

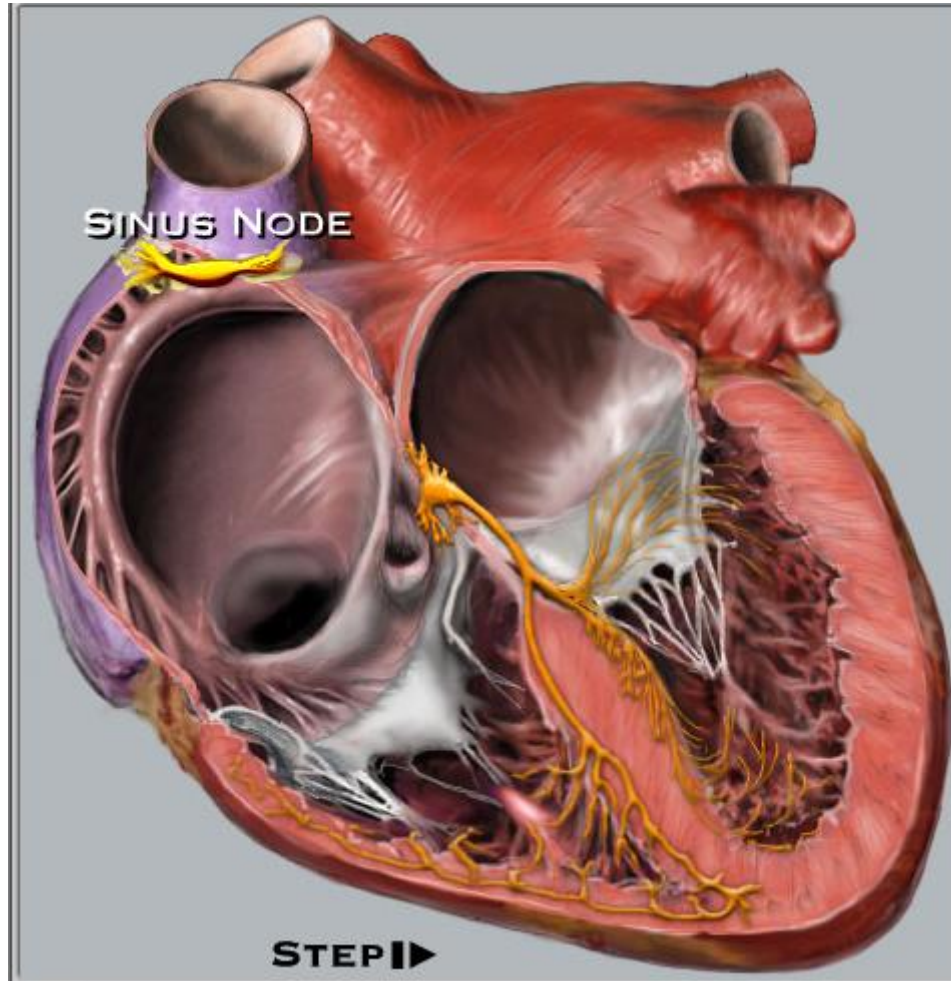
# Principles of Electrical Wave Propagation in the Heart

Dr. Alexander Lyon

Senior Lecturer and Consultant Cardiologist  
Imperial College and Royal Brompton Hospital

