Principles of Electrical Wave Propagation in the Heart

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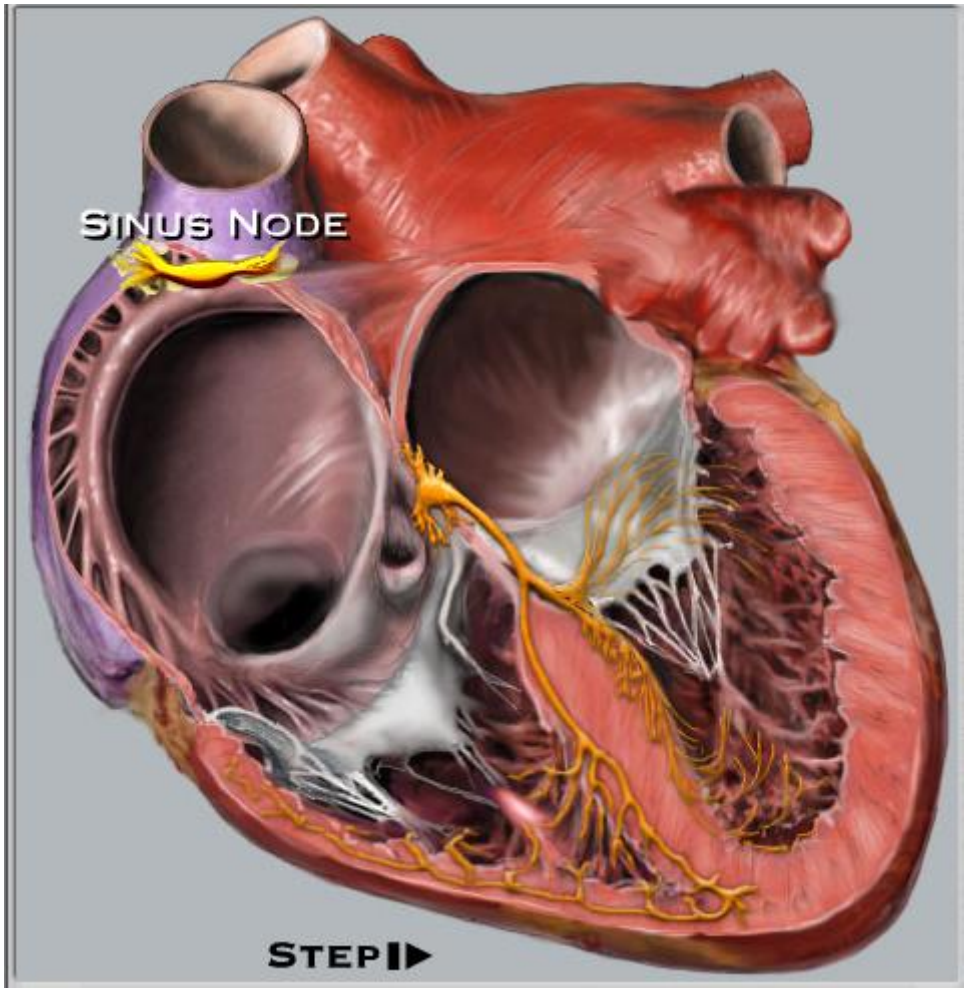
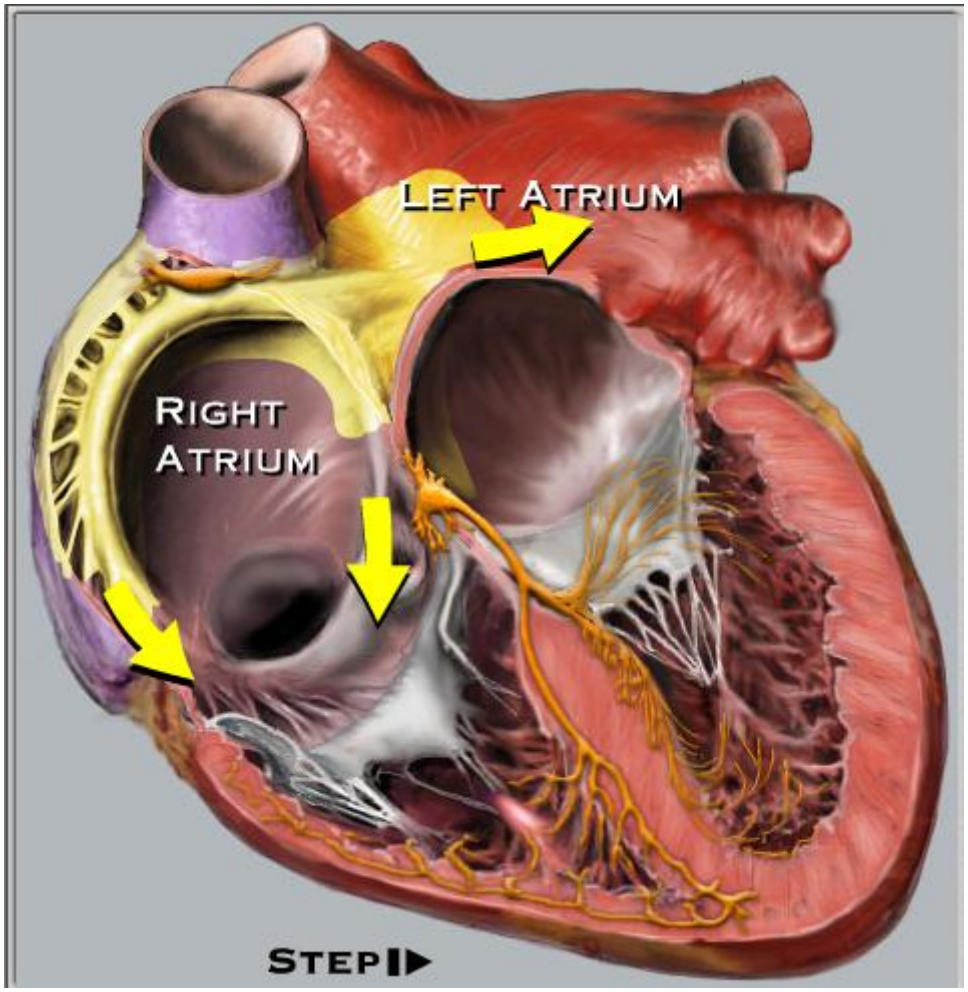
Cardiac Conduction System

