of the approximately 300,000 cases of sudden cardiac arrest caused by VF every year in the United States represents a different type of instability. *(i.e., VF)*

Evolution of activation patterns during VF in the open-chest dog



From Huang et al., Am J Physiol, 2004

Interspecies differences matter!

mouse

rabbit

pig

dog

human

Transmural gradient of excitation frequency during VF in the pig and in the dog

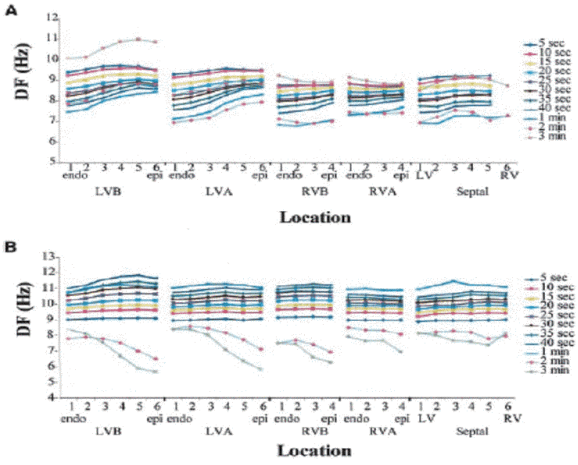


Figure 3. Mean transmural DF distribution in the pig (A) and dog (B) for all 5-second epochs of VF analyzed. Electrode regions are shown in Figure 1B and the zones are shown in Figure 1A with zone one closest to the LV endocardium. Legend on the right identifies each epoch.

From Newton et al., Circ Res, 2004

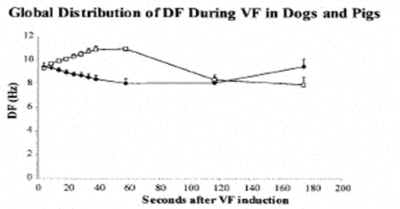
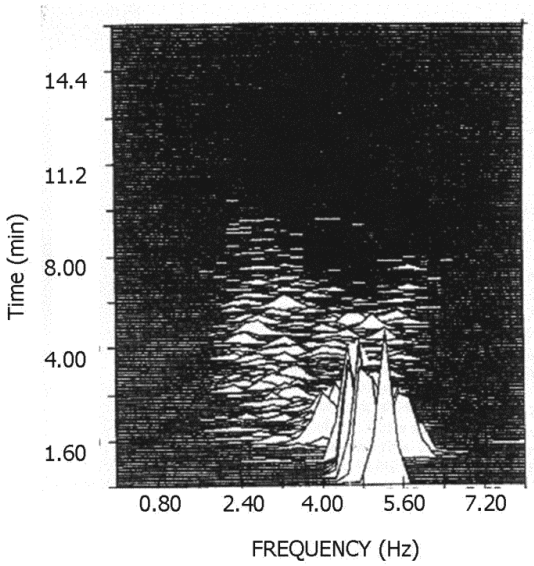


Figure 4. Mean and standard deviation of global DF at different VF durations for pigs (♦) and dogs (□).

Evolution of ECG spectrum during VF in human

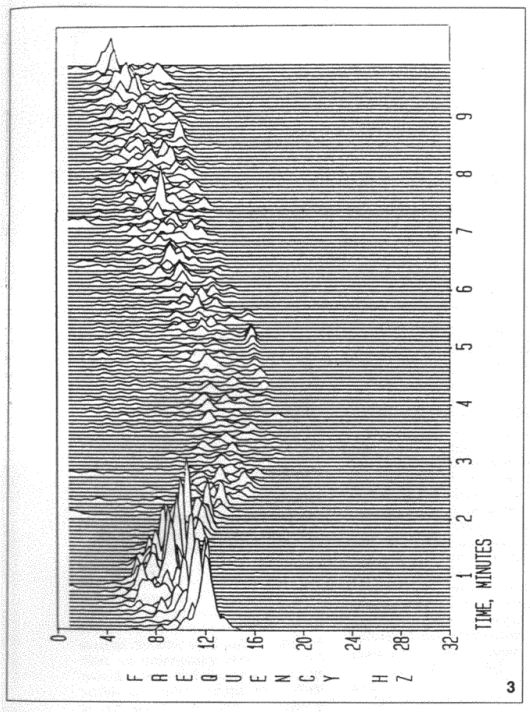


Periodicity is lost after ~ 2min of VF.

Why?

From Martin et al., Resuscitation, 1991

Evolution of ECG spectrum during VF in an anesthetized pig



Periodicity is lost after ~ 2min of VF.

Why?

From Brown et al., 1989

Human

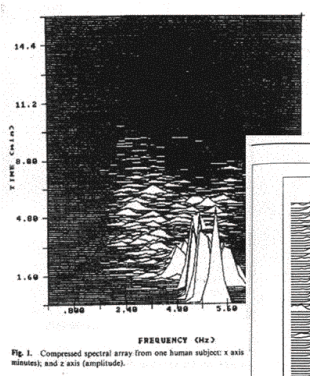
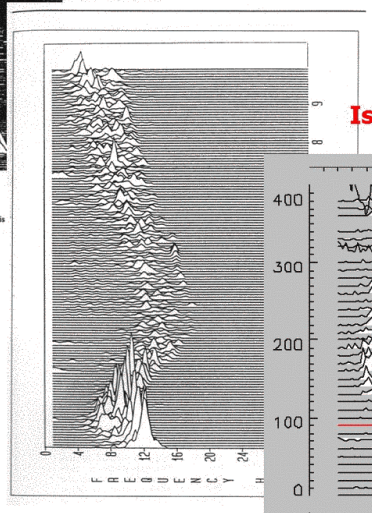
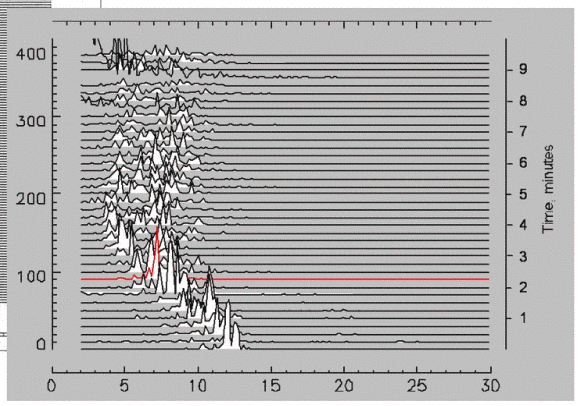


Fig. 1. Compressed spectral array from one human subject: x axis minutes); and z axis (amplitude).