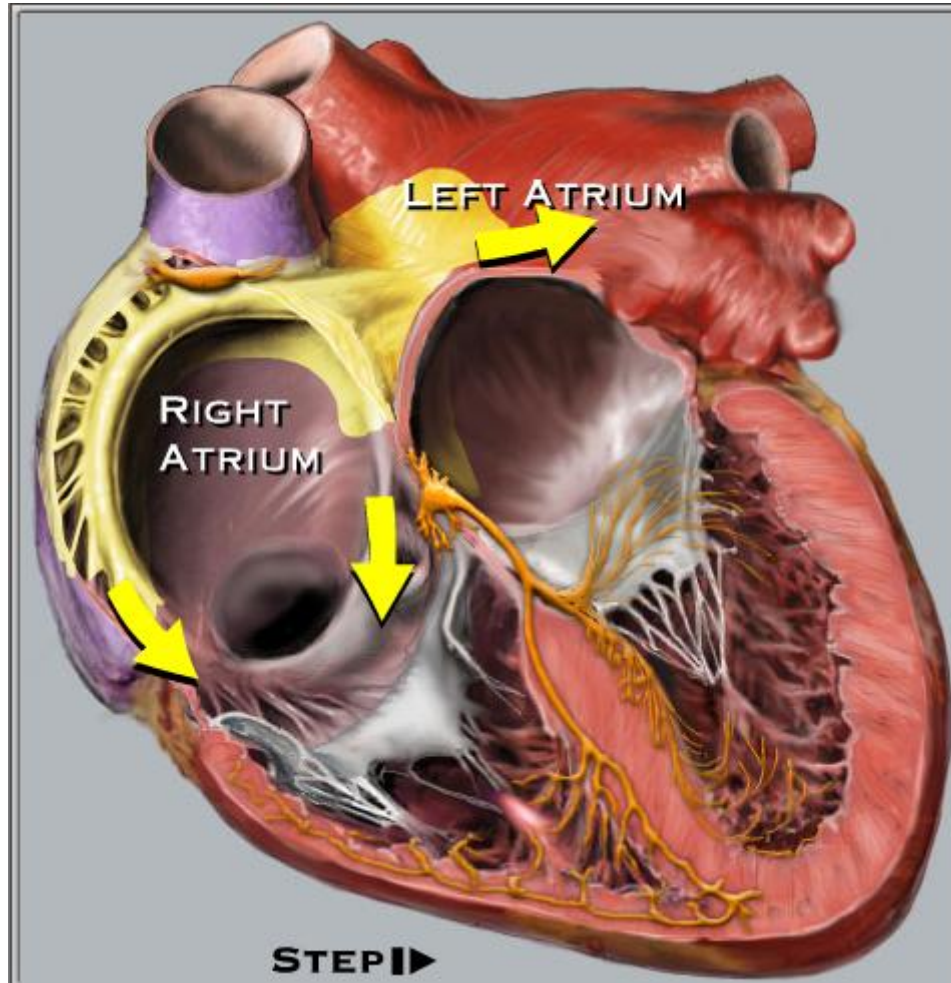
# Cardiac Conduction System

## Sinoatrial Node



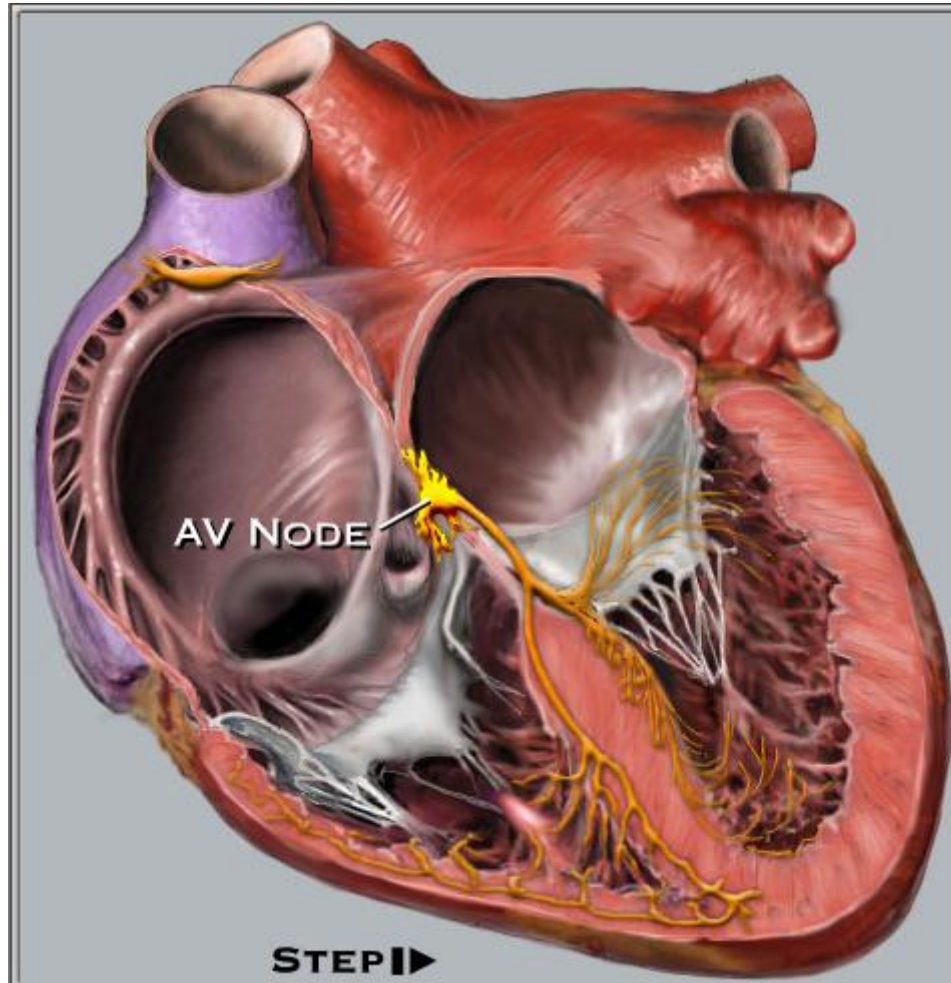
# Cardiac Conduction System

## Atrial Activation



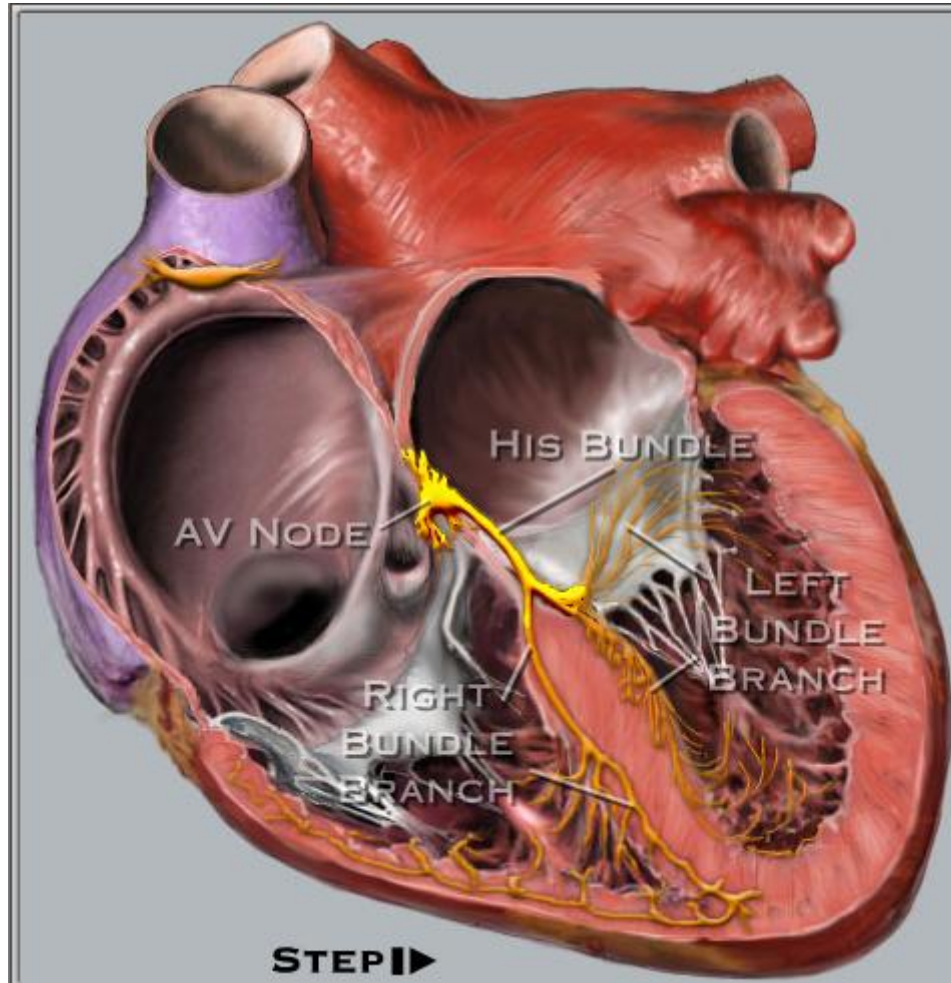
# Cardiac Conduction System

## Atrioventricular Nodal Conduction



# Cardiac Conduction System

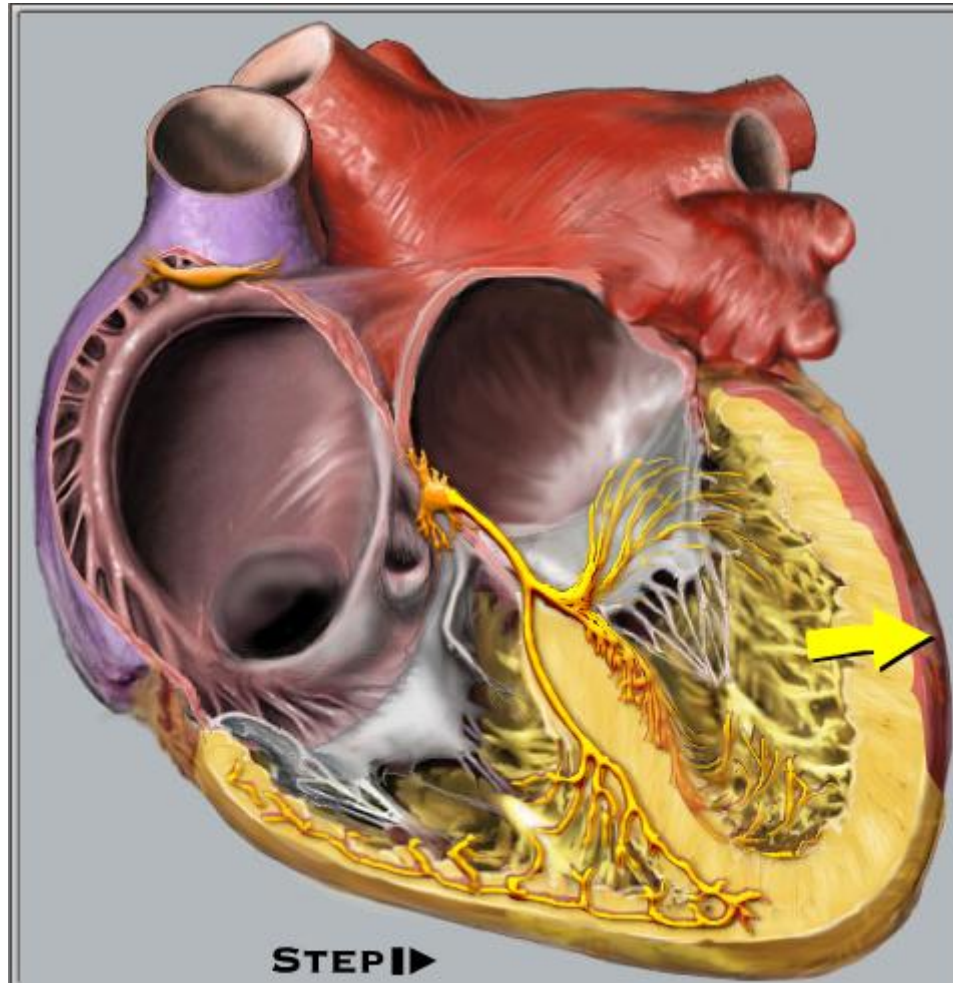
## Activation of His-Purkinje System



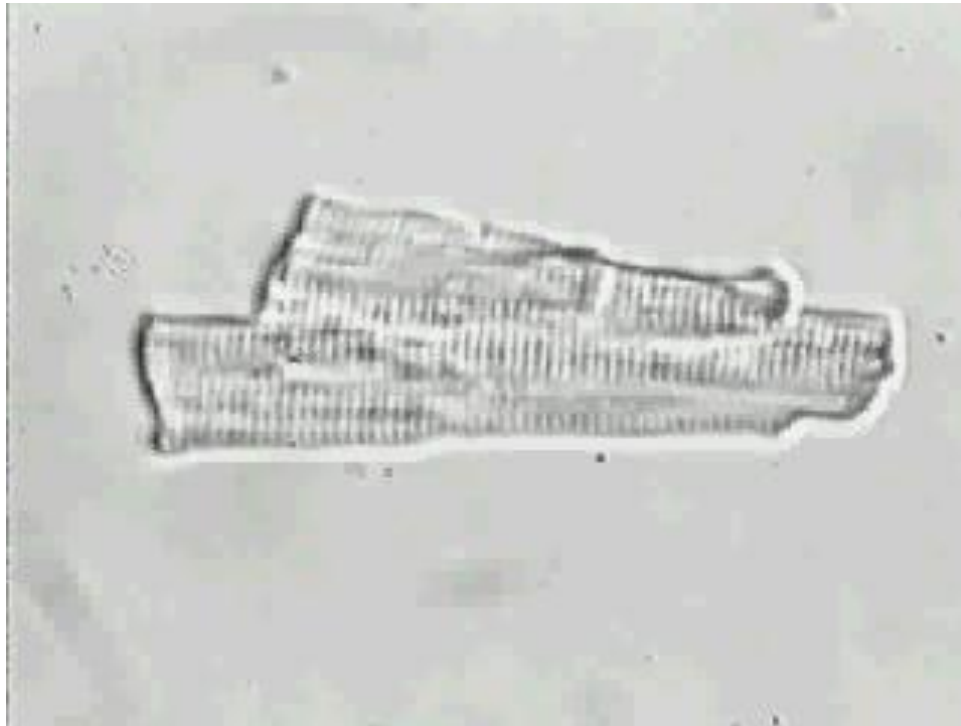


# Cardiac Conduction System

## Ventricular Activation

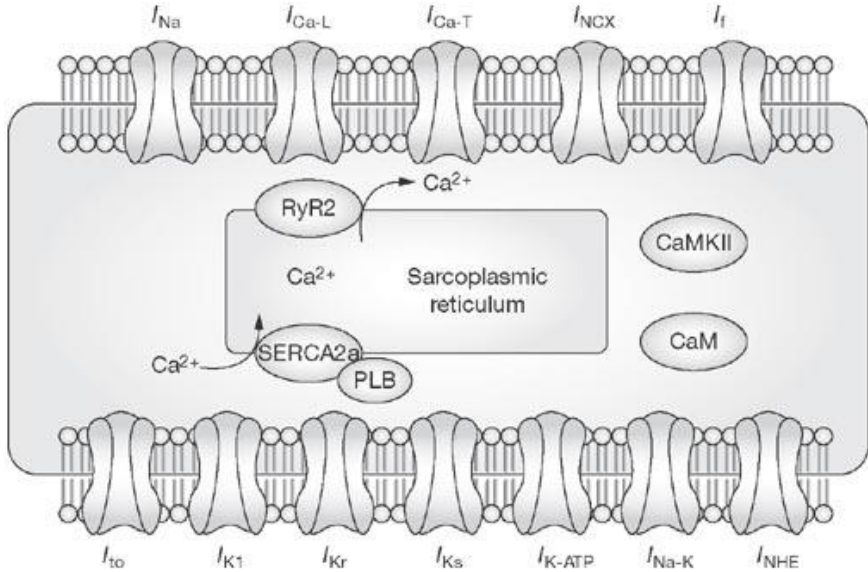
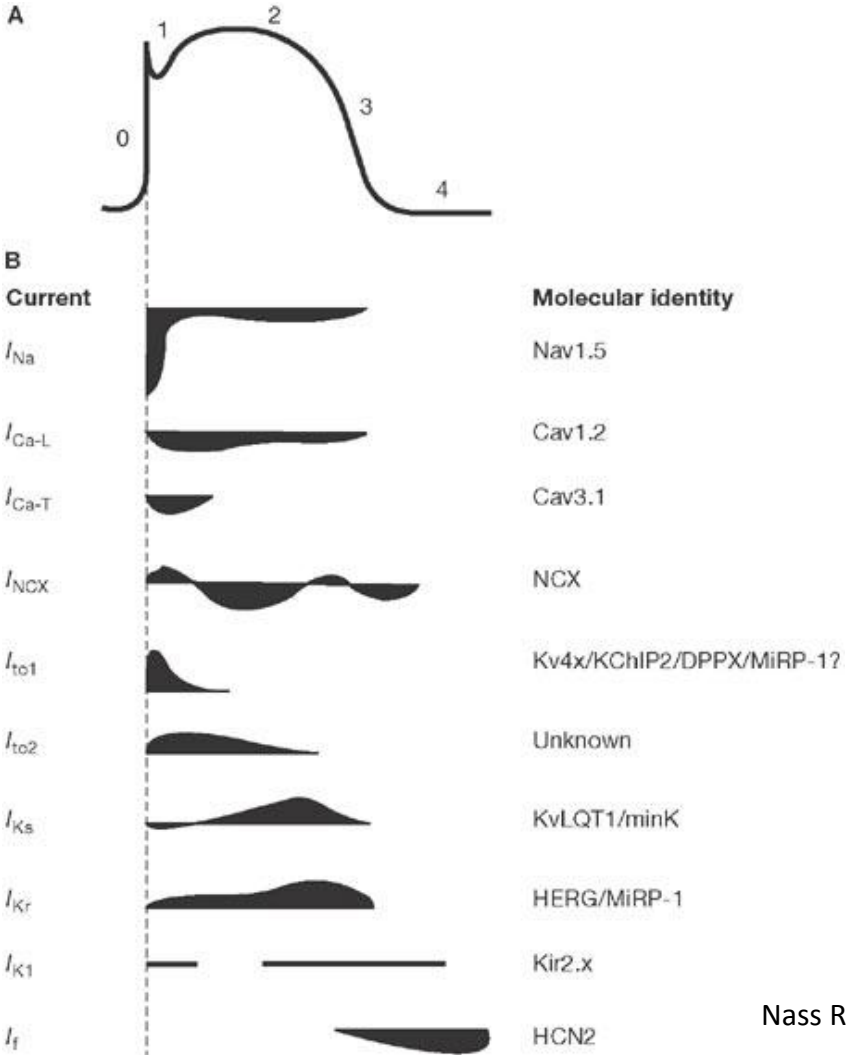


# Ventricular Cardiomyocytes



# Ventricular Cardiomyocyte Action Potential

## Ionic Currents





# Electrical Propagation

- Current source - sink

# Electrical Propagation

## $I_{K1}$ , membrane resistance and DADs

Effect of  $I_{K1}$  reduction in heart failure

**A** Control



$$V = I \times R = I / g$$

**B** Heart Failure

If  $I_{K1} \downarrow$ ,  $R \uparrow$

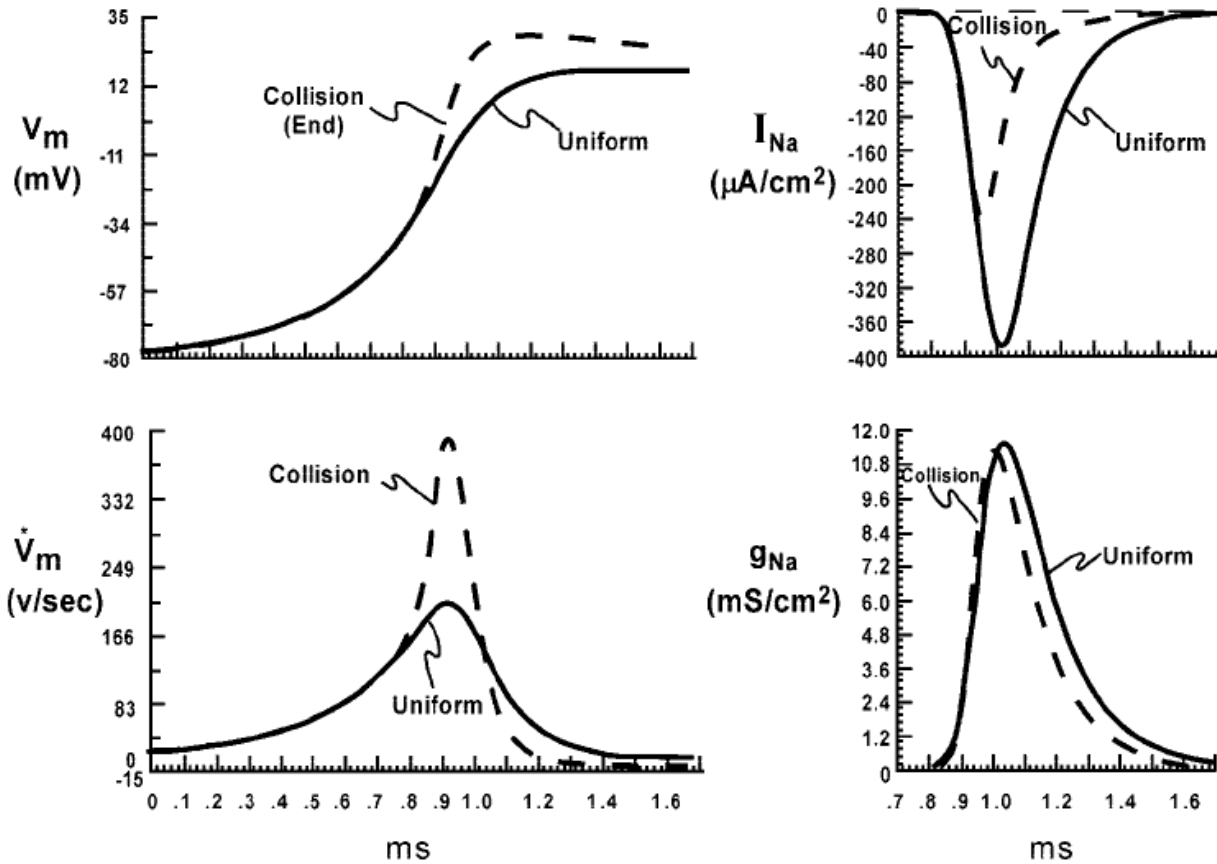


•V larger for the same I

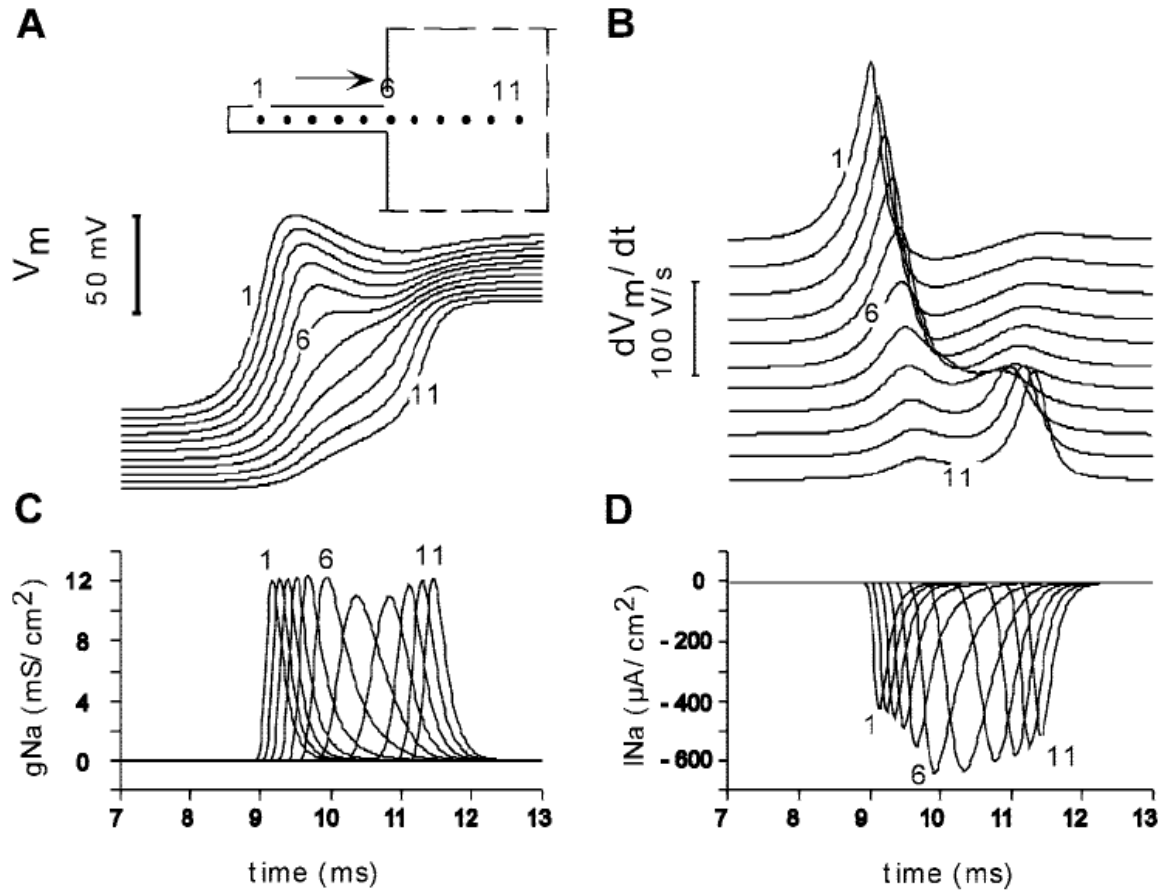
# Biophysical principles of propagation

- Continuous Propagation (linear cells/cable)
- Discontinuous Propagation
- The Safety of Propagation
- Two-dimensional propagation and curvature.

# Effects of wavefront collision on the upstroke of the AP



# Current-to-Load mismatch

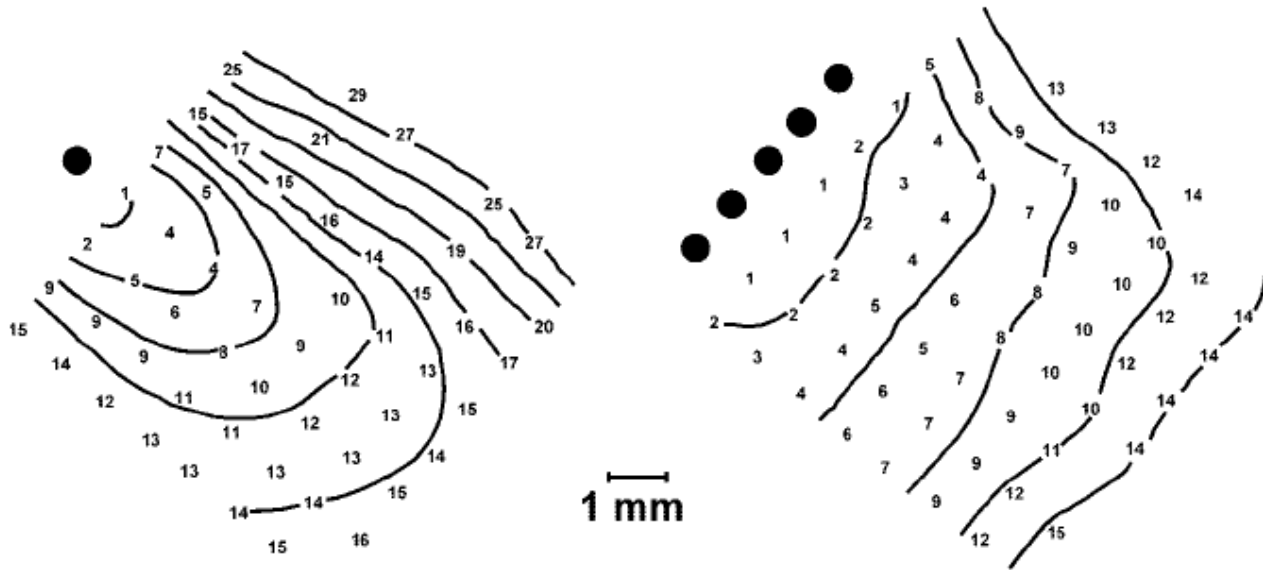




# Safety of Propagation

$$\text{SF} = \frac{\int_A I_c dt + \int_A I_{\text{out}} dt}{\int_A I_{\text{in}} dt} \quad A|Q_m > 0$$

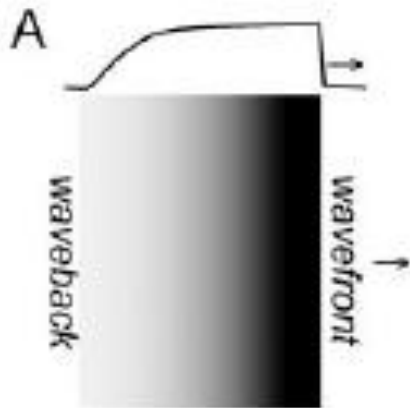
# Effect of curvature on propagation.



**Point Stimulation**

**Line Stimulation**

# Electrical Wave Propagation and Wavebreak



Stable wave  
 $\lambda = APD \cdot CV$   
( $cm = s \cdot cm/s$ )



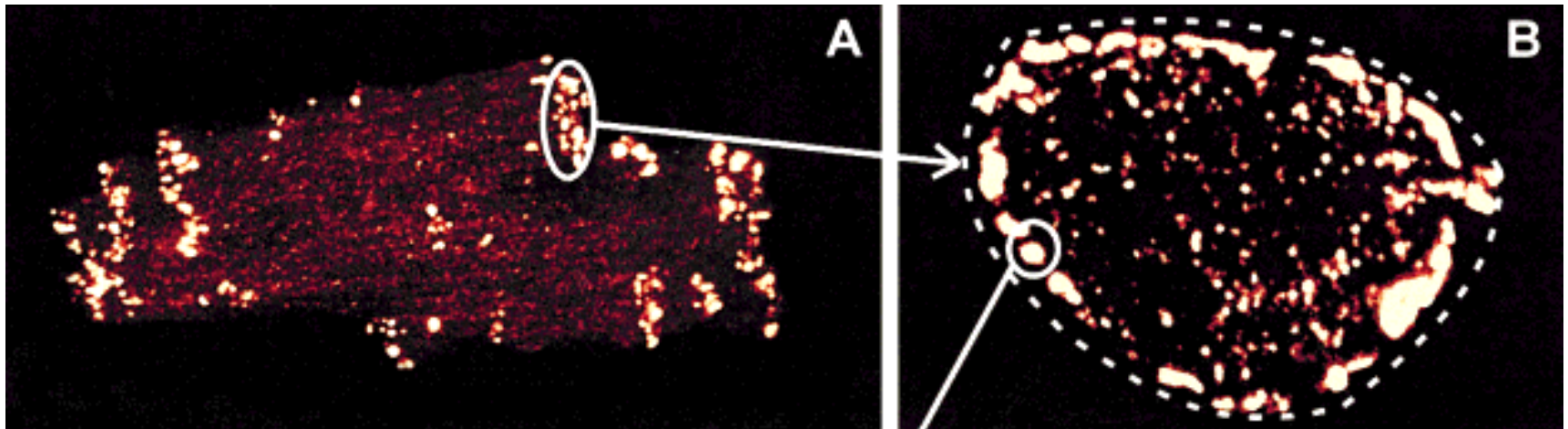
Waveback  
instability  
(steep APDR)



Wavefront  
instability  
(broad CVR)