Sinoatrial Node



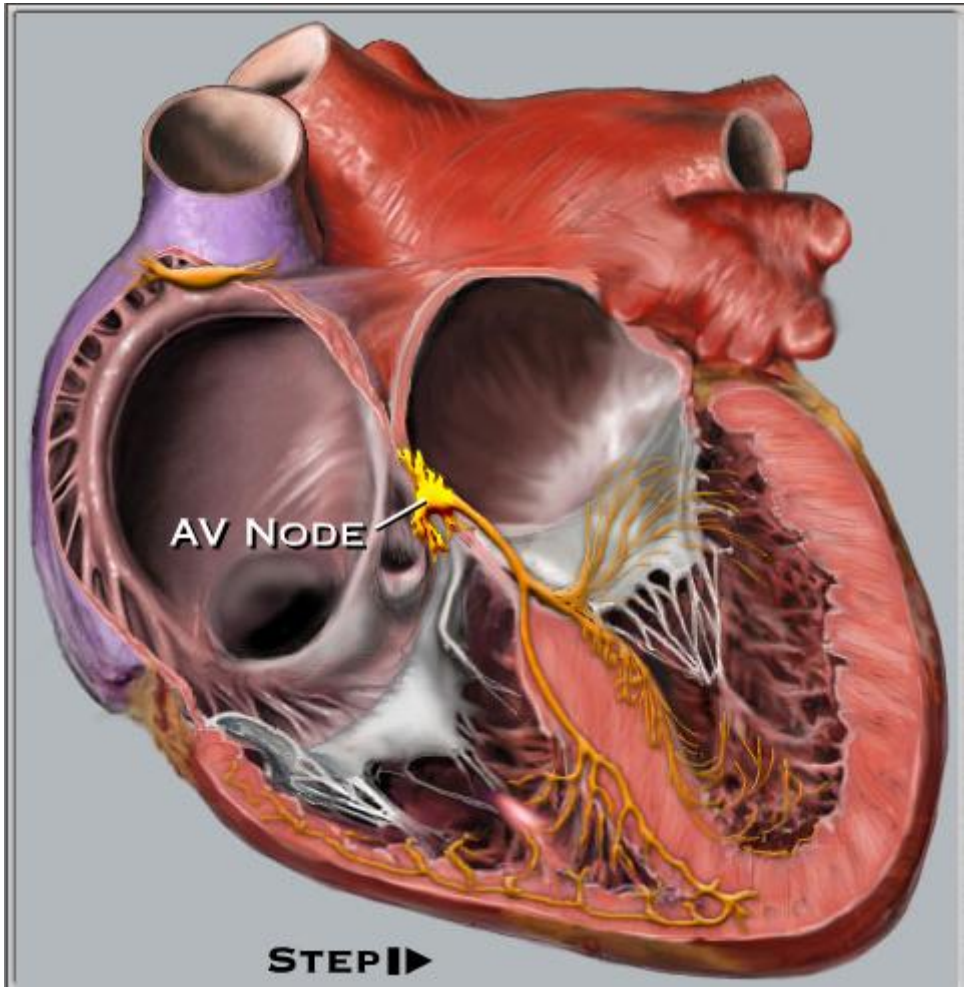
Cardiac Conduction System

Atrial Activation



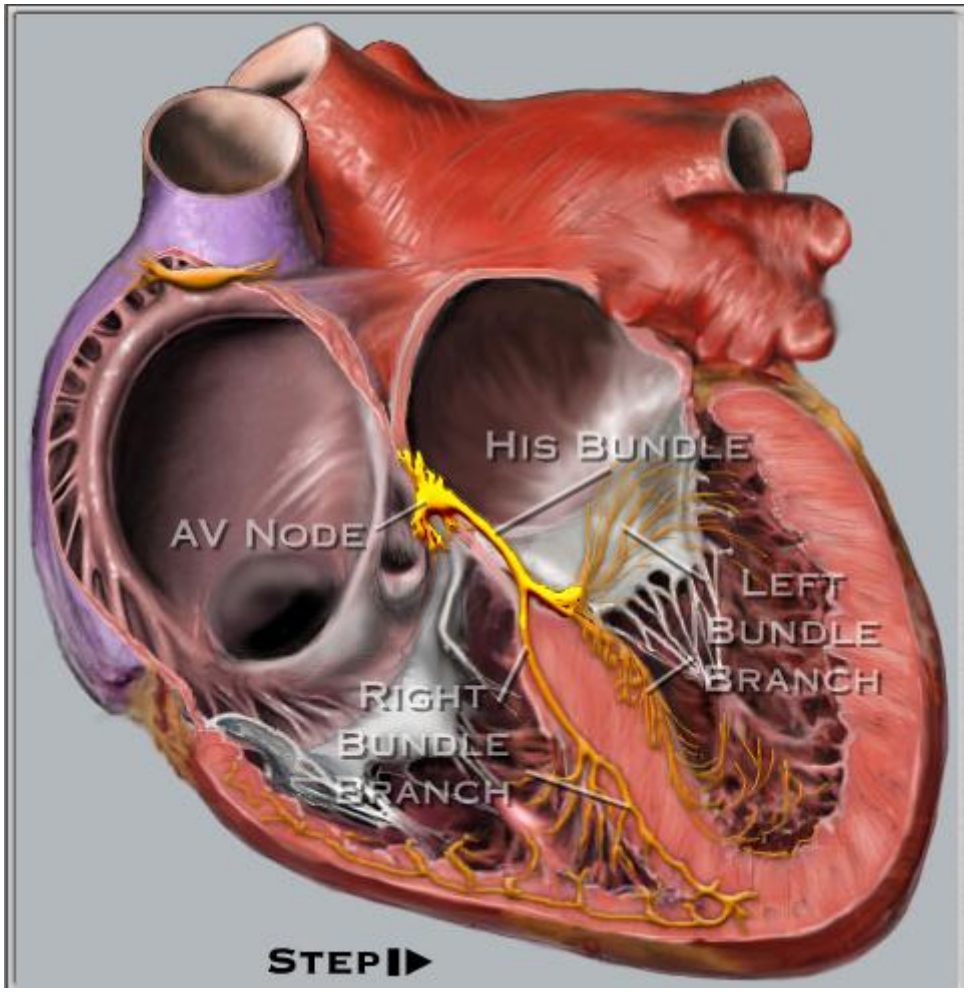
Cardiac Conduction System

Atrioventricular Nodal Conduction