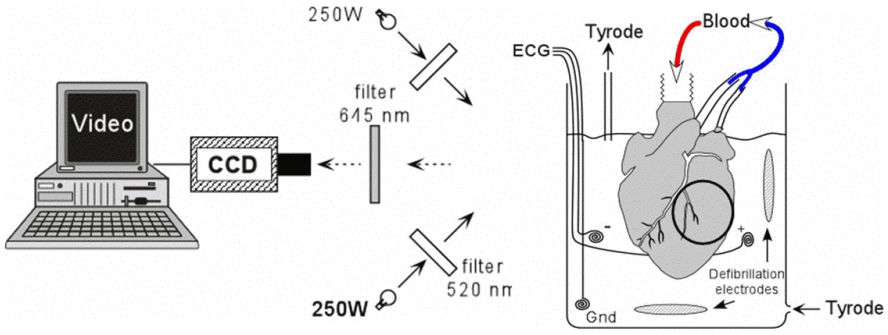
Anesthesized pig



Isolated blood-perfused pig heart

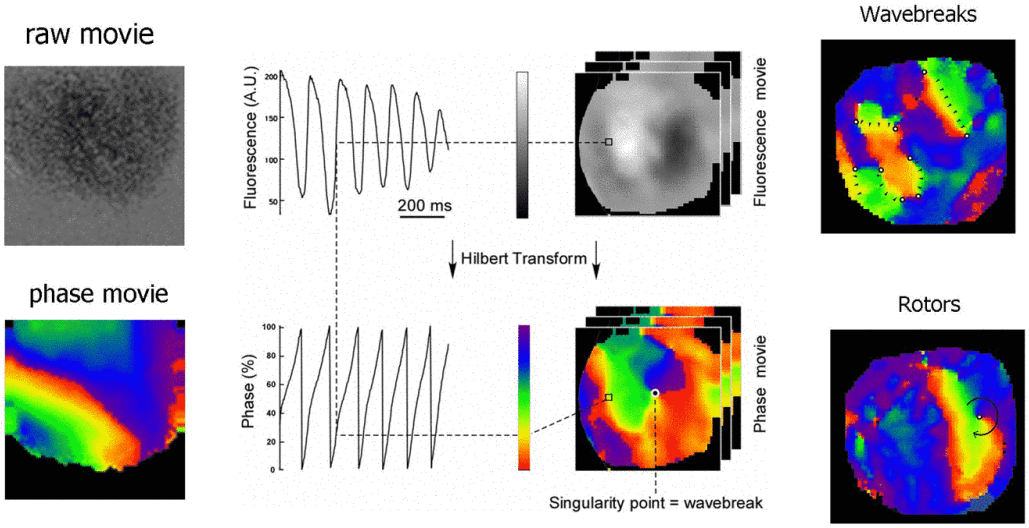


The common feature is loss of periodicity 2-3 min after onset of VF/ischemia

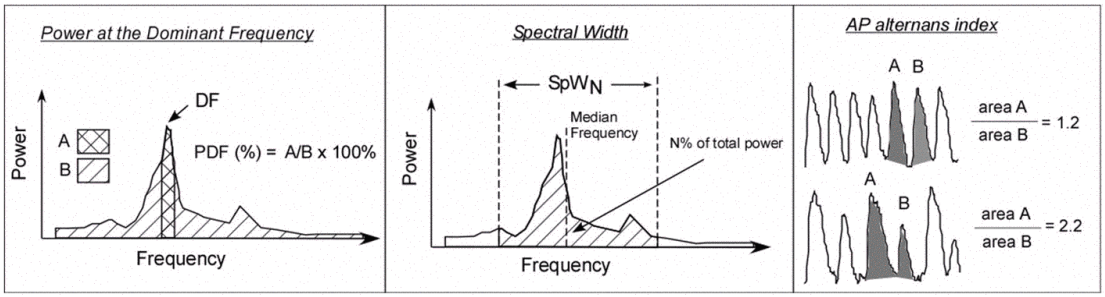


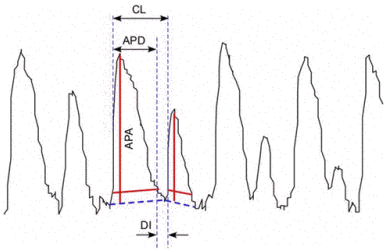
- VF was electrically induced and was allowed to reach steady state
- Optical and ECG recordings during first 10 minutes of ischemia
- Analysis of wavebreaks
- Analysis of optical action potential variability and local periodicity

Mapping of instantaneous phase during VF



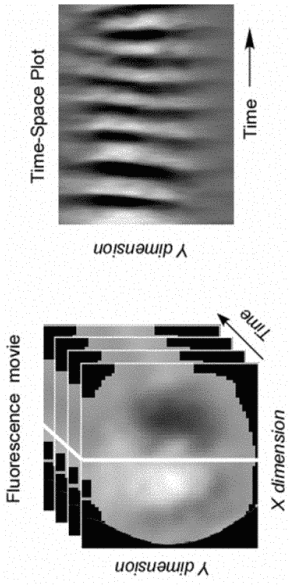
Analysis of optical Action Potential during VF