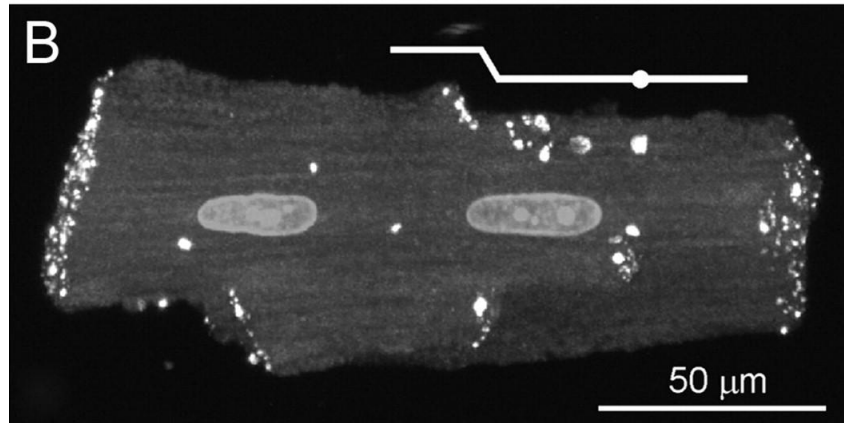
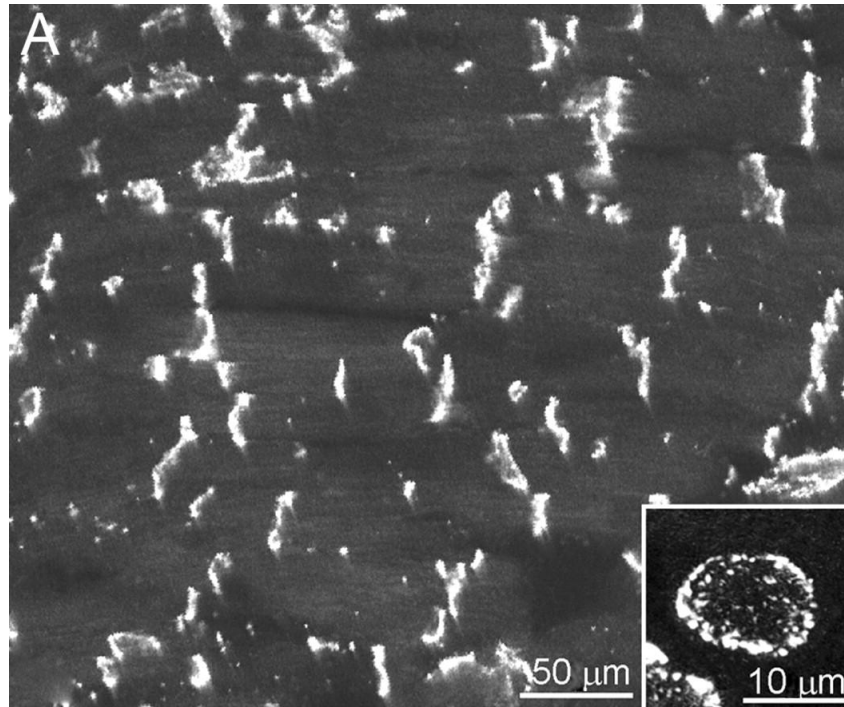
# Intercellular Electrical Conduction

## Gap junction structure



# Intercellular Electrical Conduction

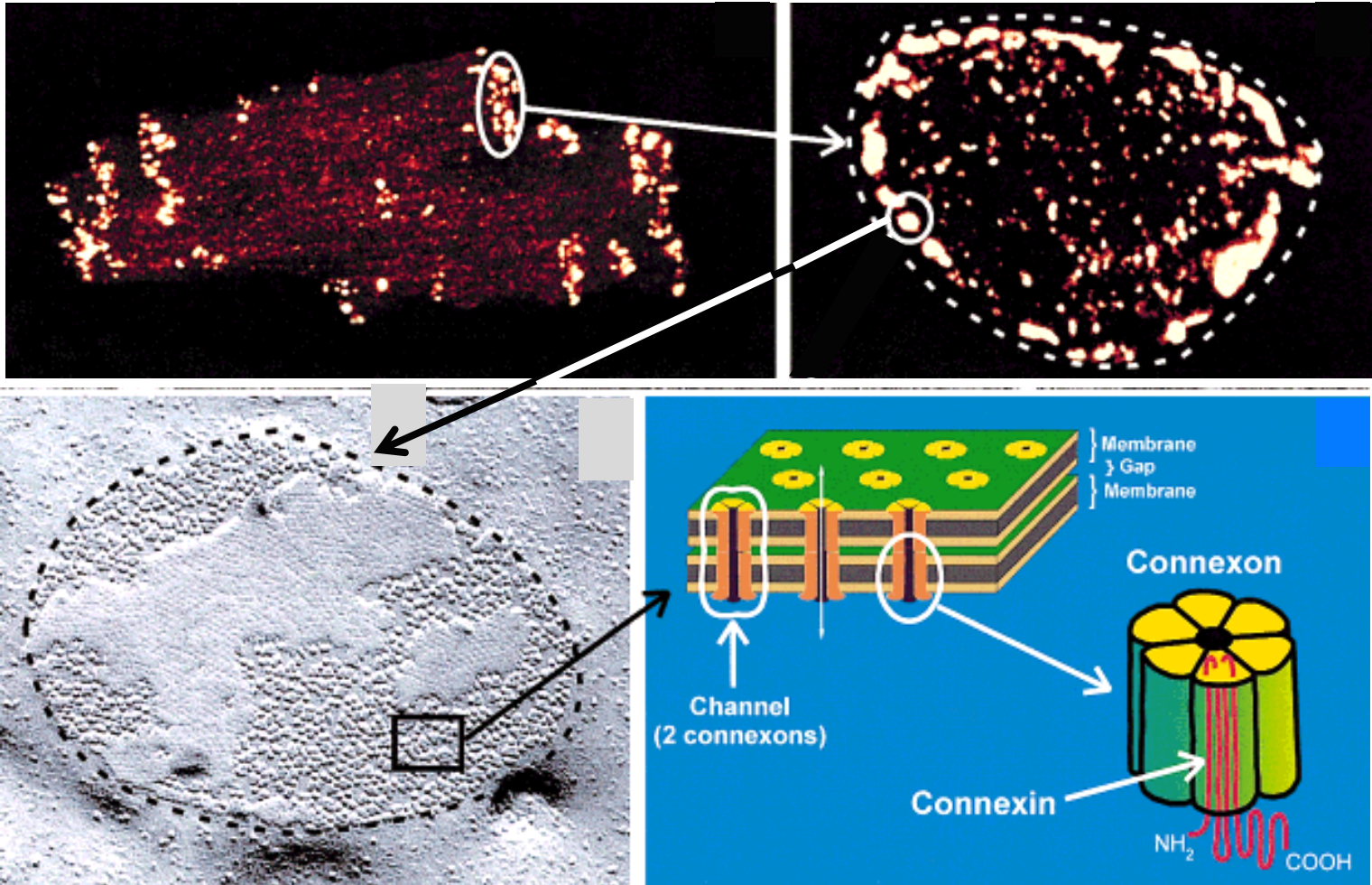
## Gap junction structure





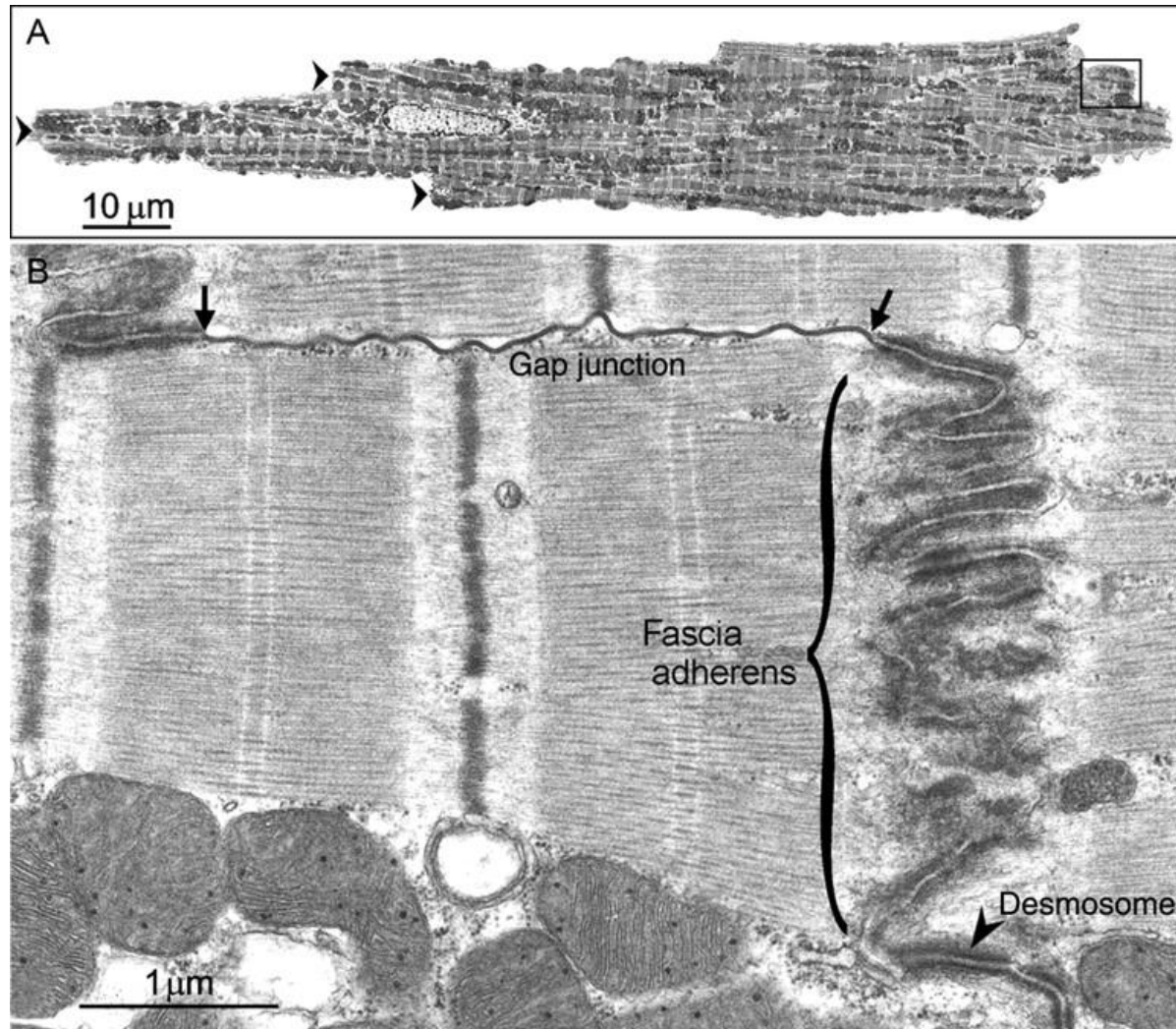
# Intercellular Electrical Conduction

## Gap junction structure



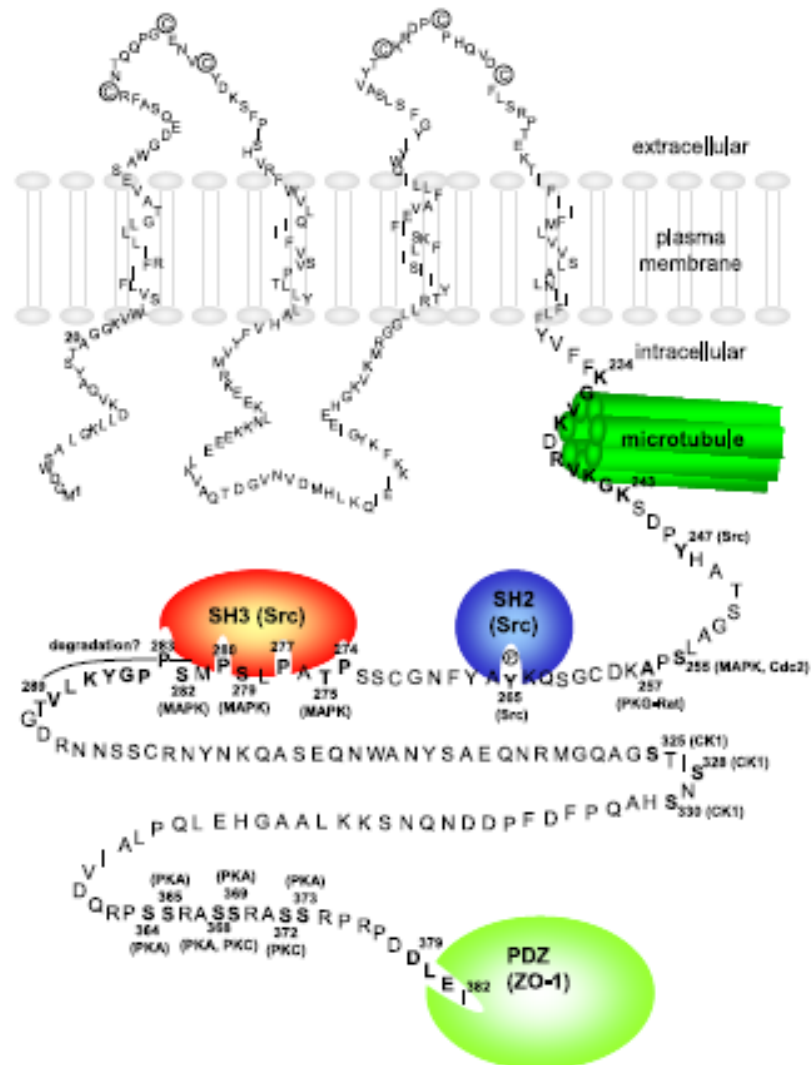
# Intercellular Electrical Conduction

## Intercalated Disc Structure



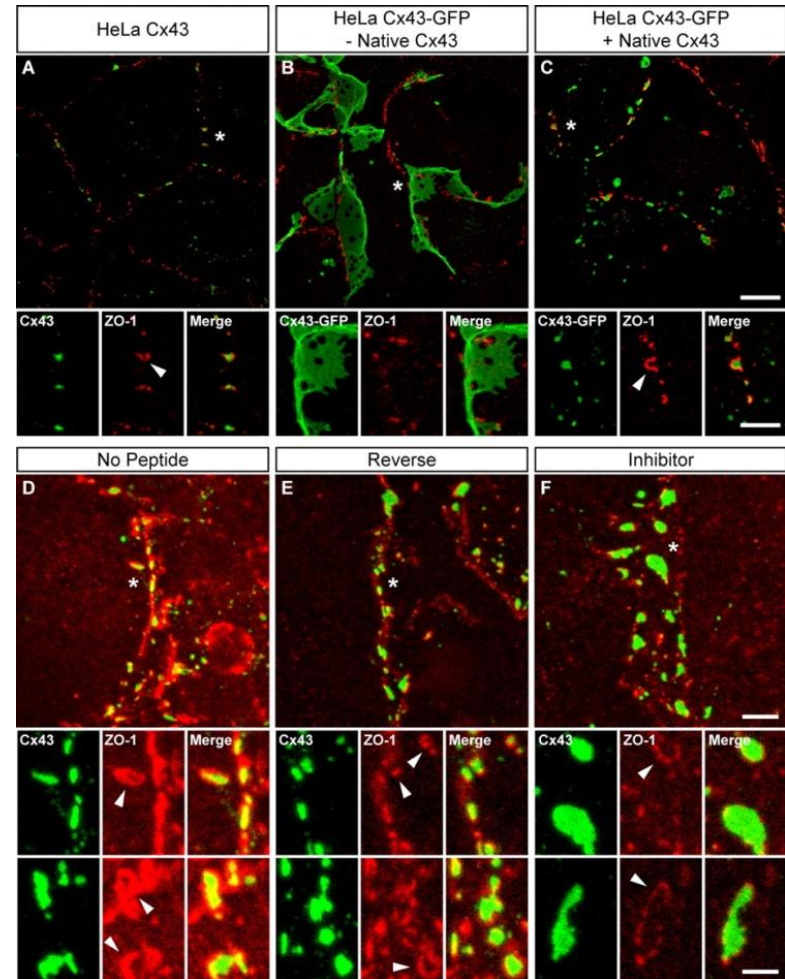
# Intercellular Electrical Conduction

## Connexin 43 structure and Posttranslational modification



# GJ Accessory Proteins

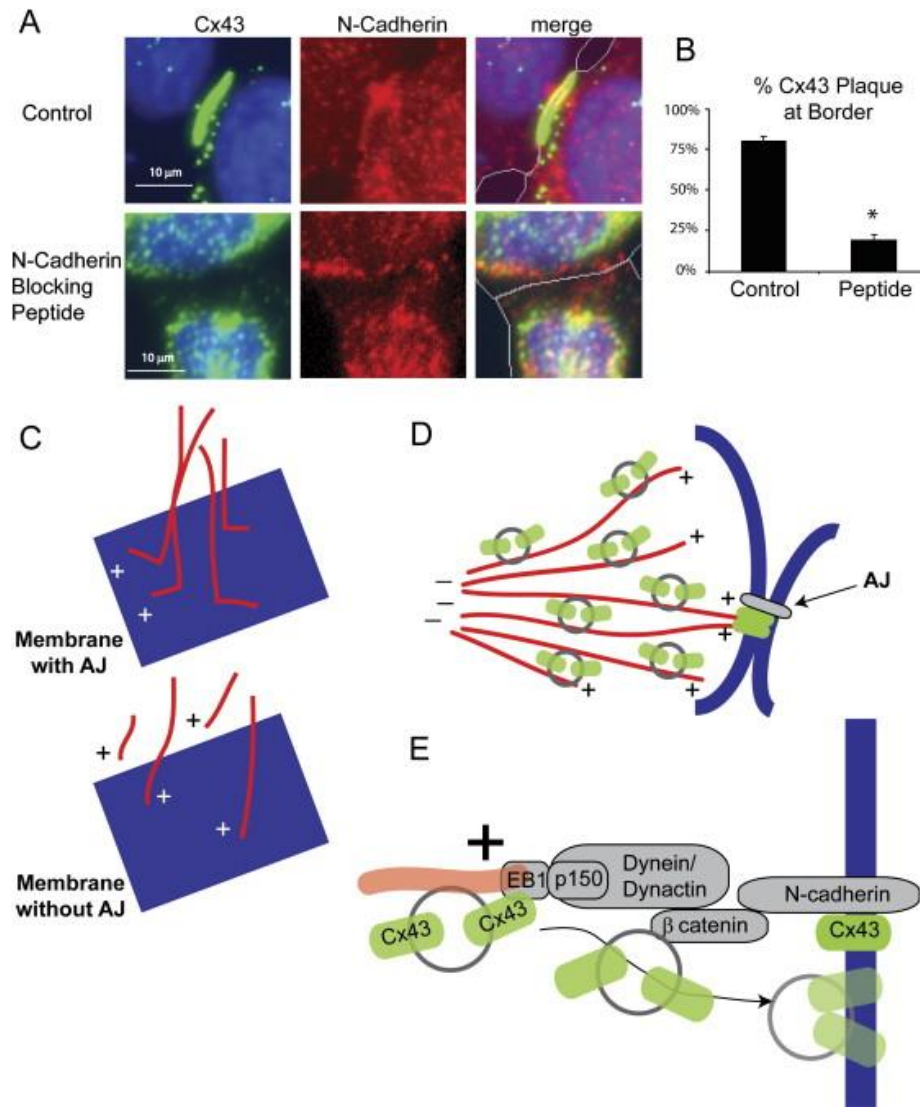
- HeLa cells co-transfected with:
  - Cx43
  - Cx43 – red
  - ZO-1 – green
- ZO-1 moves from GJ edge to centre, binds to Cx43 and internalises
- ZO-1 movement via actin filament
- PDZ2 binding site of Cx43 critical for binding ZO-1
- Inhibitory PDZ peptide (competitive antagonist) =  $\alpha$ CT-1



