Localized spontaneous activation of cardiac tissue during acute ischemia and reperfusion.

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Sudden Cardiac Death (SCD)

- Any death from a cardiac cause occurring within an hour of symptom onset.
- 300 to 450K annual deaths in the US.
- Caused by abnormal electrical activity leading to a fatal arrhythmia.
- 80% of such arrhythmias are due to coronary artery disease and its associated conditions (ischemia and infarction).

NORMAL SINUS RHYTHM
Impulses originate at S-A node at normal rate

SCD

- tachycardia
- fibrillation
- death
Coronary artery disease

Coronary artery disease → Arrhythmia → Sudden cardiac death
In the US almost 6.5 million people suffer from coronary artery disease.

- Atherosclerosis, formation of plaques within arteries
- Ischemia and arrhythmias
- Cardiomyocyte loss
- ‍↑ Workload → Hypertrophy
- Collagen & fibrotic scar
  - Propagation delays → Arrhythmogenic substrate
  - ‍↓ Cardiac output → Heart Failure
Sudden Cardiac Death

Ventricular Fibrillation

Ectopic Sources  Electrical Rotors

Altered Substrate
Underlying structural disease
Damage due to coronary artery disease

Pacing Therapies

Stem Cell Therapy

Approach: Understand pathological mechanisms to develop therapies.
Outline

1) Research tools
2) Ventricular fibrillation
3) Ischemic mechanisms of fibrillation
4) Stem cell therapy to heal damaged heart tissue
Tools for investigating causes of ventricular fibrillation

Research Methods
  Fluorescence Imaging
  Computational Models
  Data and image analysis

Experimental Models
  Excised animal hearts
  Cultures of cardiac cells

Excised animal hearts (rat)

Cultures of cardiac cells (neonatal rat myocytes)
Fluorescence imaging for monitoring living tissue.

- **Excitation wavelength**
- **Emission wavelength**

**RH237**

**Rhod-2am**

- **Vm**
  - Action potentials
- **Ca++**
  - Calcium transients

**Excitation filter**
**Emission filter**
**Dicroic mirror**
**DYE**
Fluorescence imaging of living cardiac tissue.

Cardiac myocytes

Fluo-4am
495nm peak excitation
520nm peak emission

NADH
<360nm excitation
450nm peak emission

di-4ANEPES
470nm peak excitation
625nm peak emission

[Ca^{2+}]i

Fluo-4am
495nm peak excitation
520nm peak emission
Computational Models
(The cardiac monodomain model)

- Grid discretization
- $V_m$ at each node is defined by a system of PDEs.
- Integrate by time stepping (forward Euler and 9pt Laplacians).

$$C_m \frac{\partial V_m}{\partial t} = \nabla \cdot D \nabla V_m - I_{ion}$$

$$I_{ion} = I_{K1} + I_{Na} + I_s + I_{x1}$$

Nonlinear conductances in voltage and time.

Rotor formation
Rotors can be studied in great detail using computational techniques. Rotors are also a primary mechanism of ventricular fibrillation and sudden death.
Numerical modeling validated by live tissue experiments.

Antitachycardia pacing: Pacing-induced rotor drift is a mechanism of rotor termination.

Fluorescence imaging of \([\text{Ca}^{+2}]_i\) using a cardiac myocyte cell culture.
How many rotors are there in fibrillating hearts of large animals (like humans)?

Panoramic fluorescence imaging reveals about a dozen short lived rotors in healthy fibrillating swine hearts. Rotors rarely lasted longer than 1 sec. Stable epicardial rotors do not maintain VF. Continual formation of new rotors is critical for VF maintenance.
Rotors maintain fibrillation but how is it initiated? 80% of deadly arrhythmias are due to coronary artery disease and its associated conditions (ischemia and infarction).

We are currently focused on two main areas.
1) Spontaneous ectopic activity during ischemia and reperfusion.
2) Stem cell therapy to rejuvenate infarcted (dead) tissue.

Animal heart model of localized acute ischemia
Fluorescence imaging of NADH during acute localized ischemia and reperfusion.

Spatial gradients of NADH shift during low-flow reperfusion.

Change in NADH

dNADH (i,j)
Fluorescence imaging of transmembrane potential during acute localized ischemia and reperfusion.

Occasional high frequency ectopic beats are observed during full-flow reperfusion.
A multitude of ectopic sources are observed during low-flow reperfusion!

A strong correlation exists (p<0.01) between the location of premature beats and the spatial gradient of the change in mitochondrial redox state caused by reperfusion.
Studies to understand how cell transplantation can be used to re-establish normal electrical and mechanical function and to avoid hypertrophy & fibrosis.

1) Stem cell colonies are grown in culture as embryoid bodies
2) Myocyte-like cells are selected and
3) Co-cultured with neonatal cardiac myocytes
Low frequency pacing
Region with grafted ESC-CM


High frequency pacing – precursor to rotor formation
Area of future propagation block
Is the engraftment of myocyte-like cells beneficial or not?? More work to be done....

Fluorescence imaging of $[\text{Ca}^{+2}]_i$ in a co-culture of rat cardiac myocytes and mouse embryonic stem cells.
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