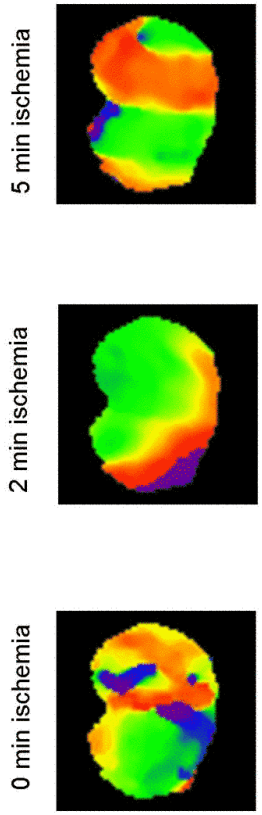


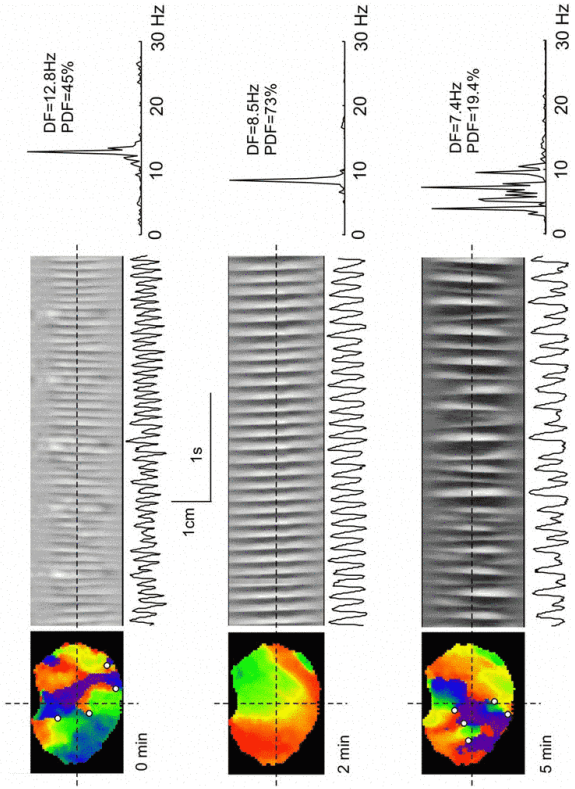


APA, action potential amplitude
APD, action potential duration
DI, diastolic interval
CL, cycle length
CL=APD+DI
APD restitution, APD as a function of the preceding DI