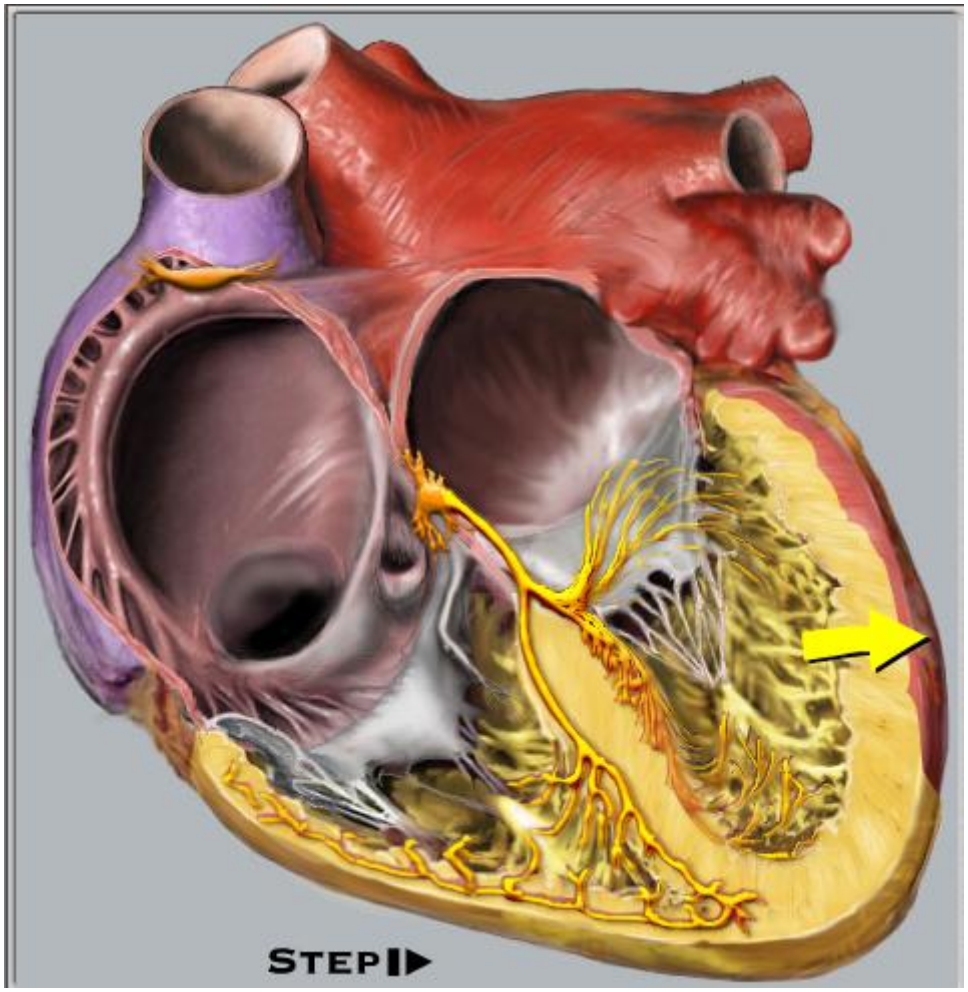
Cardiac Conduction System

Activation of His-Purkinje System

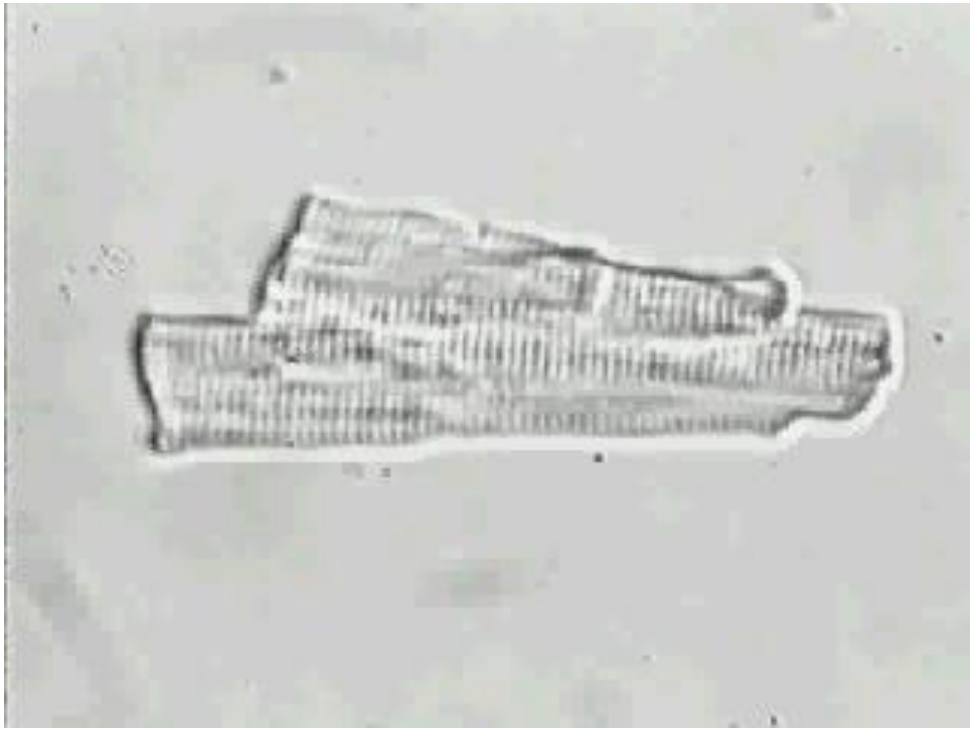


Cardiac Conduction System

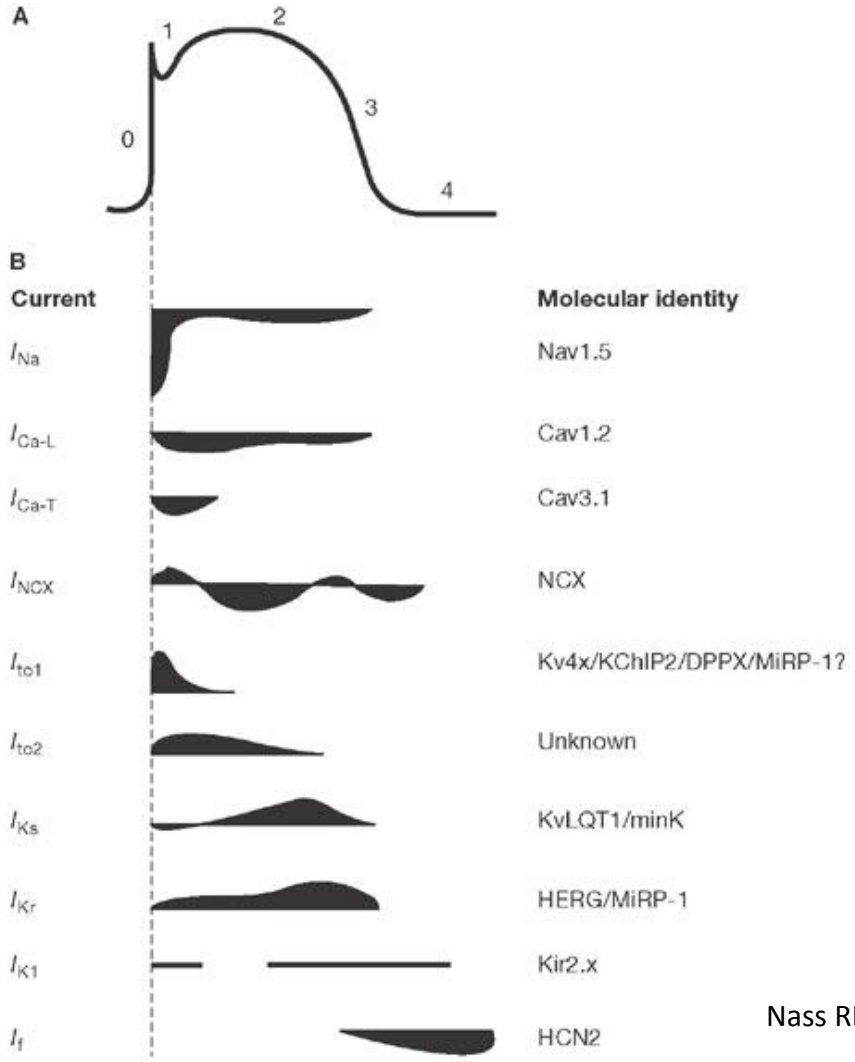
Ventricular Activation

