Evolution of Ventricular Fibrillation in the Ischemic Heart
(a link between local periodicity, wavebreak and ECG)

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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 ultimately improve treatment of VF
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Cellular effects of ischemia

VF evolution: unresolved issues

Cellular factors of ischemia  Wave dynamics during ischemic VF  Evolution of ECG during VF

Prediction, guidance

"Electrical" phase:
- shock first

"Circulatory" phase:
- CPR first

CPR, defibrillation, survival
Part I: HOW?

Part II: WHY?

Part I: HOW?
Ventricular Fibrillation – tornadoes in the heart?

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”

A Tale of Two Fibrillations

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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 quite different from one another. This is because VF can be classified into two types: Type I (fast) VF and Type II (slow) VF.

Type I (fast) VF 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?

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Editorial Comment

Ventricular fibrillation (VF) has been considered to be caused by totally disorganized electrical activity, but evidence accumulating for over half a century suggests different types and types of organization during VF. As VF progresses through different phases, it has been noted that the AFQ restitution curves remain constant in the phase of reentry consistent with type II VF, whereas the slope increased in the anisotropy region consistent with type I VF. They also found that the frequency of conduction block was increased in all portions of the mapped myocardium after reentry i.e., in the isotropic zone, in the transitional zone, and in the anisotropic zone.

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

From Newton et al., Circ Res, 2004

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

Figure 5. 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 1A and the zones are shown in Figure 1A with zone one closest to the LV endocardium. Legend in the right identifies each epoch.
Evolution of ECG spectrum during VF in human

Periodicity is lost after ~2 min of VF.

Why?

From Martin et al., Resuscitation 1981

Evolution of ECG spectrum during VF in an anesthetized pig

Periodicity is lost after ~2 min of VF.

Why?

From Brown et al., 1989
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

**Power at the Dominant Frequency**
- DF
- \( \text{PDF} = \frac{A}{B} \times 100\% \)

**Spectral Width**
- \( \text{SpW}_N \)
- % of total power

**AP alternans index**
- Area A
- Area B

**Abbreviations**
- 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

5 min ischemia

2 min ischemia

0 min ischemia
Time course of wavebreak incidence during VF/global ischemia

From Huang et al., Am J Physiol, 2004
Dr. Alexey Zaitsev, Utah State Univ (KITP 7-24-06) Evolution of Ventricular Fibrillation in a Globally Ischemic Heart:

Time course of AP variability during VF/global ischemia.

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

07(0min). var x=40, y=32
06(1min). var x=40, y=32
00(2min). var x=40, y=32
10(3min). var x=40, y=32
11(4min). var x=40, y=32
12(5min). var x=40, y=32

Relationship between AP variability, wavebreak and ECG

Wavebreak (WB) density
AP alternans index = \frac{\text{area A}}{\text{area B}}
Spectral width (SpW)

ECG SpW\alpha=50Hz
Correlation between AP variability and ECG spectrum

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
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
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:

<table>
<thead>
<tr>
<th>VF type/phase</th>
<th>Fast</th>
<th>Slow periodic</th>
<th>Slow aperiodic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excitation Frequency</td>
<td>high</td>
<td>intermediate</td>
<td>low/intermediate</td>
</tr>
<tr>
<td>Local periodicity</td>
<td>intermediate</td>
<td>high</td>
<td>low</td>
</tr>
<tr>
<td>Wavebreak density</td>
<td>high</td>
<td>low</td>
<td>intermediate</td>
</tr>
</tbody>
</table>
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)

![Ca transient at baseline](image1) ![Ca transient alternans at 3 min of ischemia](image2)

from Qian et al., Circulation, 2001

Hypothesis:
aperiodic phase of VF is due to an abnormal [Ca]i cycling

- [Ca], 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

Time of ischemia (minutes)

Average Life Span (cycles)
Verapamil establishes conditions for “type II VF” during VF/ischemia

7 min of ischemia

Important clues for the search of mechanism:

- CICR-mediated [Ca]i cycling contributes to the slow aperiodic phase, although it is relatively unimportant for earlier phases of VF

- Verapamil abolishes the slow aperiodic phase and establishes conditions for “type II VF” during VF/ischemia
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Dr. Kenneth Spitzer, Director
supported by
Nora Eccles Treadwell Foundation
American Heart Association