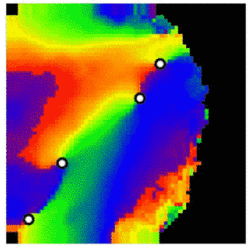
Time-Space Plot

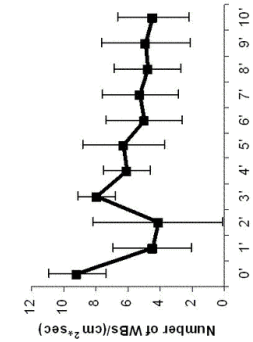


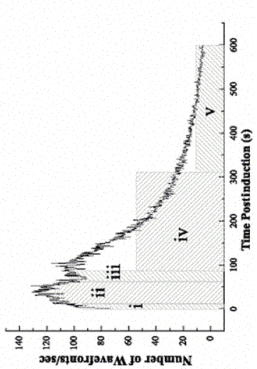




Time course of wavebreak incidence during VF/global ischemia

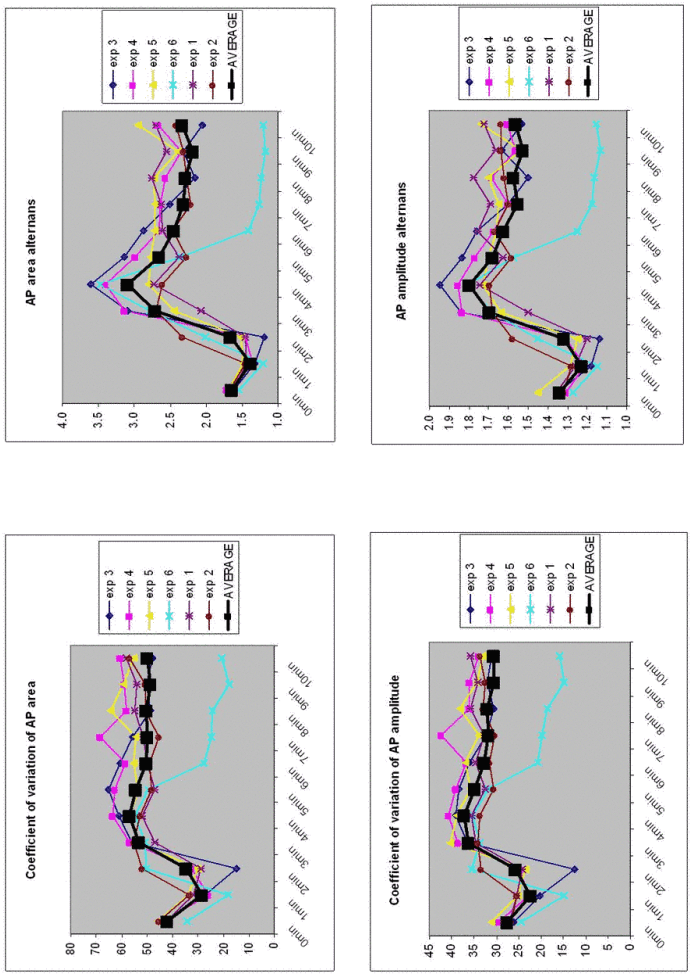




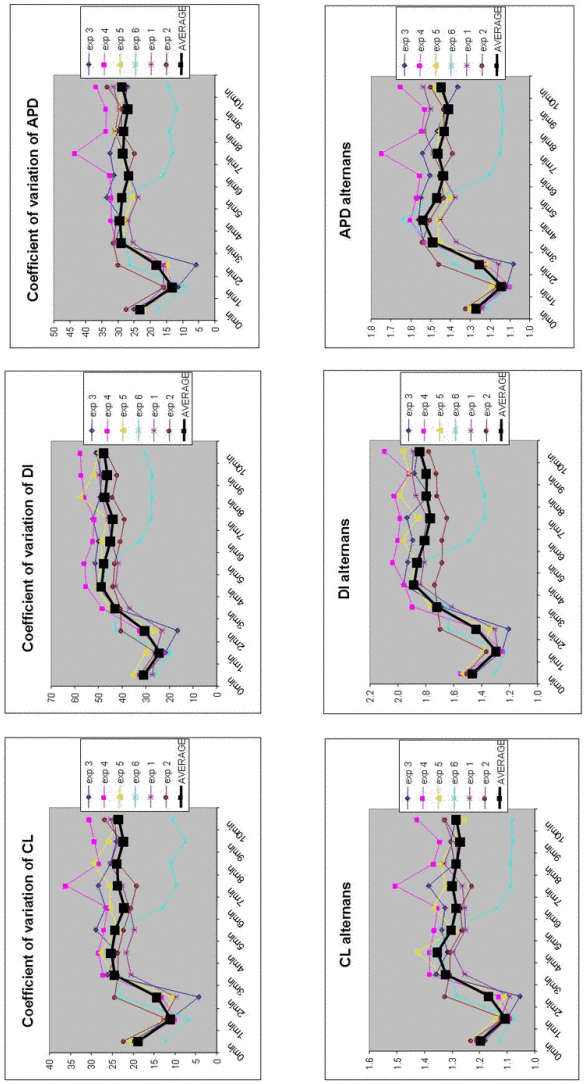


From Huang et al., Am J Physiol, 2004

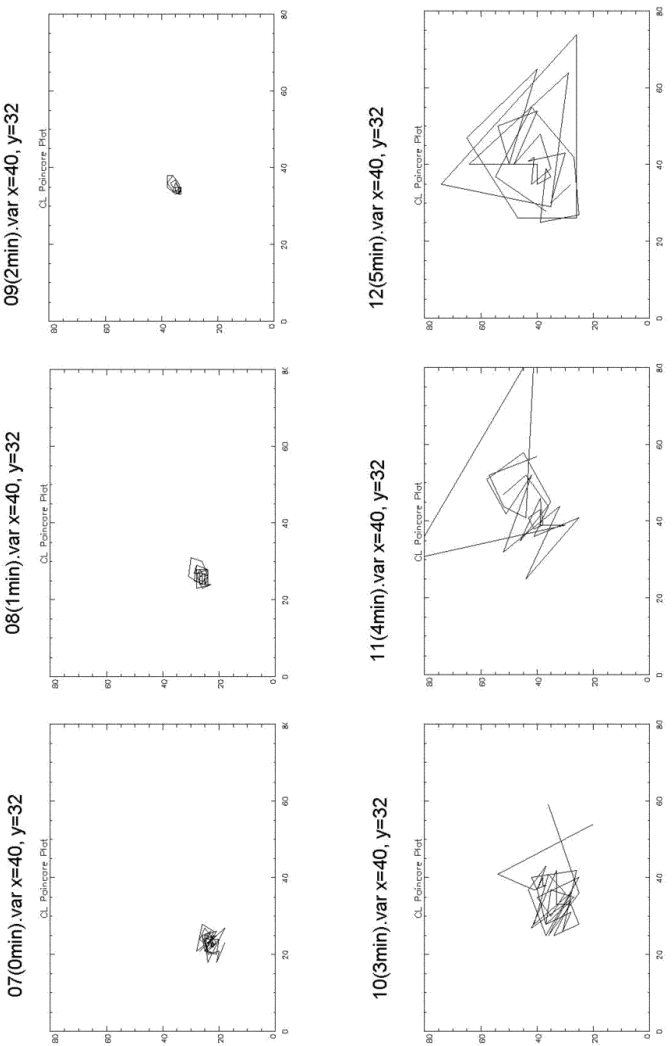
Time course of AP variability during VF/global ischemia



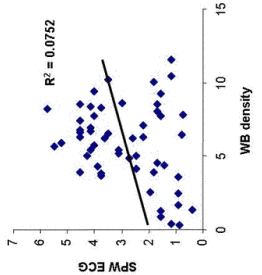
Time course of AP variability during VF/global ischemia (2)

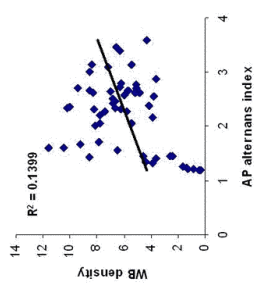


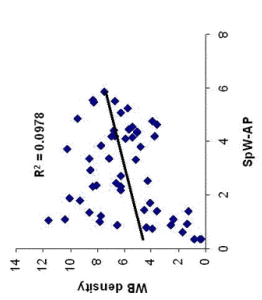
Poincare plots

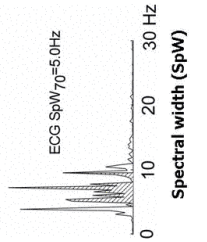


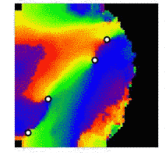
Relationship between AP variability, wavebreak and ECG