\* Hunter et al Mol. Biol. Cell 2005  
Vol. 16, Issue 12, 5686-5698



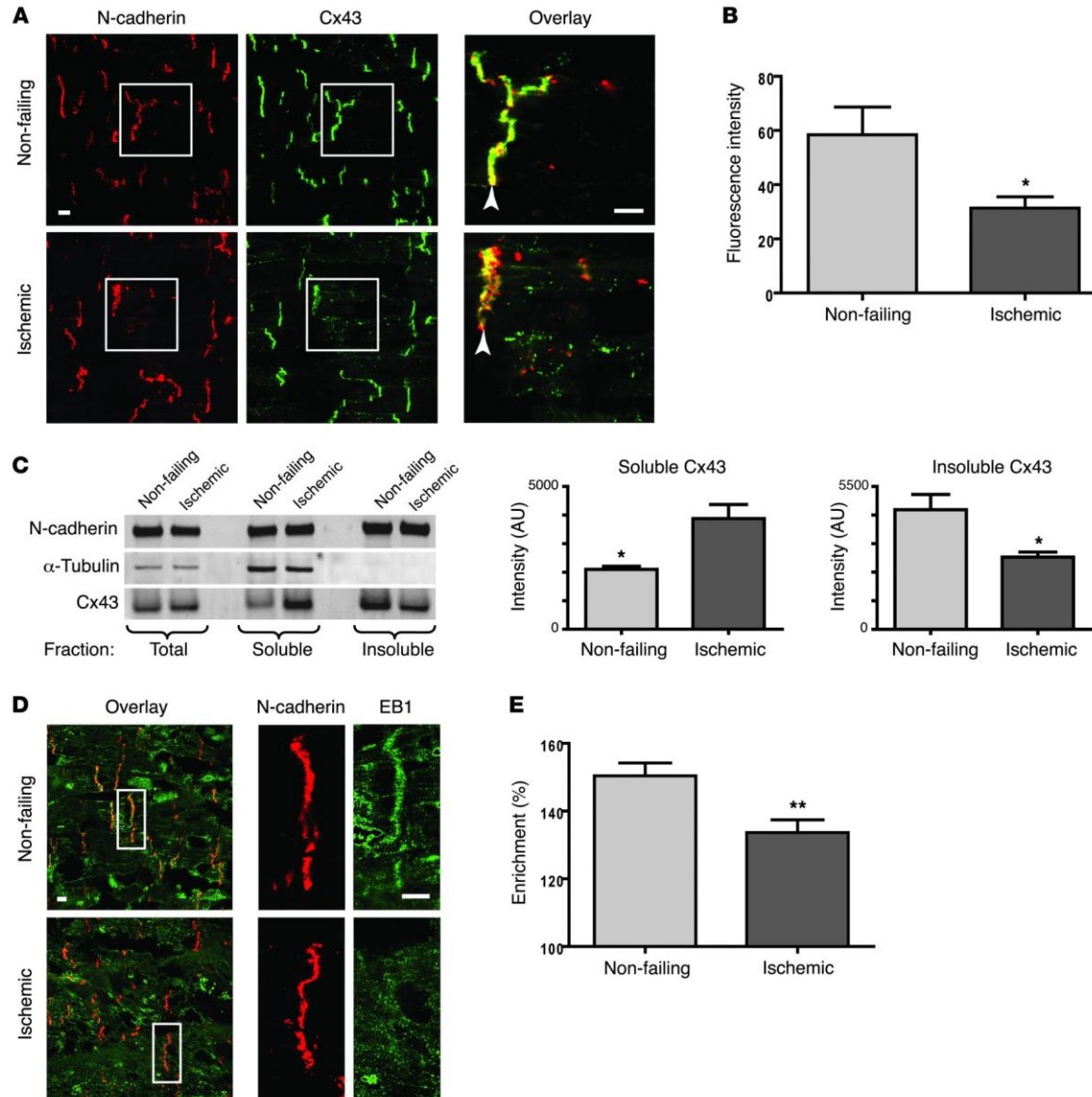
# Connexin 43 Trafficking to Intercalated Disc





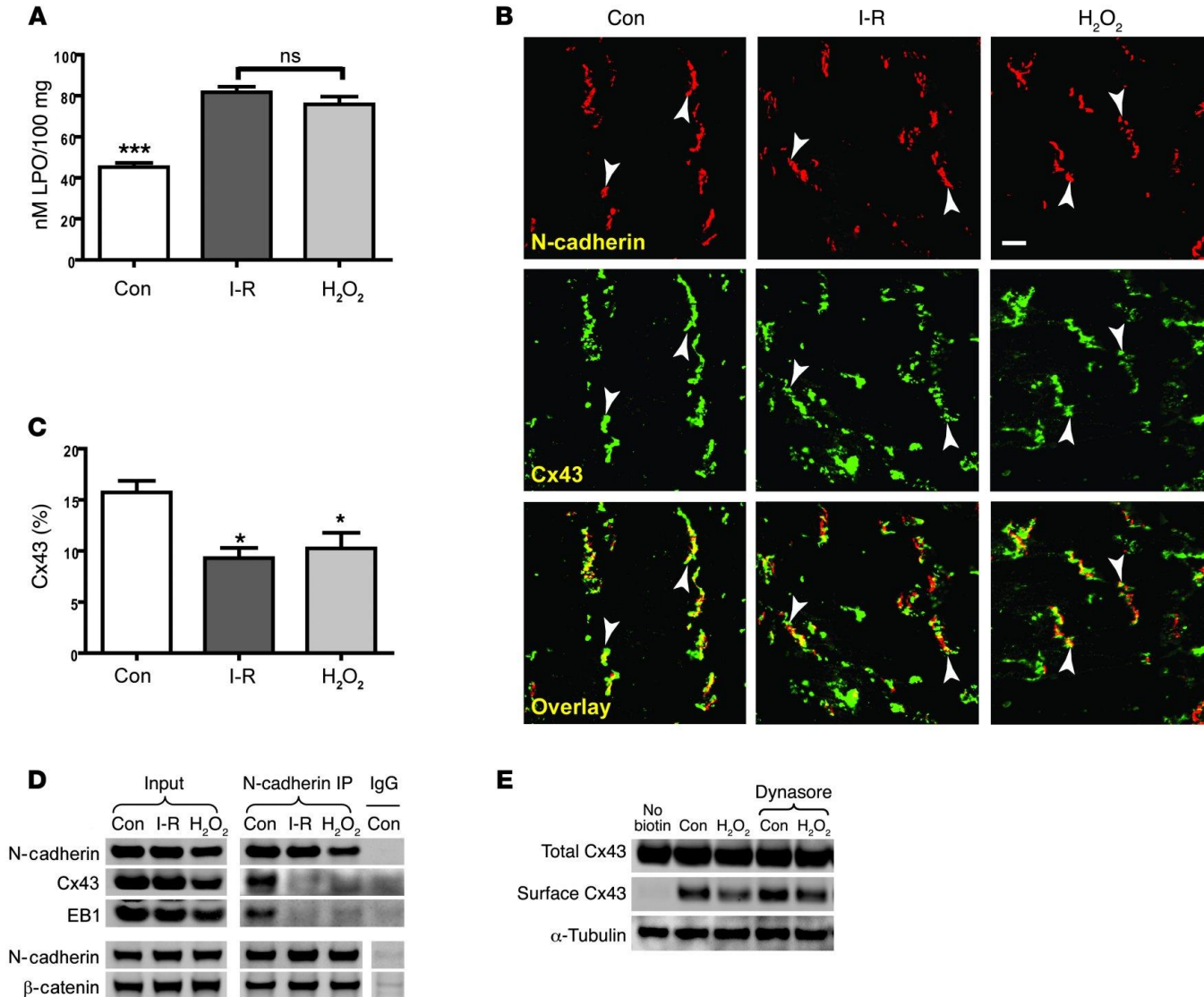
# Reduced Cx43 at Gap Junctions in Human Failing Hearts

Smyth et al *J Clin Invest.* 2010; 120(1):266



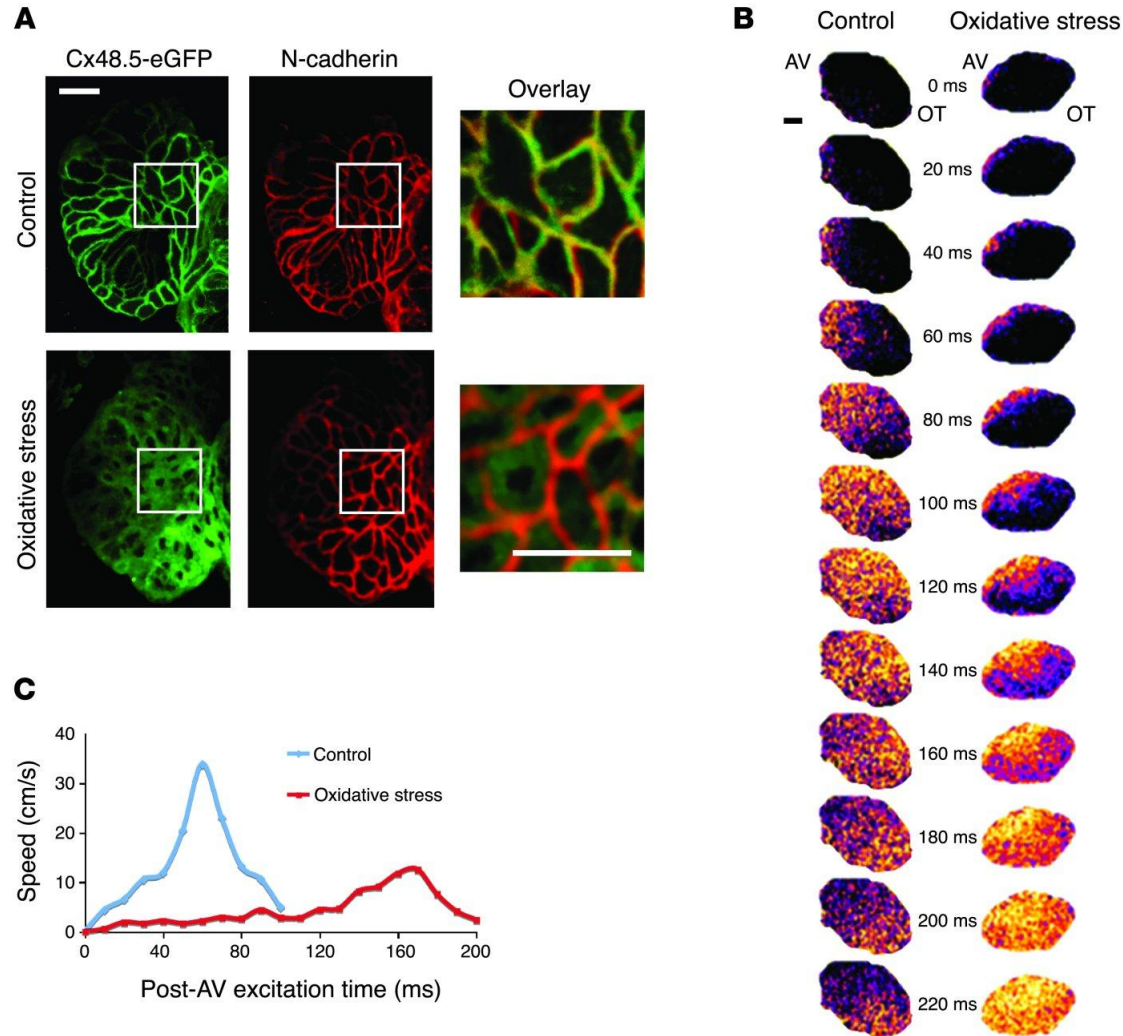
# Oxidative Stress Reduces Cx43 delivery to Intercalated Discs

Smyth et al *J Clin Invest.* 2010; 120(1):266



# Oxidative Stress Reduces Conduction Velocity

Smyth et al *J Clin Invest.* 2010; 120(1):266

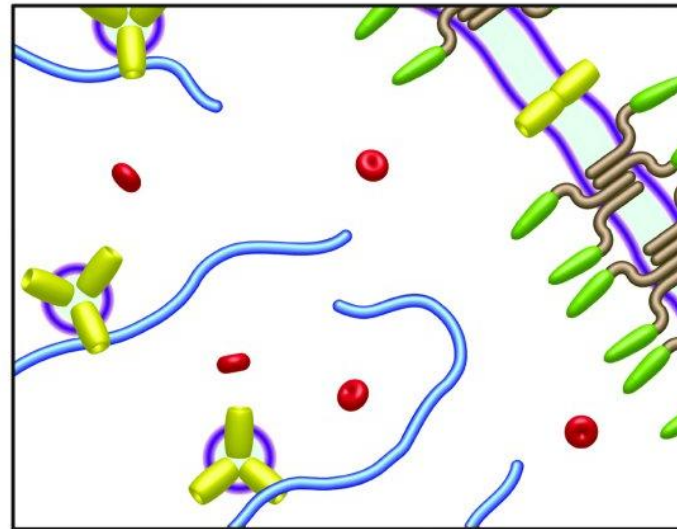
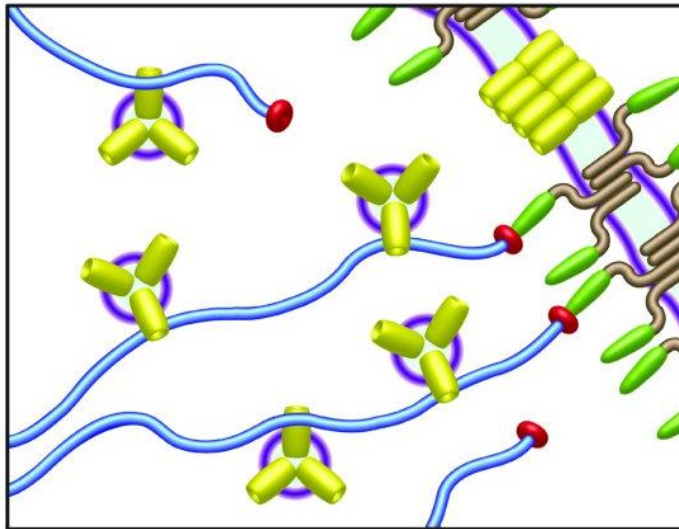