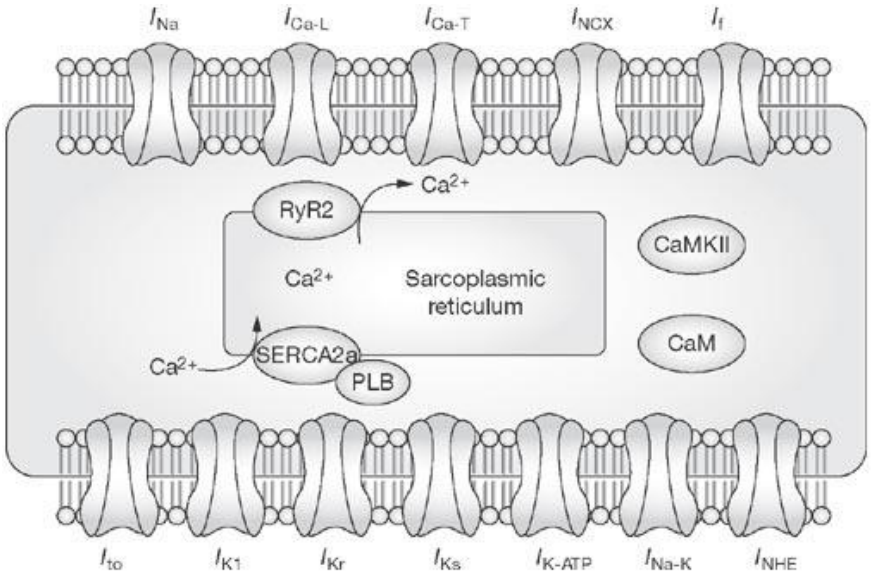


Ventricular Cardiomyocytes



Ventricular Cardiomyocyte Action Potential Ionic Currents





Nass RD *et al. Nature Clinical Practice Cardiovascular Medicine* (2008) **5**, 196-207