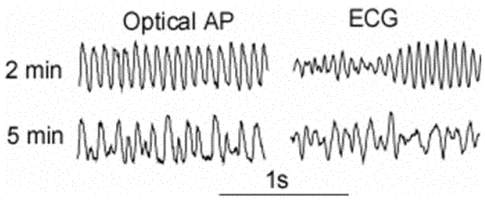


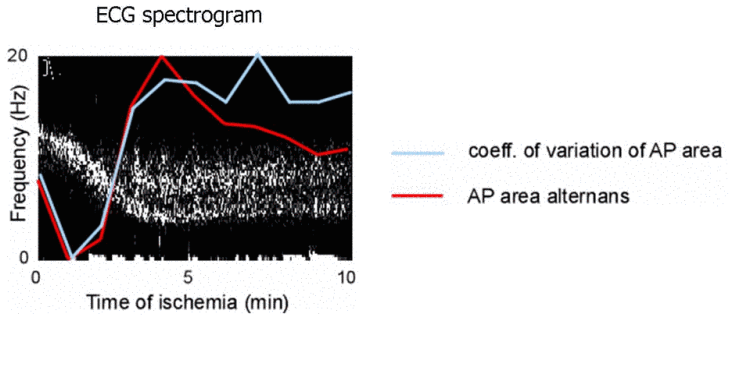






Correlation between AP variability and ECG spectrum





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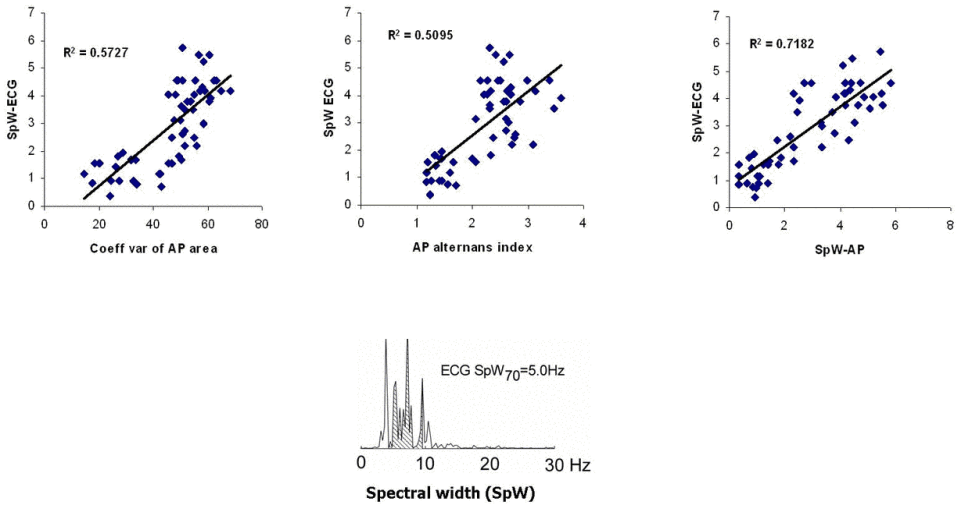
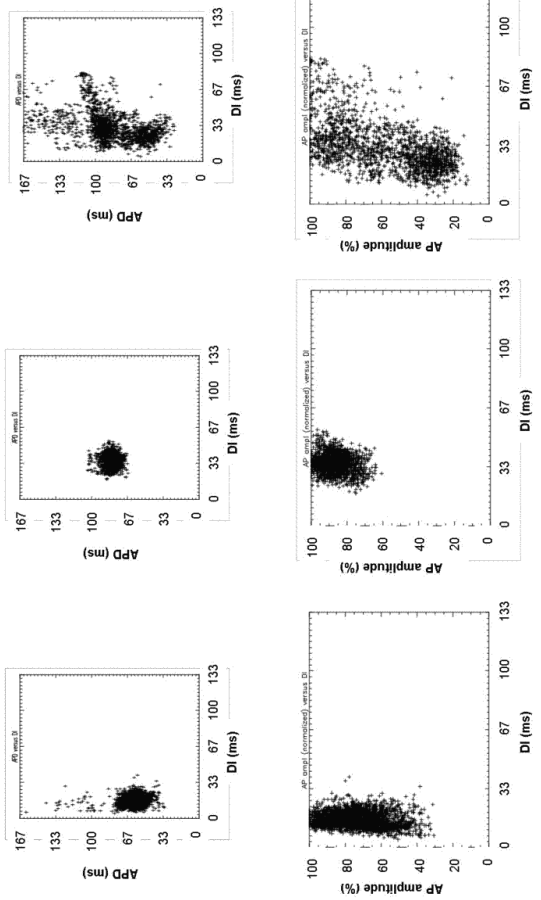
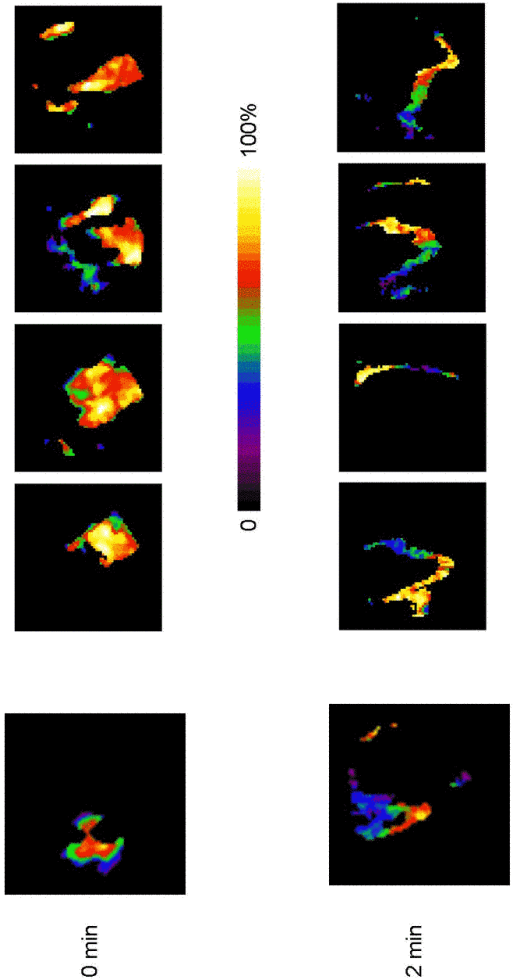


During VF, ECG spectrum reflects local periodicity without knowledge of spatial dynamics

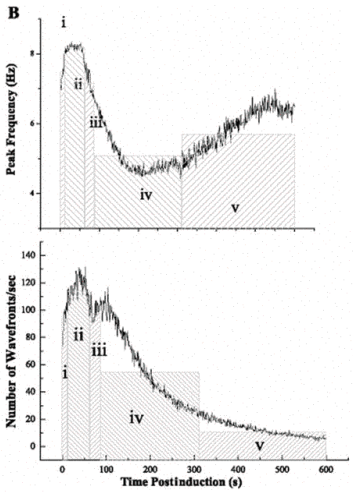
Restitution of APD and AP amplitude during VF/ischemia