# Schematic Model for Microtubule-mediated Cx43 delivery to Gap Junctions

**D**

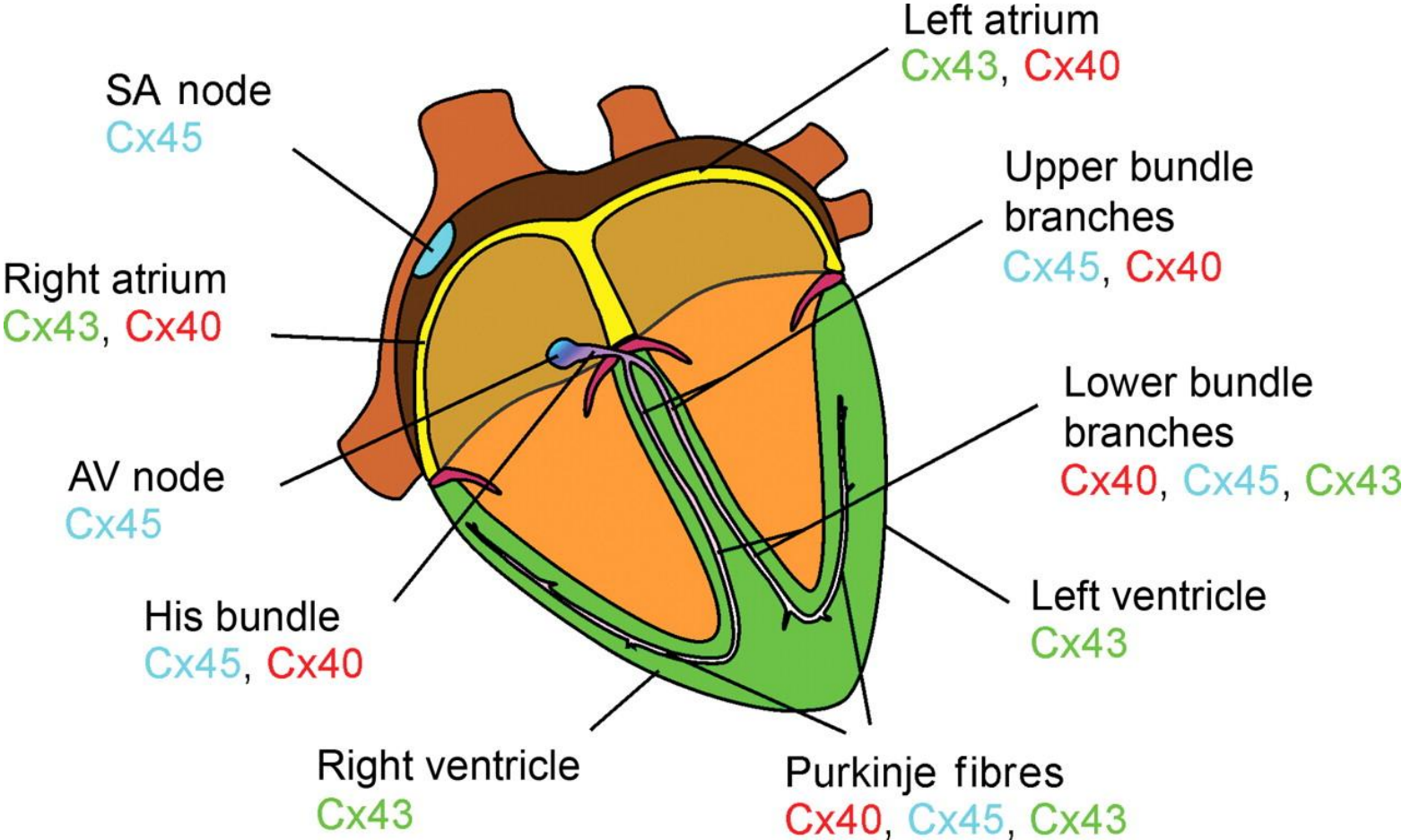
Normal conditions

Oxidative stress



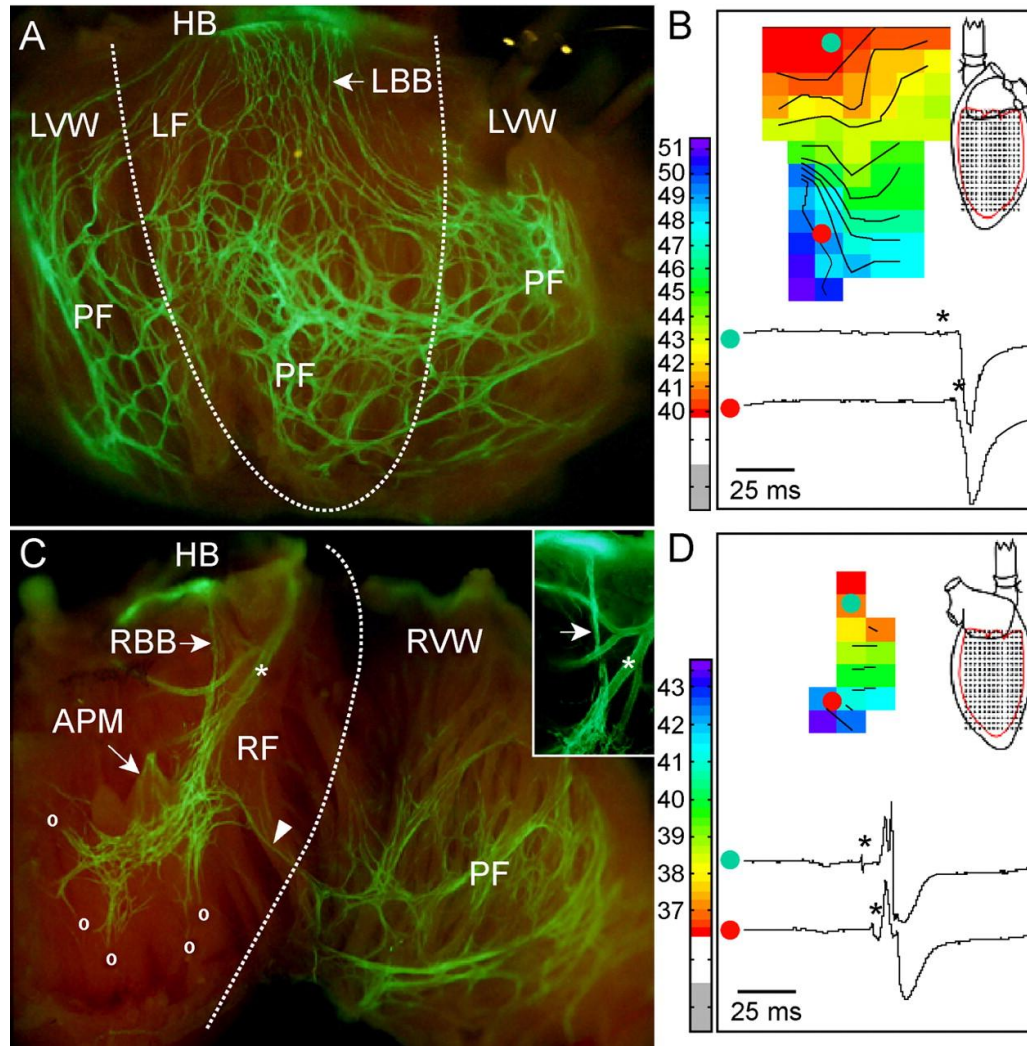
- Cx43 hemichannel
- Microtubule
- N-cadherin
- Vesicle
- $\beta$ -catenin
- EB1
- Plasma membrane

# Cardiac Connexin Isoform Expression/Distribution

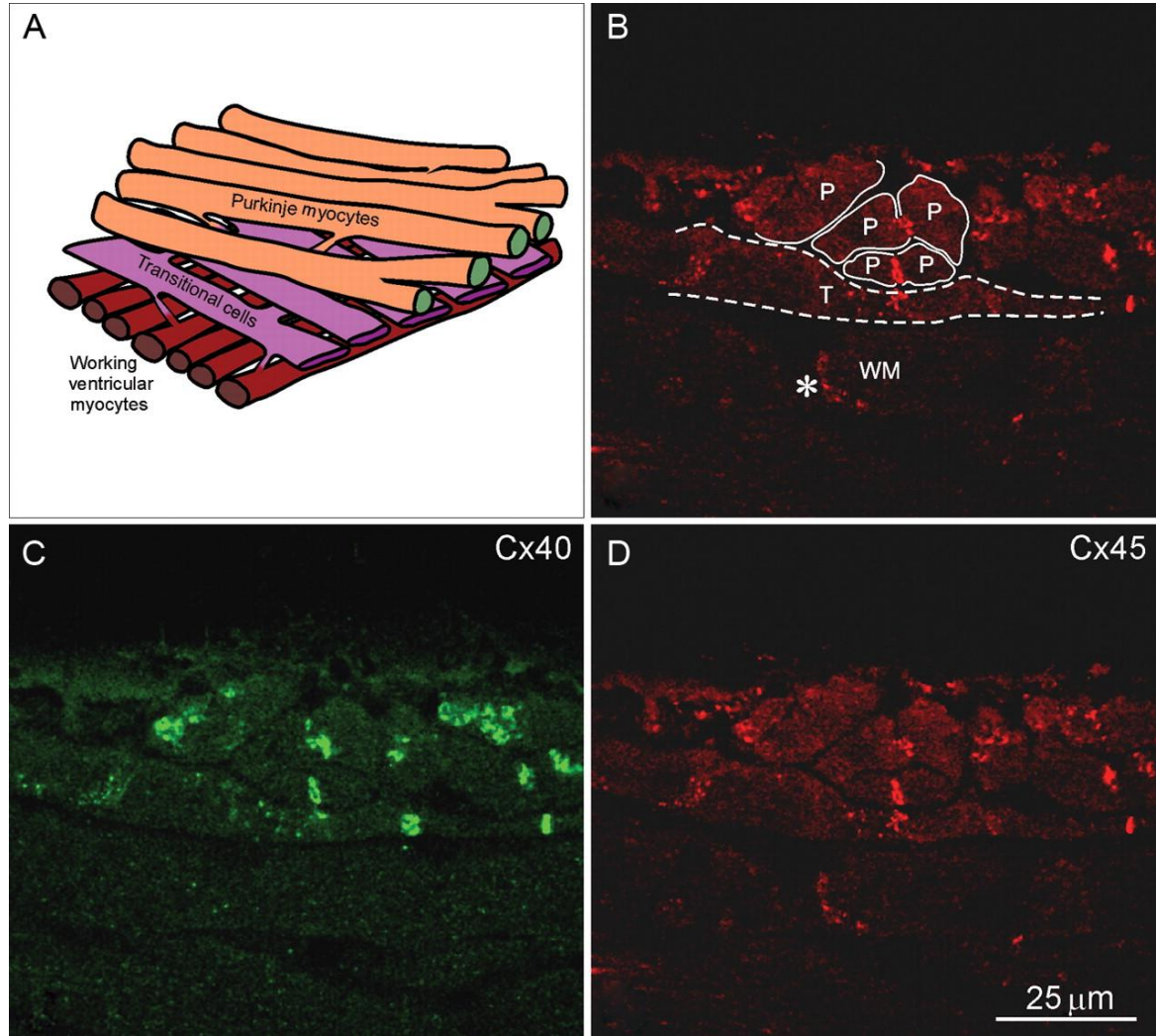




# Transgenic Cx40-GFP Mouse Cardiac Purkinje Fibre Network



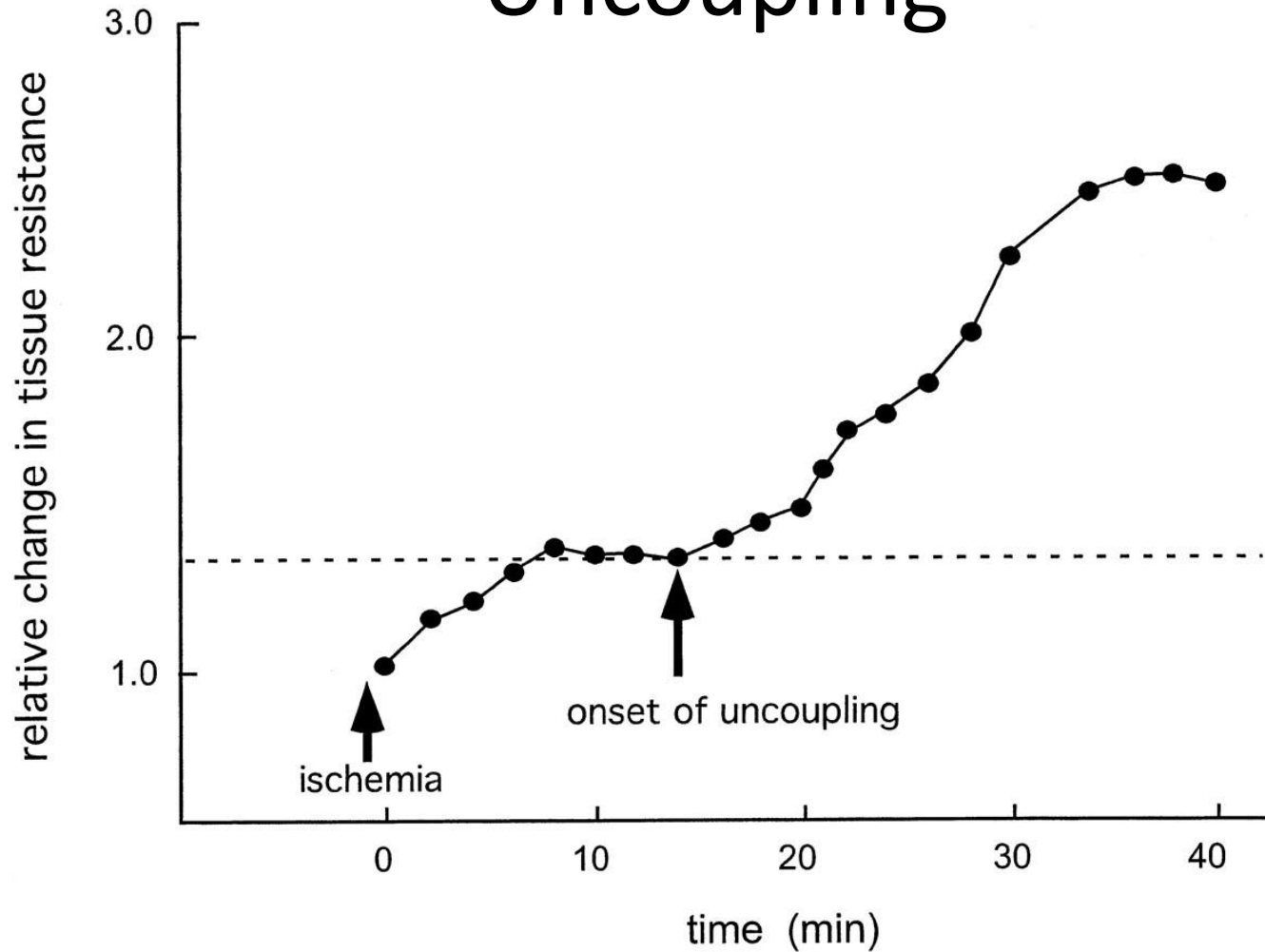
# Purkinje Fibre-Cardiomyocyte Interface



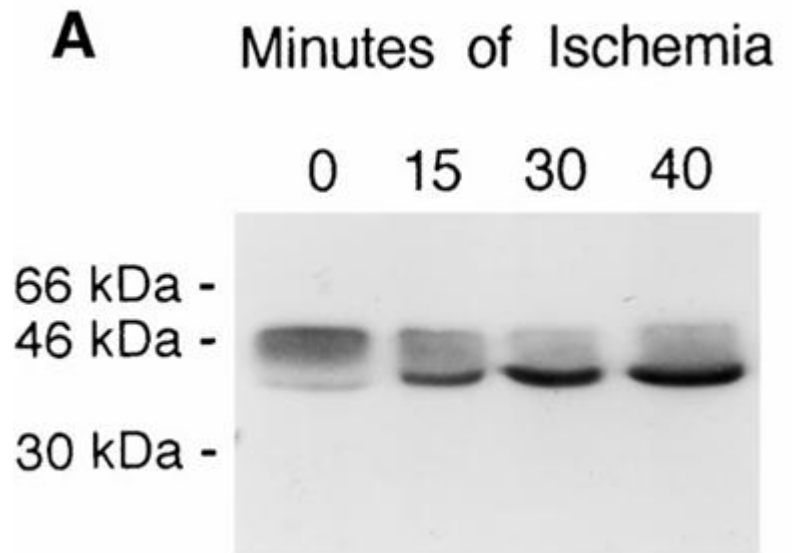
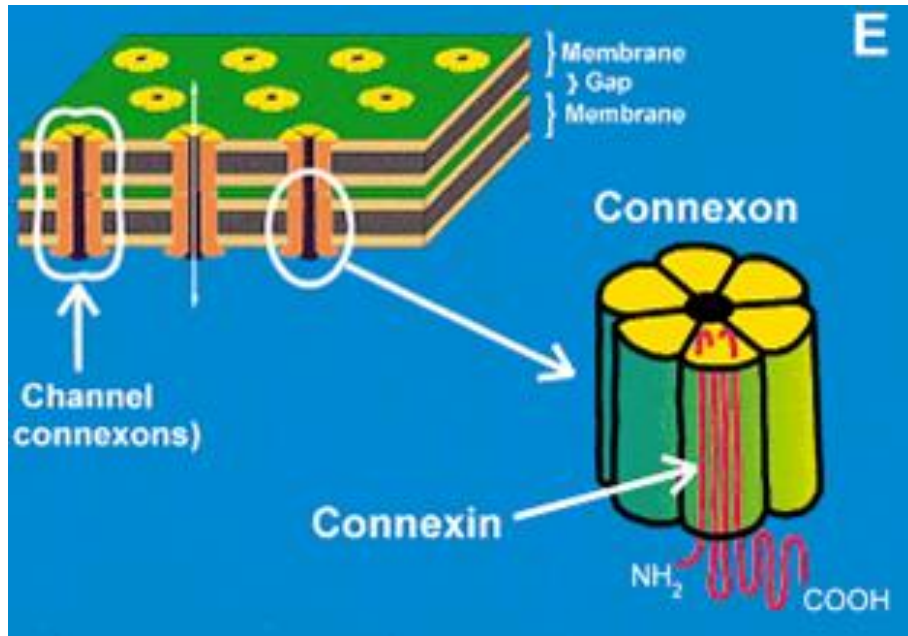
# Gap Junction Function in Disease

## 1. Myocardial Ischaemia

# Background – Acute Ischaemia Associated with Gap Junctional Uncoupling



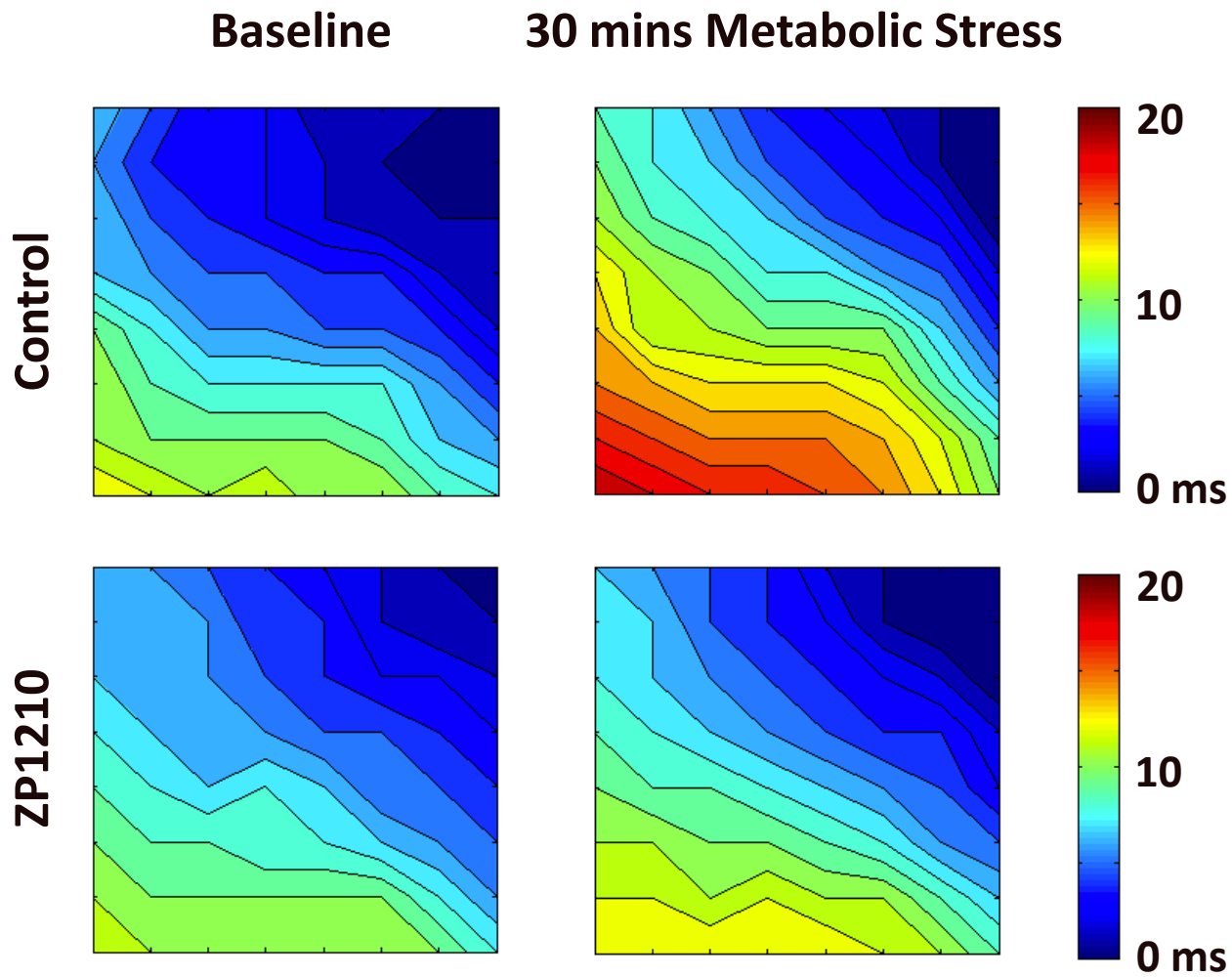
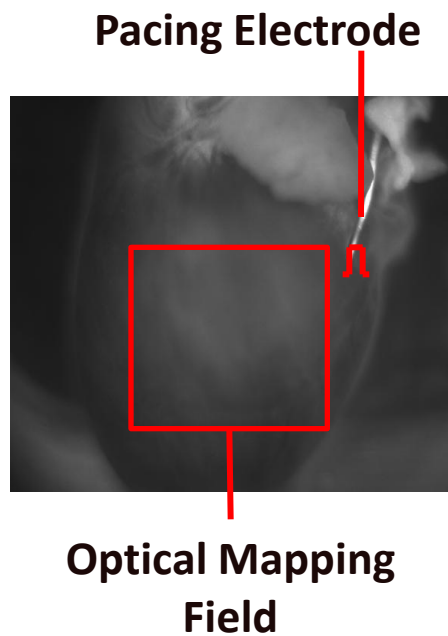
# Background – Connexin43 Dephosphorylation in Ischaemia