Electrical Propagation

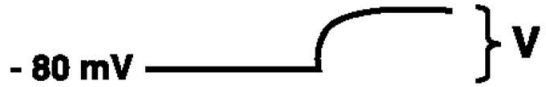
- Current source - sink

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

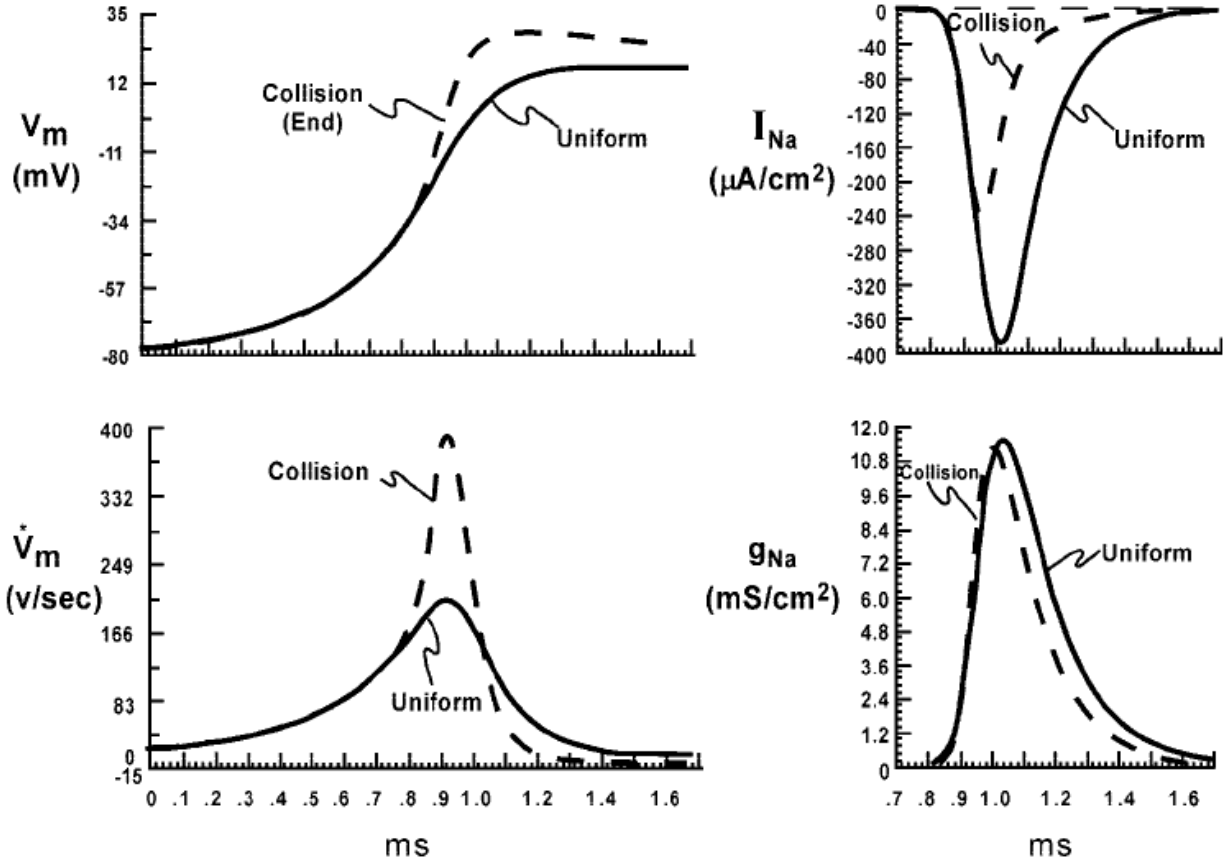
If $I_{K1}\downarrow$, $R\uparrow$