Variability in the amplitude of propagating waves

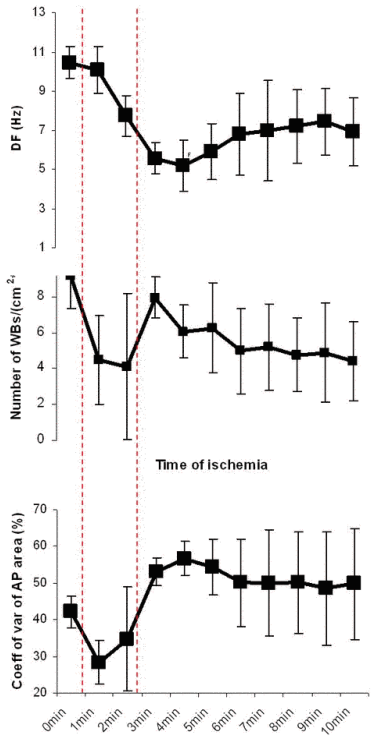


VF evolution in open-chest dog



From Huang et al., Am J Physiol, 2004

VF evolution in isolated pig heart

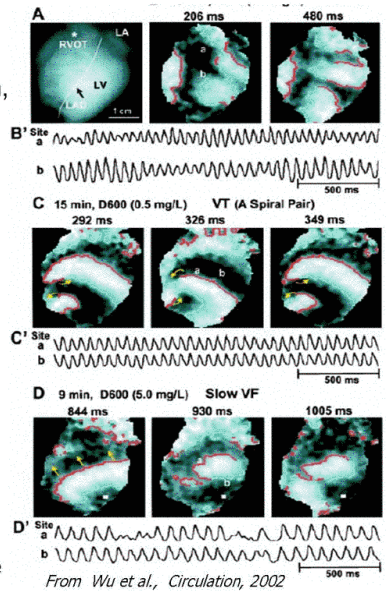


Are "two types of VF" sufficient to describe VF during ischemia?

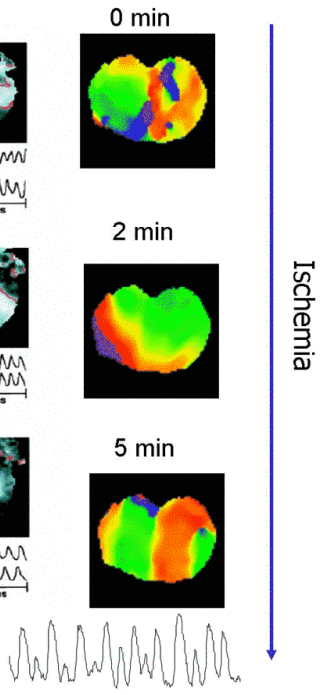
"Fast VF" (Type I)
Steep APD restitution,
Multiple wavelets

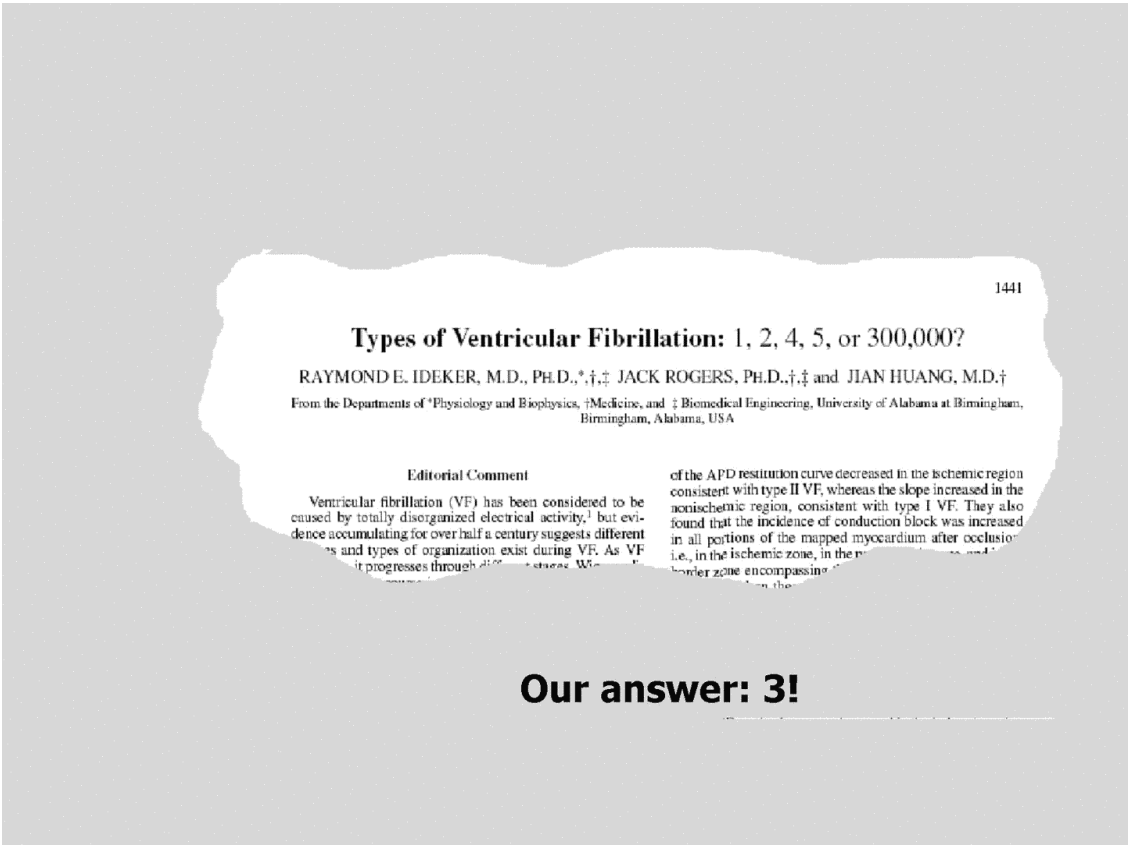
VT: Stable reentry

Slow VF (Type II):
Mother source,
flat APD restitution
wavebreaks
away from the source



From Wu et al., Circulation, 2002





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Types of Ventricular Fibrillation: 1, 2, 4, 5, or 300,000?