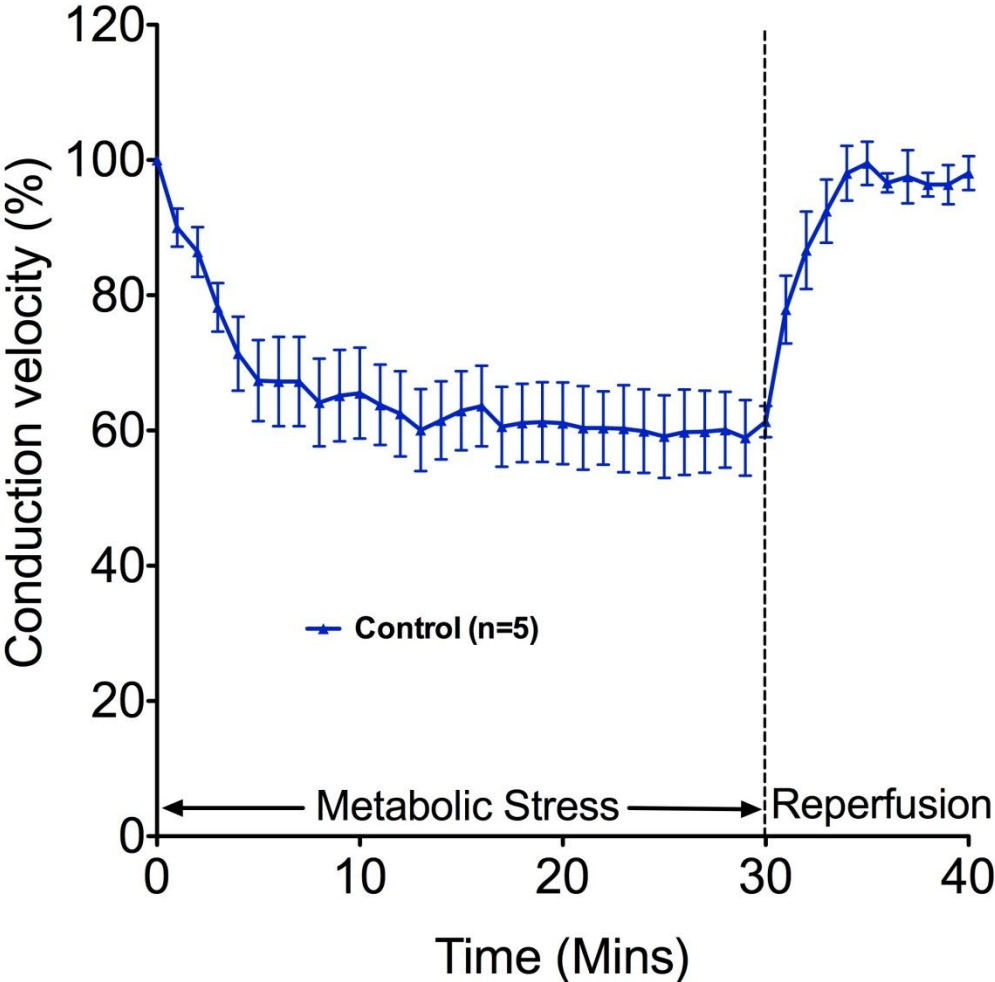
Severs NJ. Bioessays. 2000 Feb;22(2):188-99.

Beardslee MA et al. Circ Res. 2000 Oct 13;87(8):656-62

# Epicardial Activation Maps

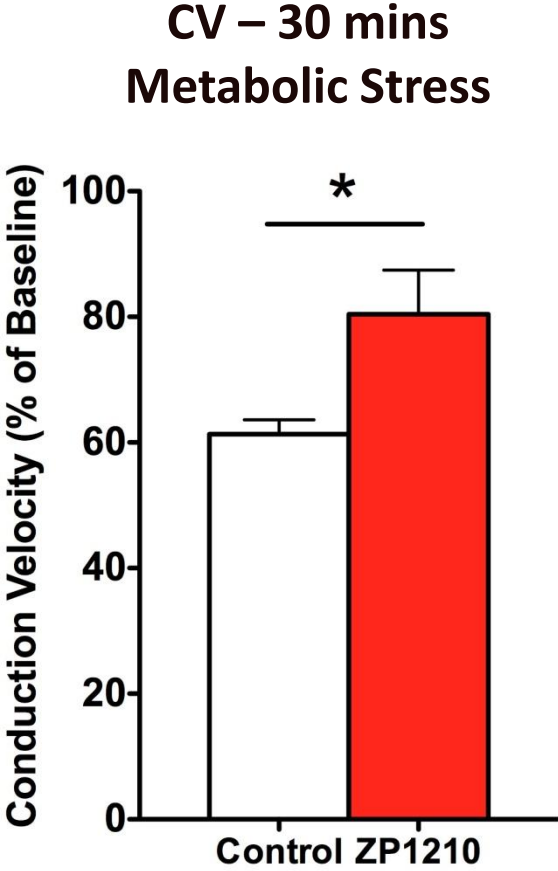
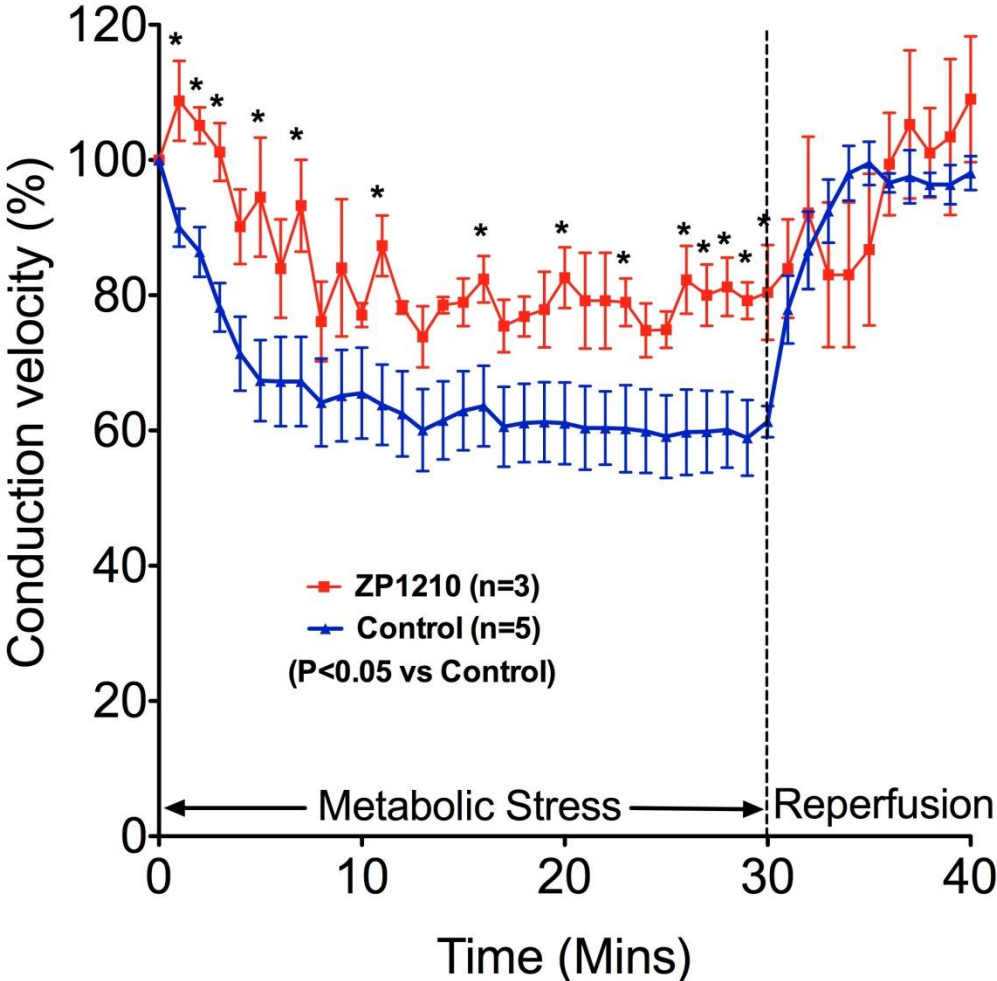


# Conduction slowing with Metabolic Stress



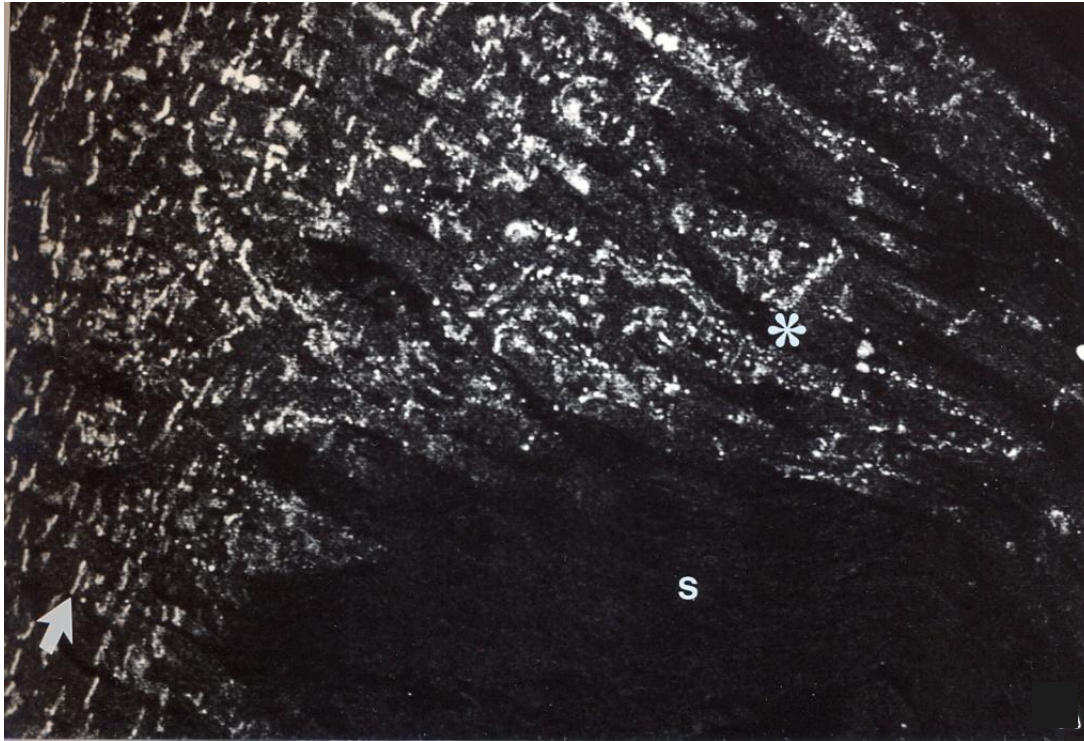


# Conduction slowing with Metabolic Stress

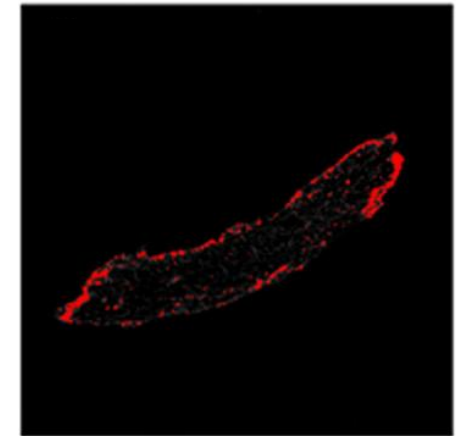
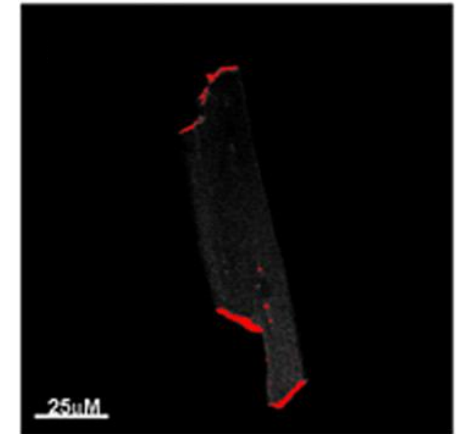




# Substrate – Gap junction lateralisation



Peters *et al.* J Cardiovasc Electrophysiol. 2000



Cabo *et al.* Cardiovasc. Res. 2006

# Gap Junction Function in Disease

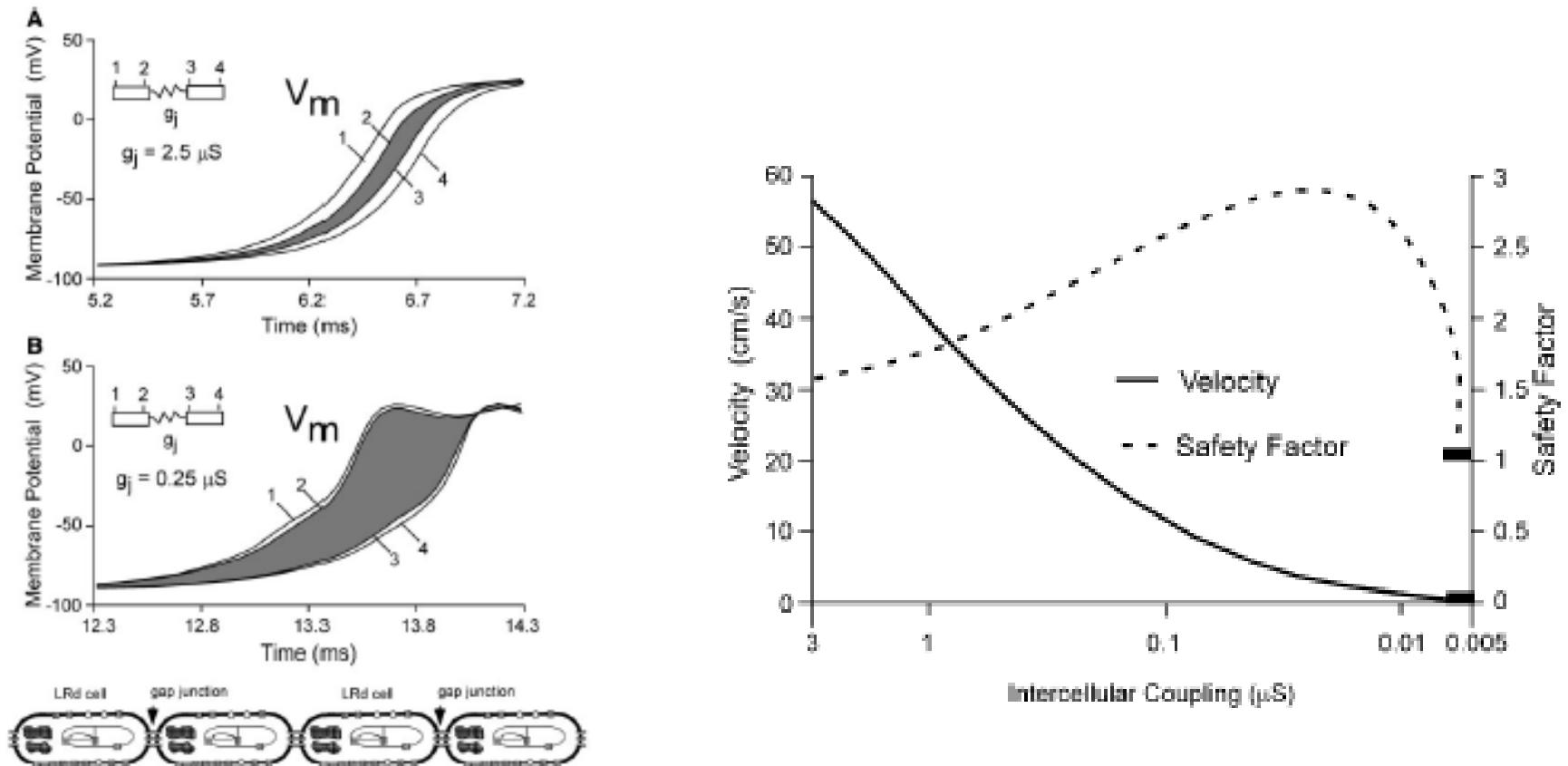
## 2. Myocardial Infarction

# Mechanism of Slow Conduction

- Slow conduction and conduction failure due to reduced membrane excitability
- Slow conduction related to reduced cell-to-cell coupling
- Slow conduction related to tissue structure.