•V larger for the same I

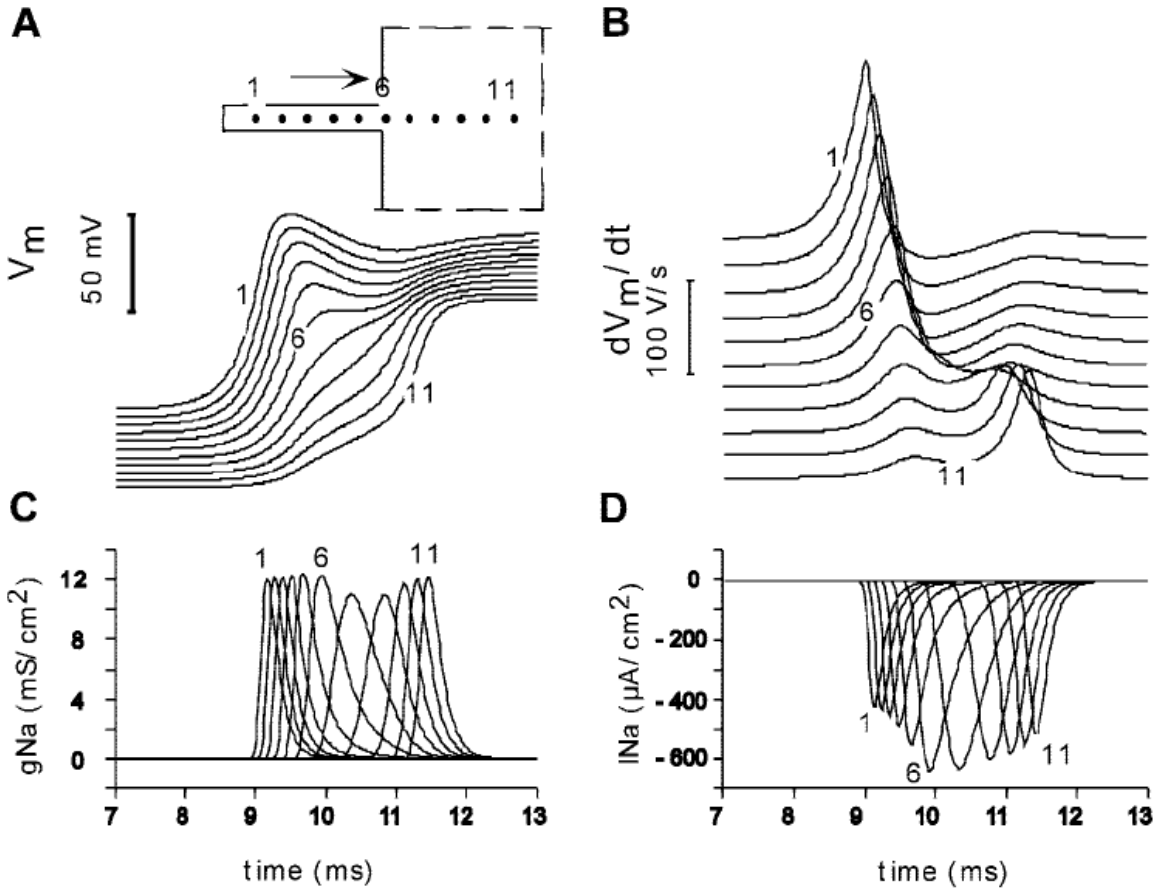
Biophysical principles of propagation

- 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



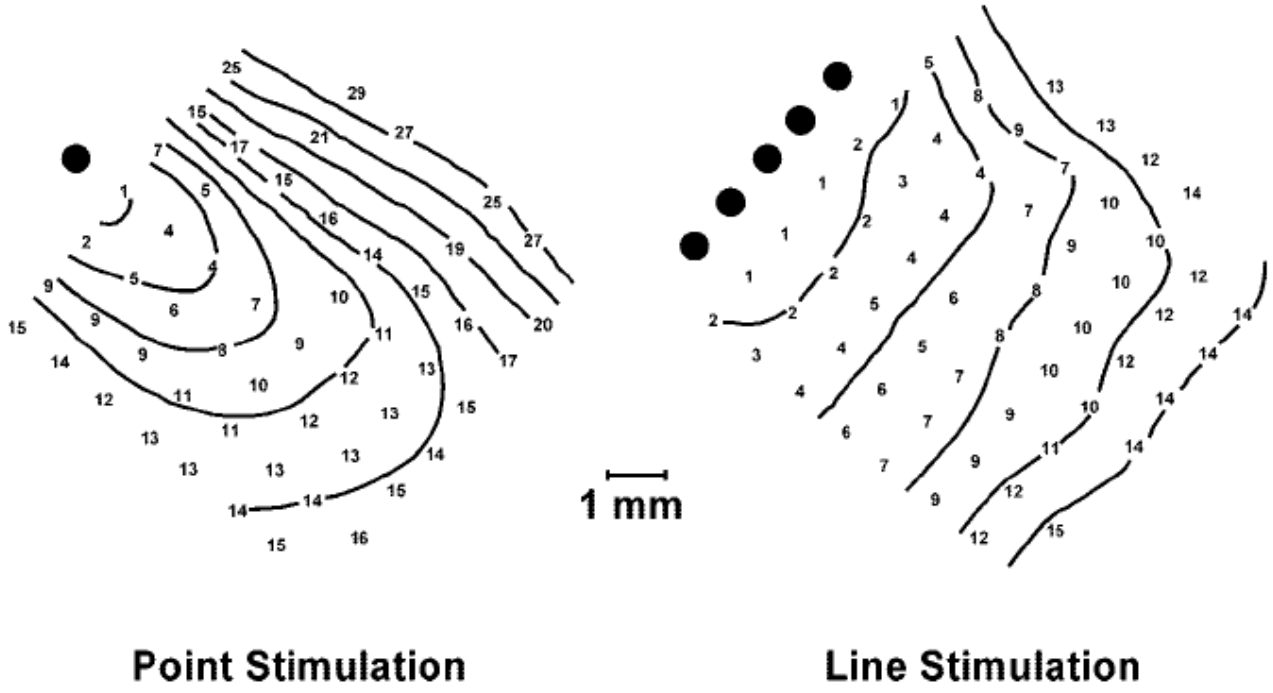