RAYMOND E. IDEKER, M.D., PH.D.,*,†,‡ JACK ROGERS, PH.D.,†,‡ and JIAN HUANG, M.D.†

From the Departments of *Physiology and Biophysics, †Medicine, and ‡Biomedical Engineering, University of Alabama at Birmingham, Birmingham, Alabama, USA

Editorial Comment

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Our answer: 3!

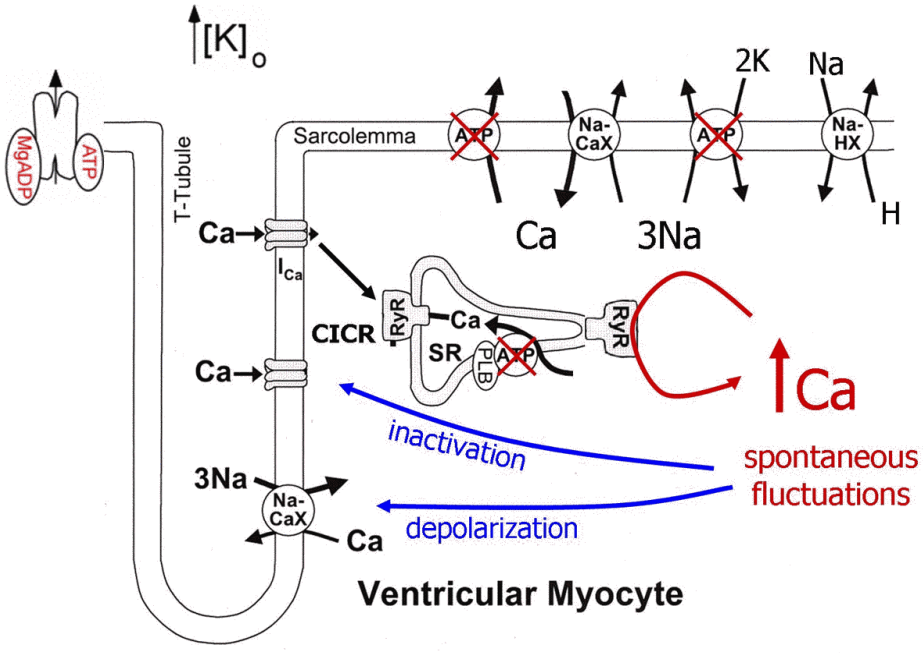
Conclusions for Part 1:

- During VF evolution in the isolated globally ischemic pig heart the breakdown of global organization is correlated with the onset of locally aperiodic behavior
- There are three qualitatively distinct phases of electrical activity during established VF in globally ischemic pig heart:

VF type/phase	Fast	Slow periodic	Slow aperiodic
Excitation Frequency	high	intermediate	low/intermediate
Local periodicity	intermediate	**high**	**low**
Wavebreak density	**high**	**low**	intermediate

Part II: WHY?

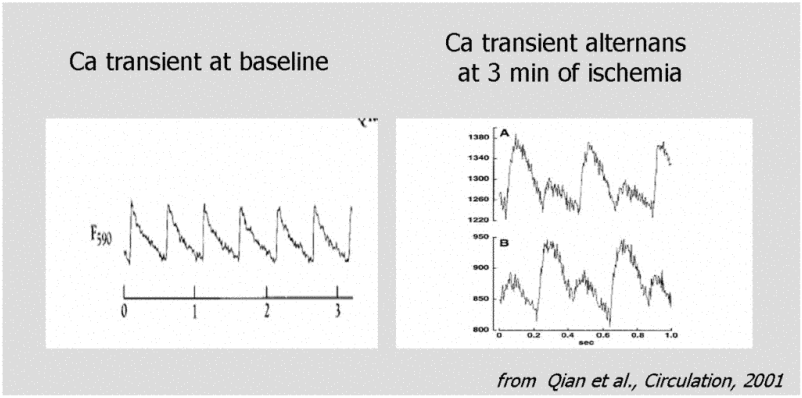
Cellular effects of ischemia



Hypothesis:

aperiodic phase of VF is due to an abnormal $[Ca]_i$ cycling

- Ca cycling is altered in myocardial ischemia
- Ca overload causes spontaneous fluctuations of [Ca]i mediated by CICR channel (ryanodine receptor)
- [Ca]i alternans develop after 2-3 min of ischemia (Wu and Clusin, 1997, Qian et al., 2001)



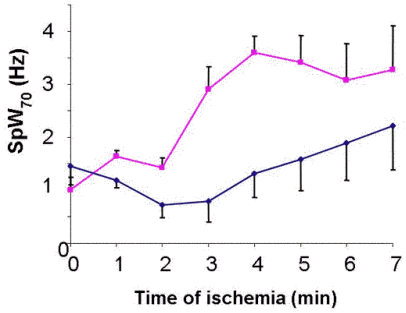
from Qian et al., Circulation, 2001

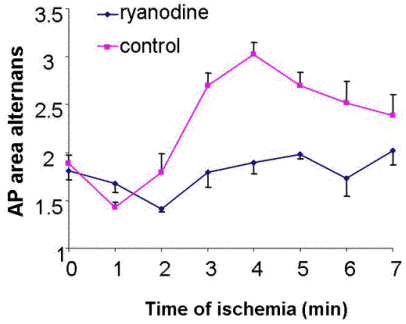
Hypothesis:

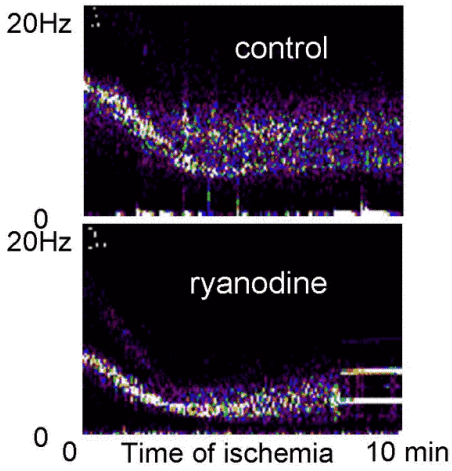
aperiodic phase of VF is due to an abnormal $[Ca]_i$ cycling