# Anatomical Reentry 1

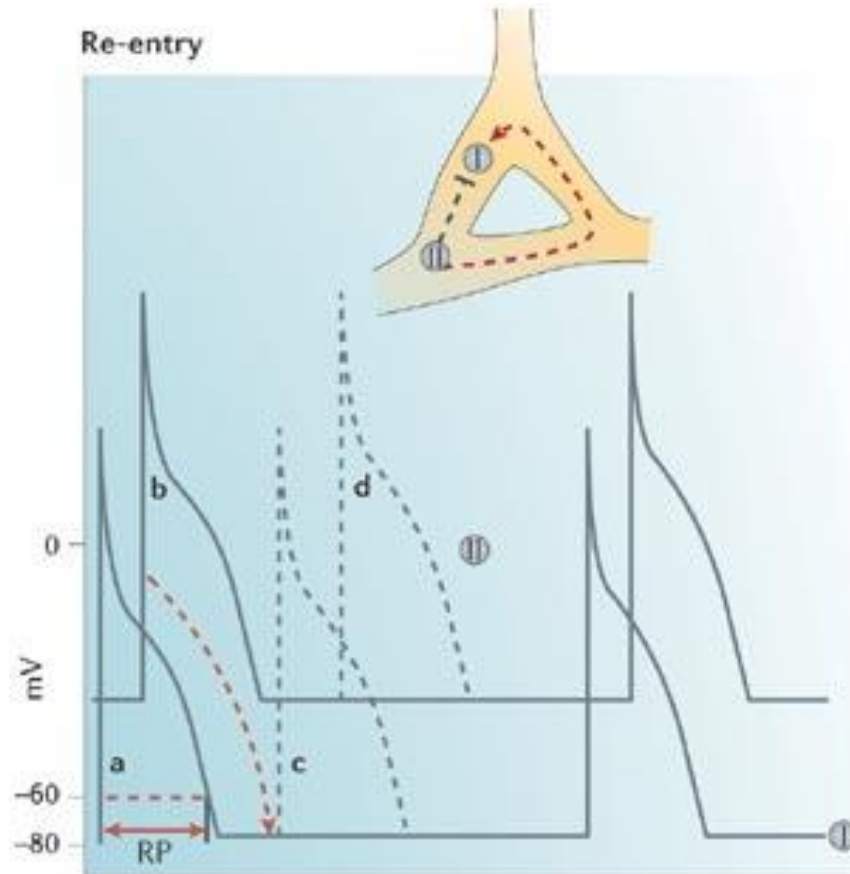
## Conduction Slowing



# Reentry

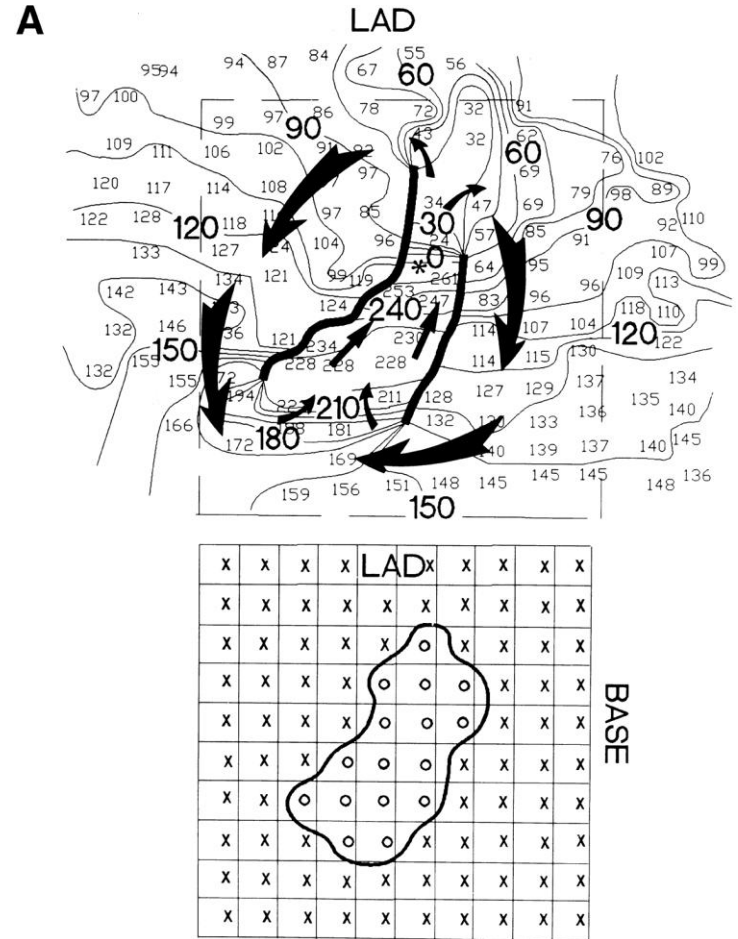
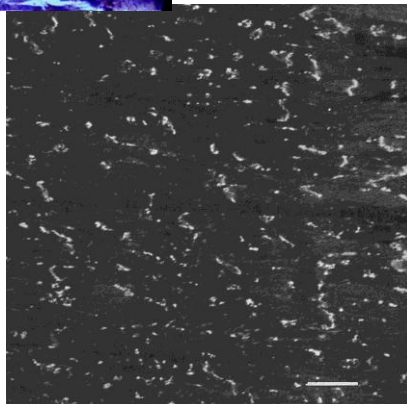
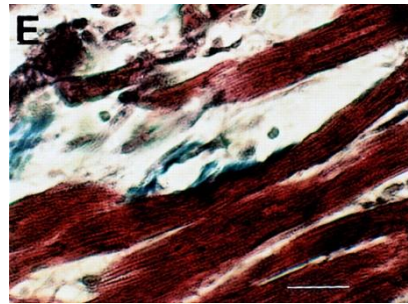
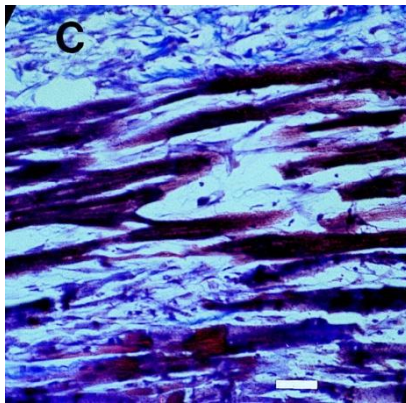
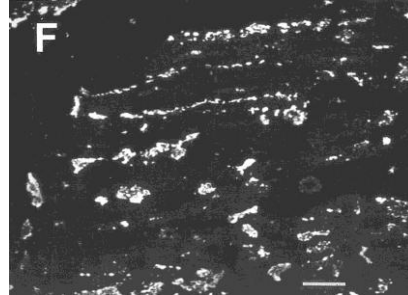
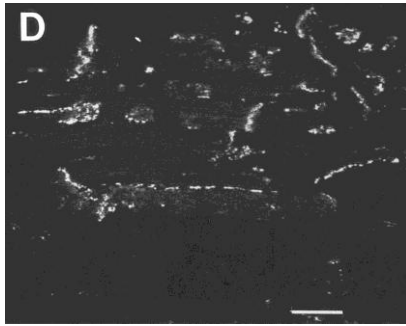
- Excitable gap
- Anatomical
  - Infarction scar / fibrosis
  - Purkinje fibres / bundle branches
  - Inexcitability
    - Metabolic sink / block
- Functional
  - Conduction Slowing
  - Repolarisation heterogeneity
    - APD prolongation e.g. long QT
    - $\text{Ca}^{2+}$  Alternans = T wave alternans

# Anatomical Reentry 1



# Anatomical Reentry 2

## Myocardial Infarction Scar

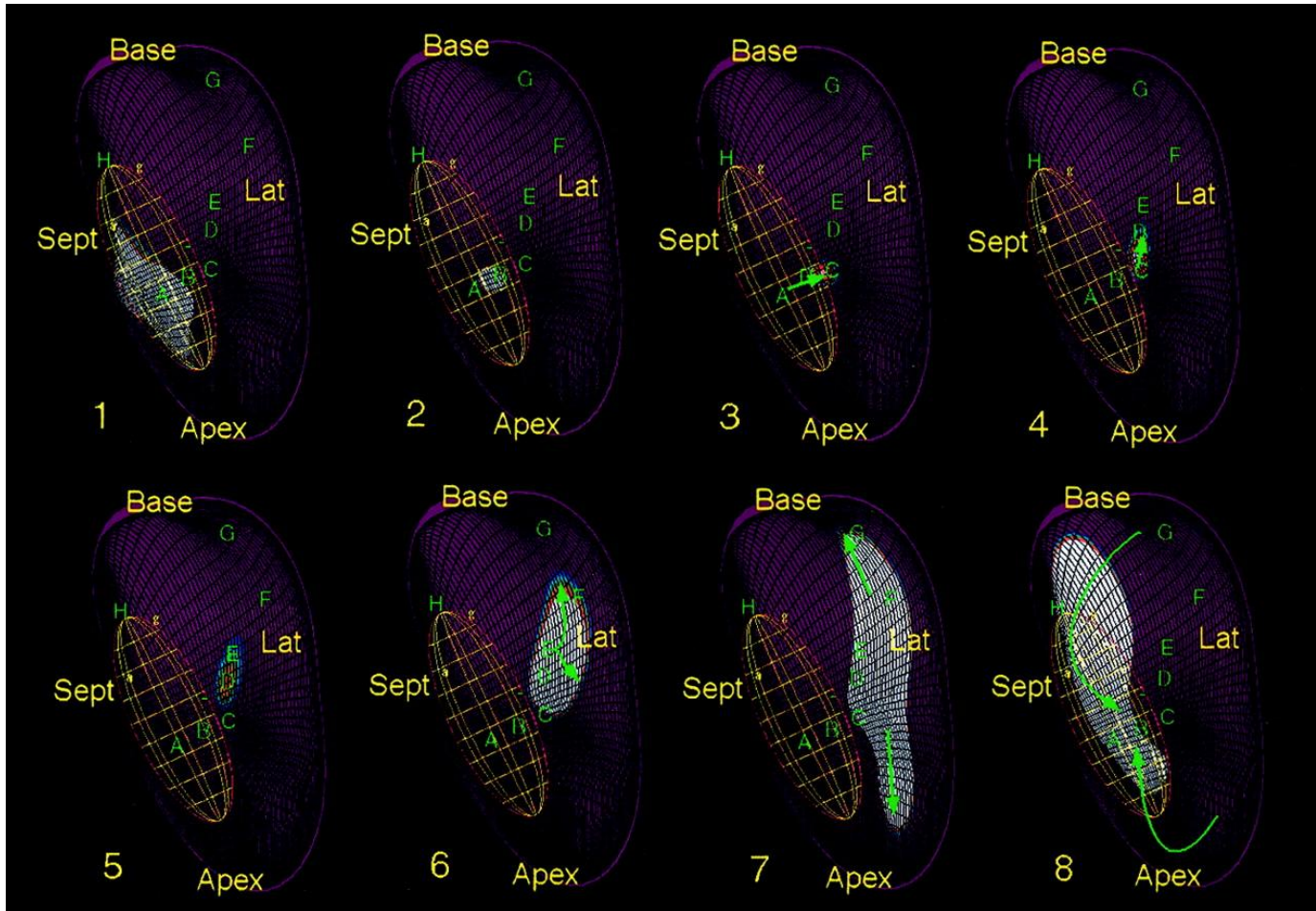




# Anatomical Reentry 2

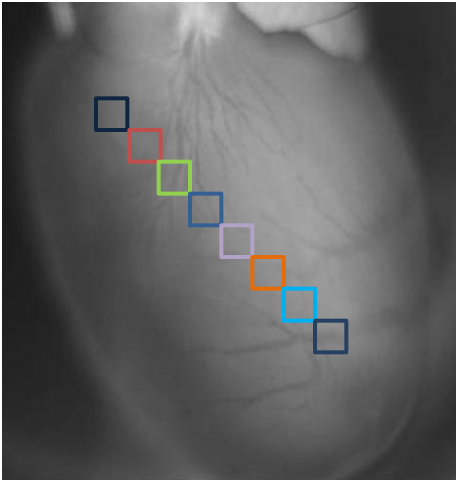
## Myocardial Infarction Scar

Sequence of isopotential maps during VT with a turn within the diastolic pathway

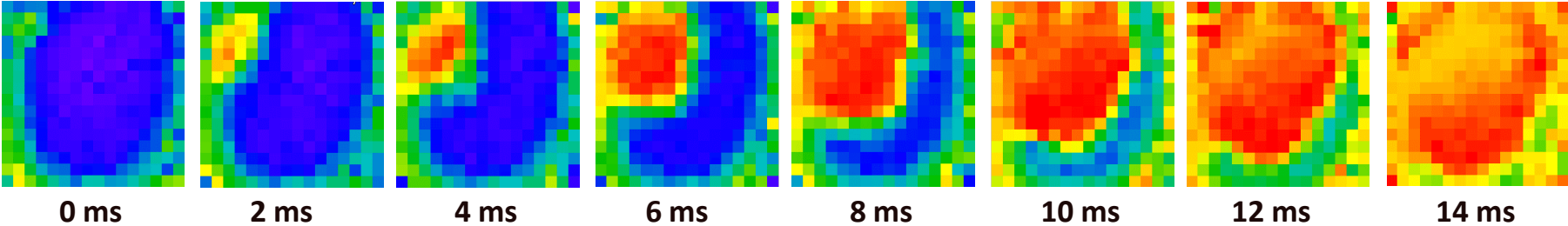
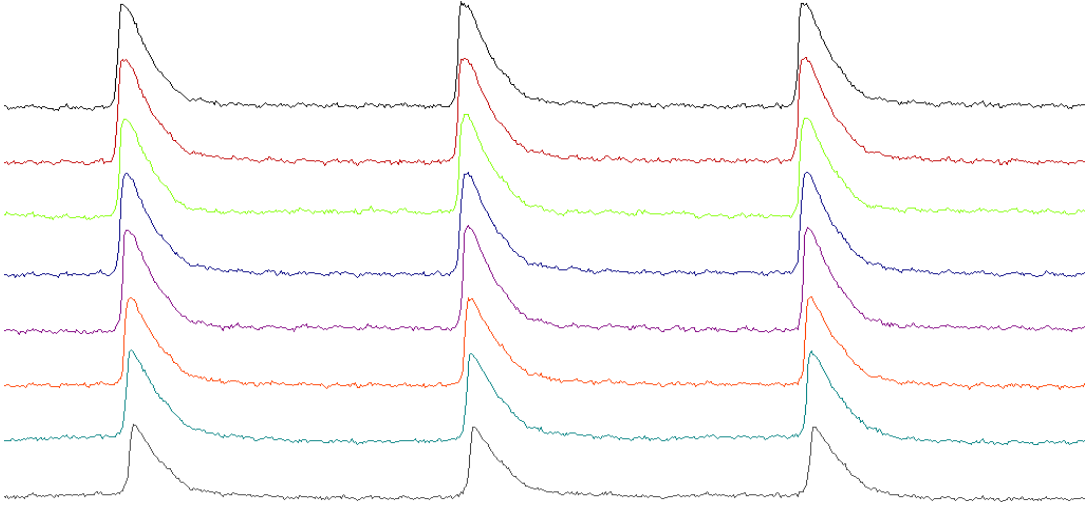




# Methods - Optical mapping

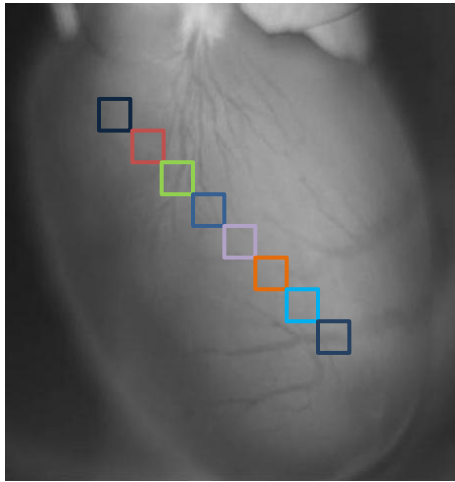


Optical  
Action  
Potentials  
for  
selected  
pixels



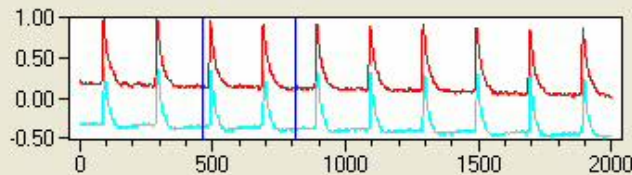
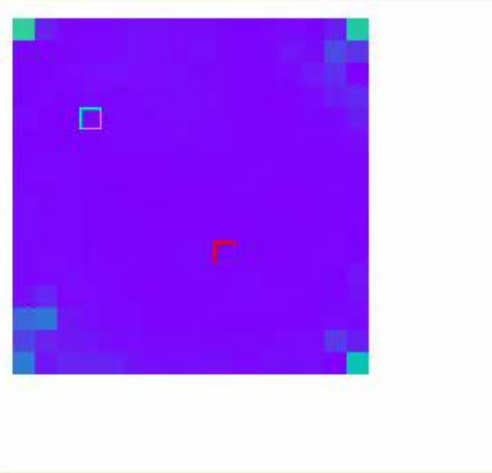
# Optical mapping

## Voltage-Sensitive Fluorescent Dyes



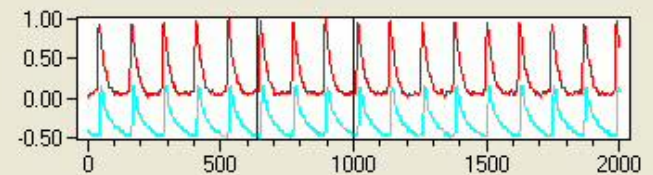
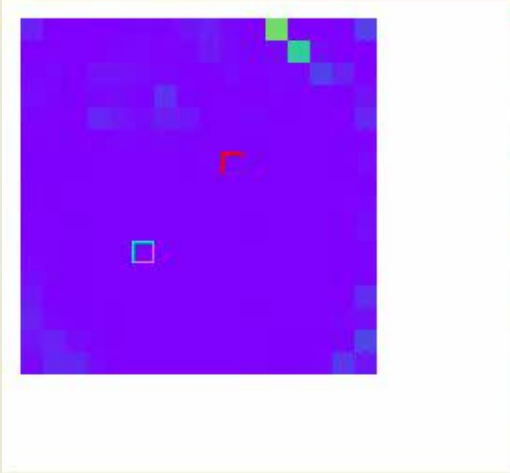
Sinus Rhythm