Current-to-Load mismatch



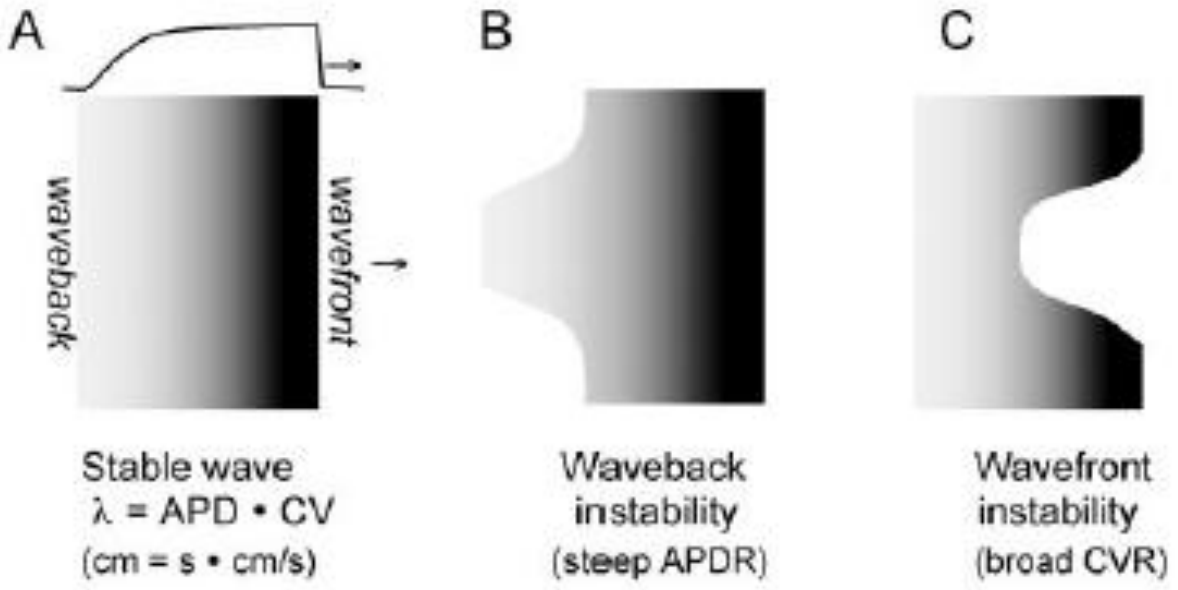
Safety of Propagation

$$\mathrm{SF} = \frac{\int_A I_c \mathrm{d}t + \int_A I_{out} \mathrm{d}t}{\int_A I_{in} \mathrm{d}t} \qquad A|Q_m > 0$$