- $[Ca]_i$ fluctuations have been implicated in the mechanism of wavebreak during VF (Chudin et al., 1999; Omichi et al., 2004)
- We hypothesized that the role of intracellular Ca cycling increases as ischemia progresses and is responsible for the breakdown of VF organization.
- As a first step, we used pharmacological approach (CICR blocker, ryanodine; Ca channel blocker, verapamil)

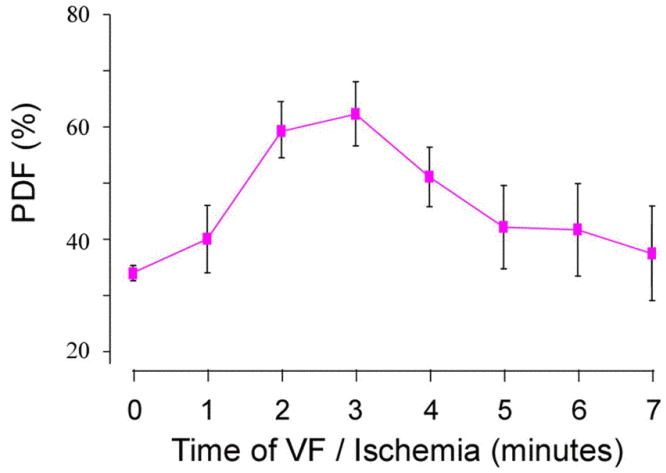
Effect of ryanodine on AP variability and ECG



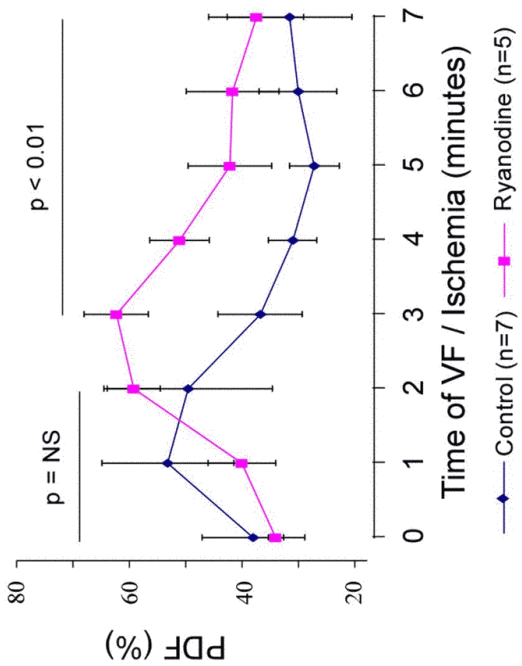




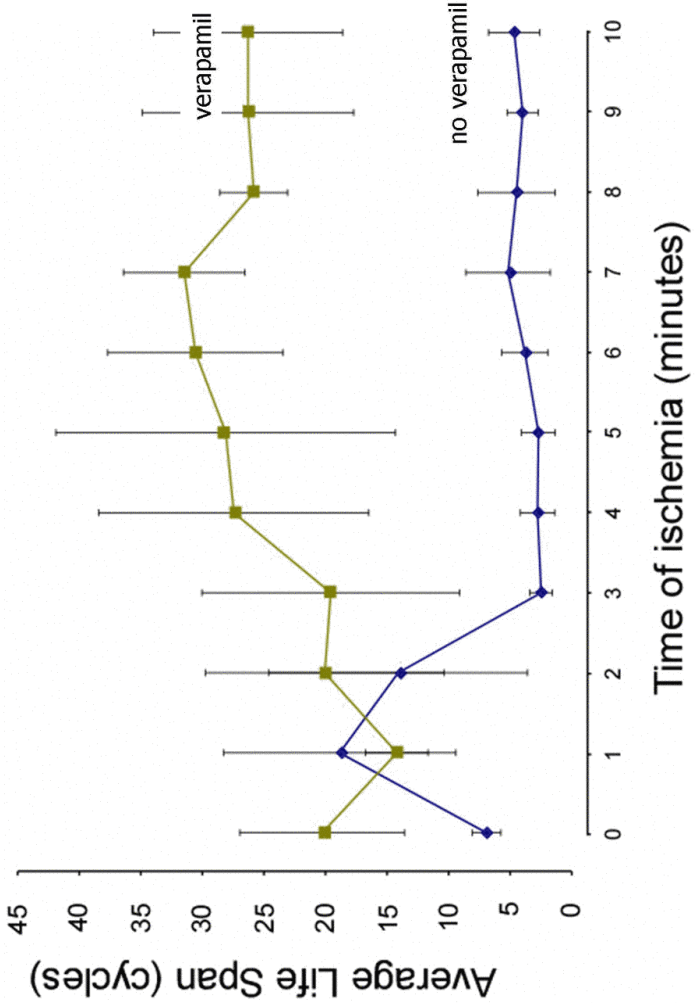
Ryanodine prolongs transient periodic phase and increases organization of VF during global ischemia



Ryanodine prolongs transient periodic phase and increases organization of VF during global ischemia

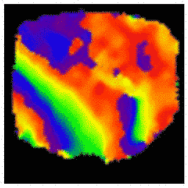


Verapamil eliminates aperiodic phase of VF



Verapamil establishes conditions for "type II VF" during VF/ischemia

7min of ischemia



Important clues for the search of mechanism:

- CICR-mediated $[Ca]_i$ cycling contributes to the *slow aperiodic phase,* although is relatively unimportant for earlier phases of VF
- Verapamil abolishes the *slow aperiodic phase* and establishes conditions for "type II VF" during VF/ischemia

SUNY, Syracuse:

- Jose Huisar, MD
- Rebecca Smith, BS
- Jerome Kalifa, MD,
- Javier Moreno, MD
- Sergey Mironov, PhD
- Arcady Pertsov, PhD
- José Jalife, MD

University of Utah, Salt Lake City:

- Mark Warren, PhD
- Alexander Shvedko, PhD

Nora Eccles Harrison
Cardiovascular Research and Training Institute

Dr. Kenneth Spitzer, Director

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