Dual mapping at 8.5Hz pacing



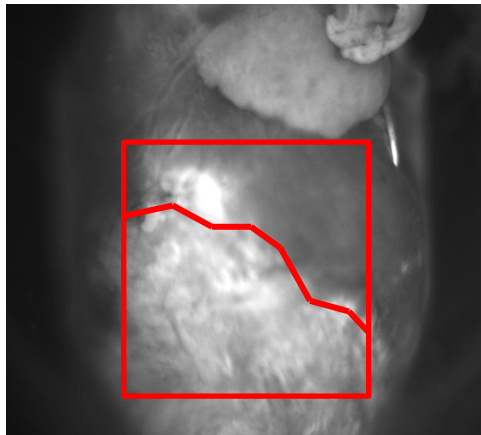
Epicardial Pacing

Dual mapping at 8.5Hz pacing

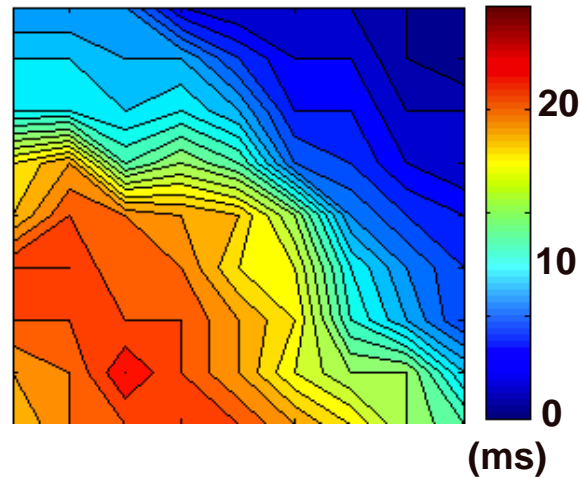


# Optical Mapping of Chronically Infarcted Hearts

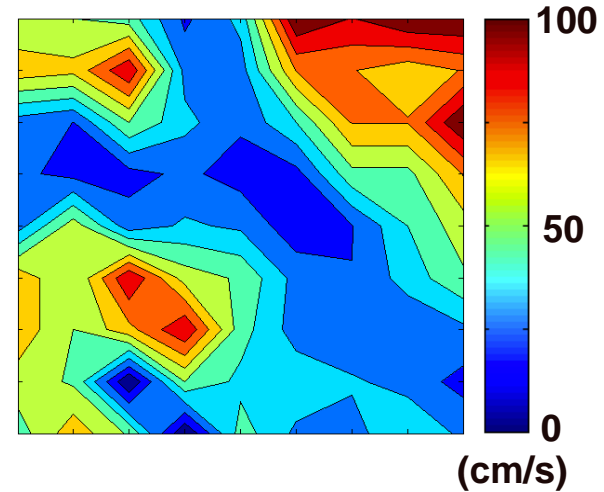
Heart in mapping chamber



Local Activation Map  
(Isochronal Map)



Local Conduction Velocities  
(Iso-Velocity Map)



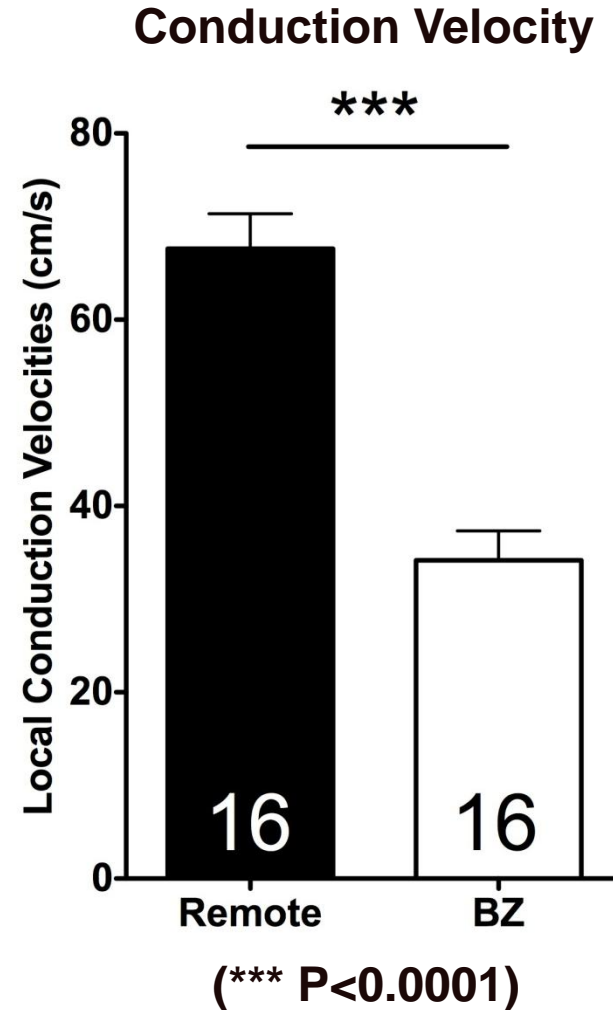
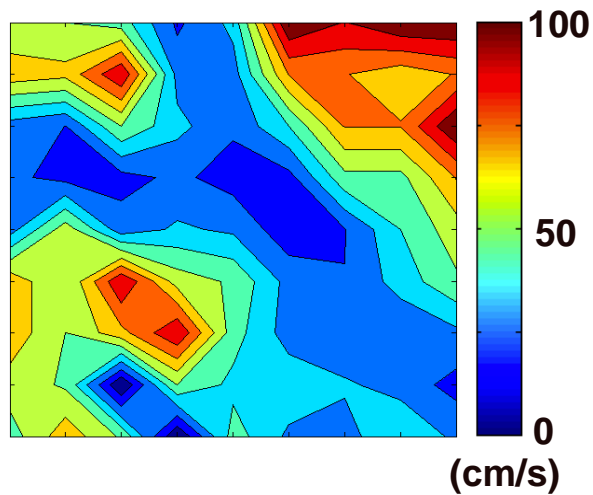
Non-infarcted: >50cm/s

BZ: 15-25 cm/s

Infarct: Variable

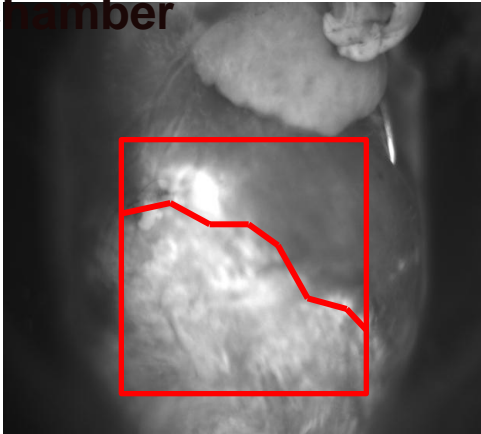
# Slower Conduction Velocities at Infarct Border Zone

Local Conduction Velocities  
(Iso-Velocity Map)

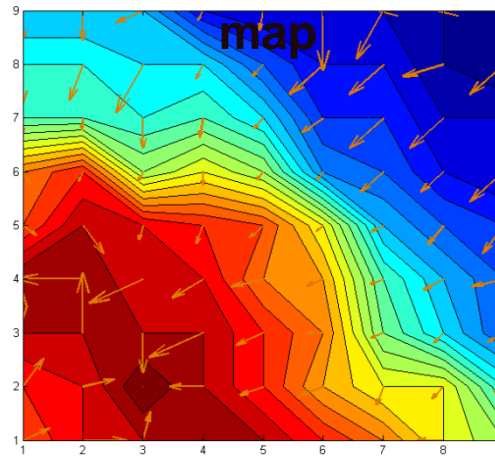


# Local Activation Vectors and Conduction Velocities

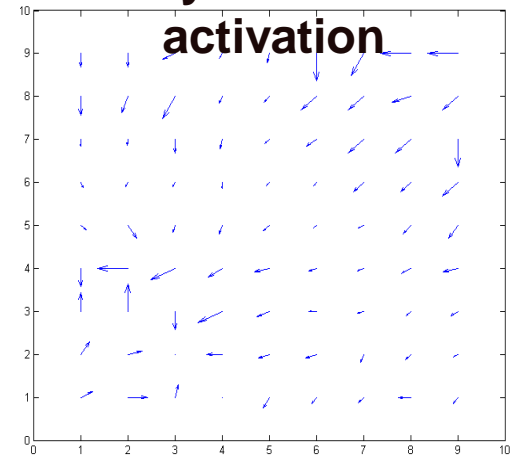
Heart in mapping chamber



CV Vectors superimposed on isochronal activation



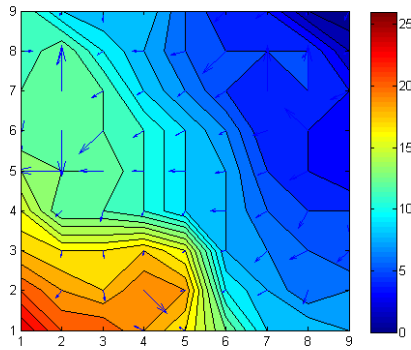
Local Conduction Velocity and vector of activation



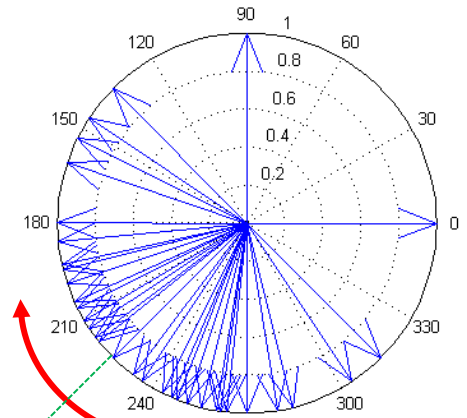
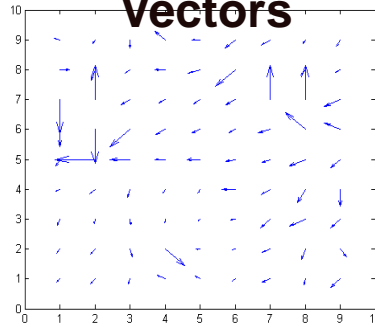
- Length of arrow proportional to CV
- Direction of arrow denotes direction of activation

# Assessing Dispersion of Local Conduction Velocities

## Activation Maps (Isochronal Map)

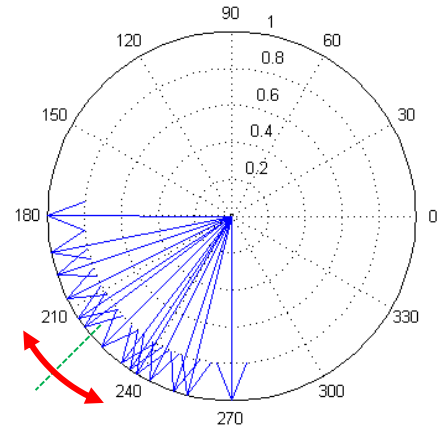
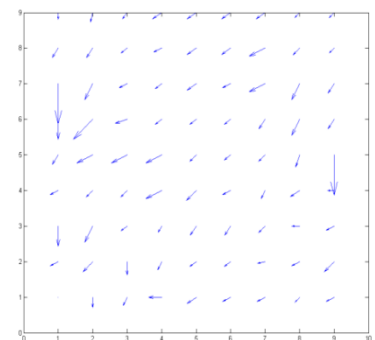
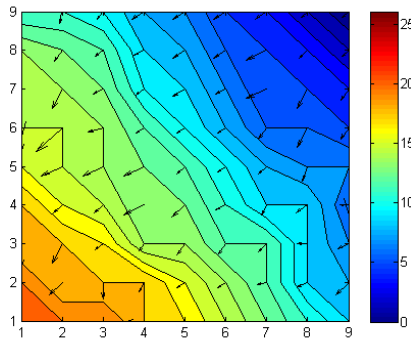


## Local Conduction Vectors

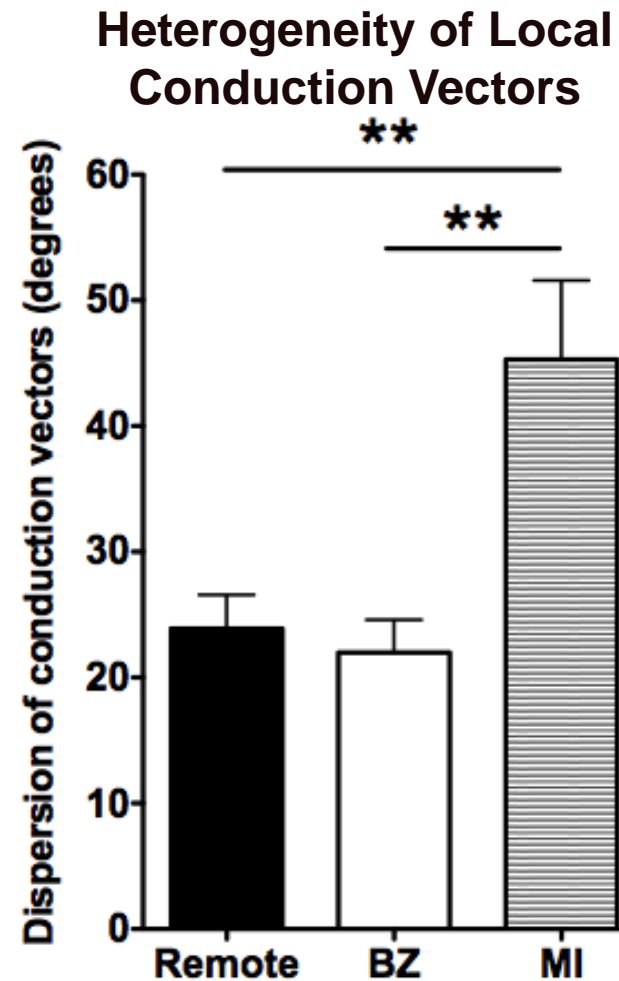
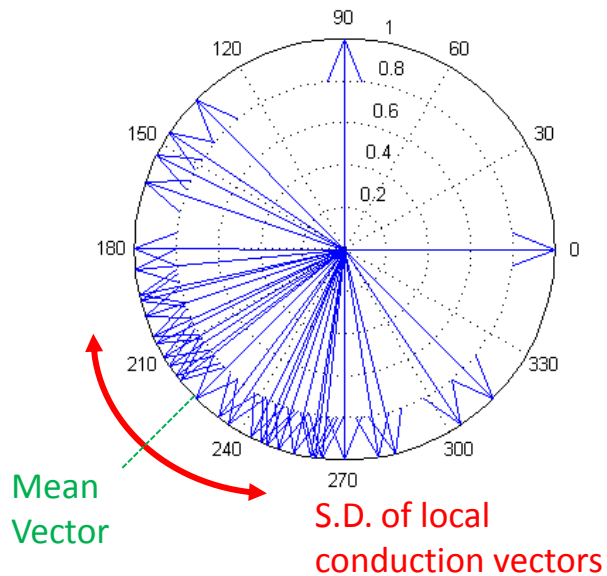


Mean  
Vector

S.D. of local  
conduction vectors



# Heterogeneous Conduction Vectors in Infarct Zone



(ANOVA  $P < 0.001$ , Post-hoc t-test \*\*  
 $P < 0.01$ )

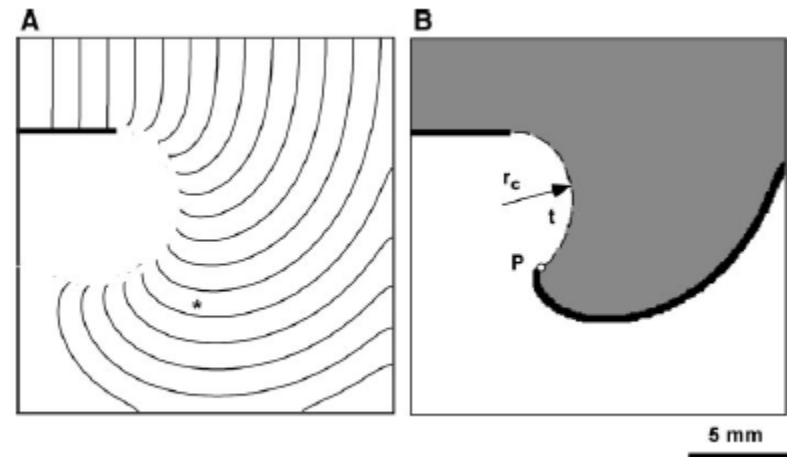


# Action Potential Propagation in Cardiac cellular networks-Structure Function Relationships

- Macroscopic anisotropic propagation
- The structural basis of propagation at the cellular level
- Cellular parameters affecting normal propagation
- Propagation and the shape of the cardiac action potential
- Conduction and cell-to-cell interaction between myocytes and non-myocytes.
- Determination of local activation from the extracellular electrogram

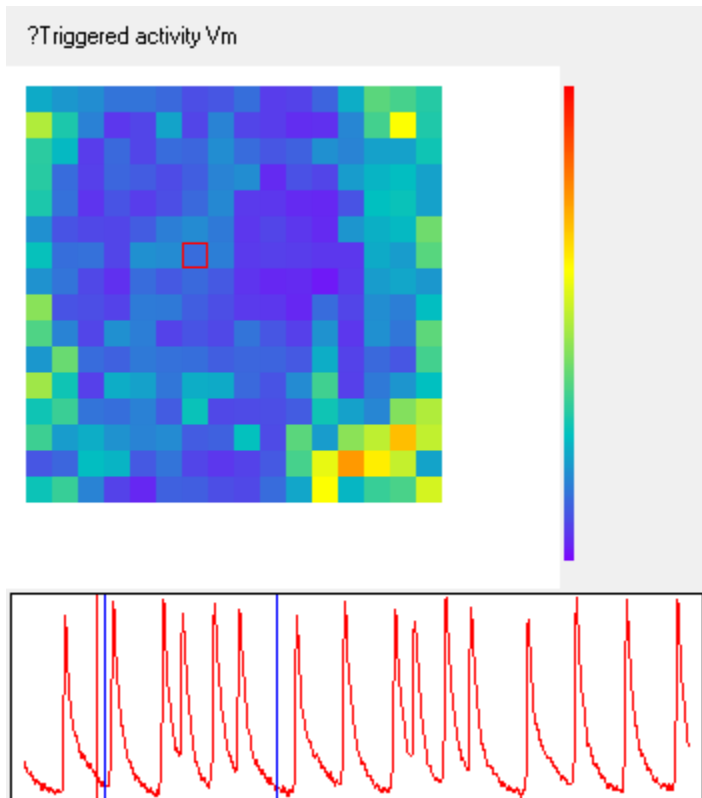
# Wavebreak Initiation in VF

- Wavebreak occurs at points of functional conduction slowing/block
- Occurs at highest curvature, where greatest source-sink mismatch
- Resulting wave forms a rotor
  - 2D = spiral wave
  - 3D = scroll wave
- Short cycle length with resulting fast tachycardia



# Optical Mapping Arrhythmias

## Triggered Activity



## Ventricular Fibrillation