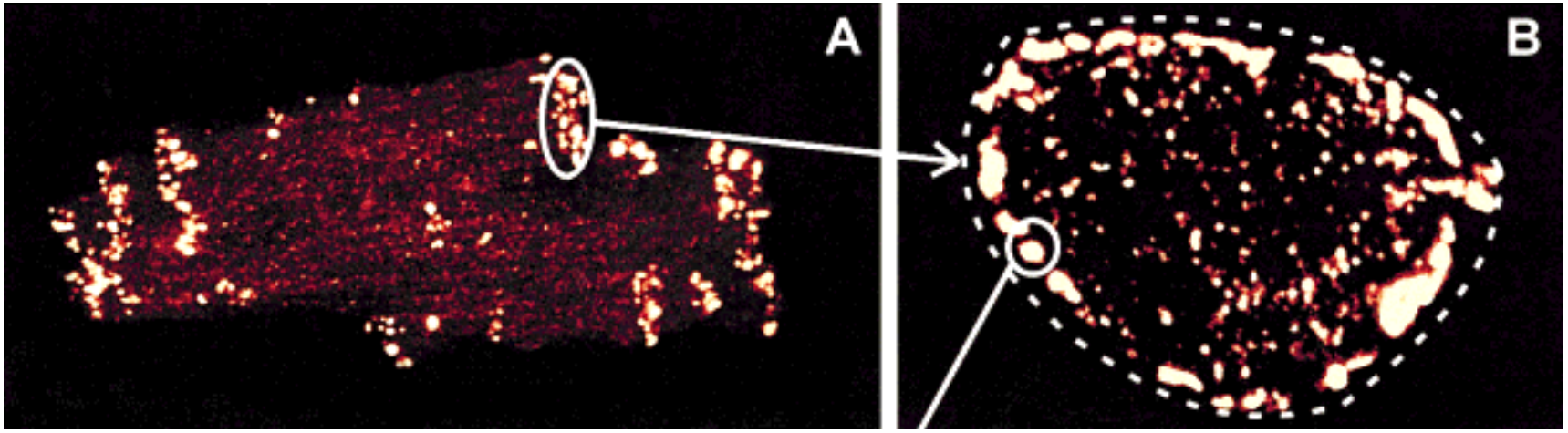
Effect of curvature on propagation.



Electrical Wave Propagation and Wavebreak

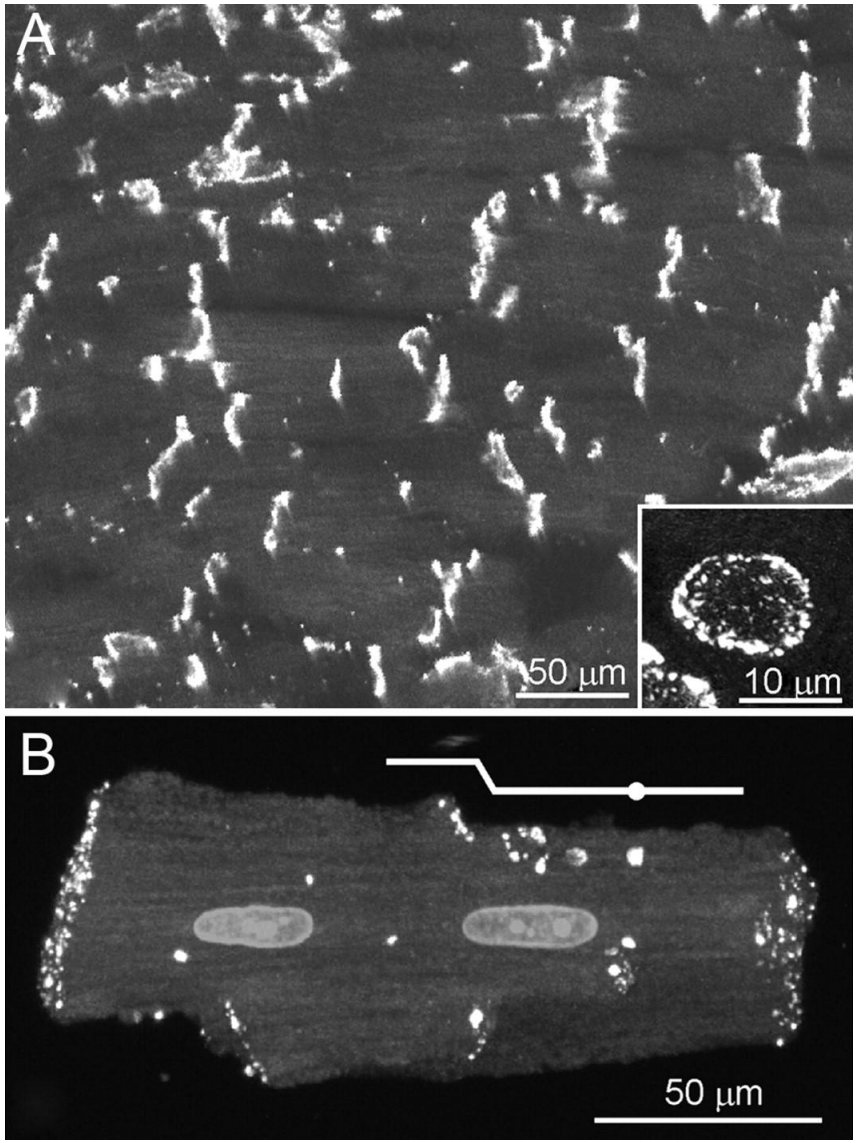


Intercellular Electrical Conduction
Gap junction structure



Severs NJ, Bioessays 2000

Intercellular Electrical Conduction
Gap junction structure



Intercellular Electrical Conduction
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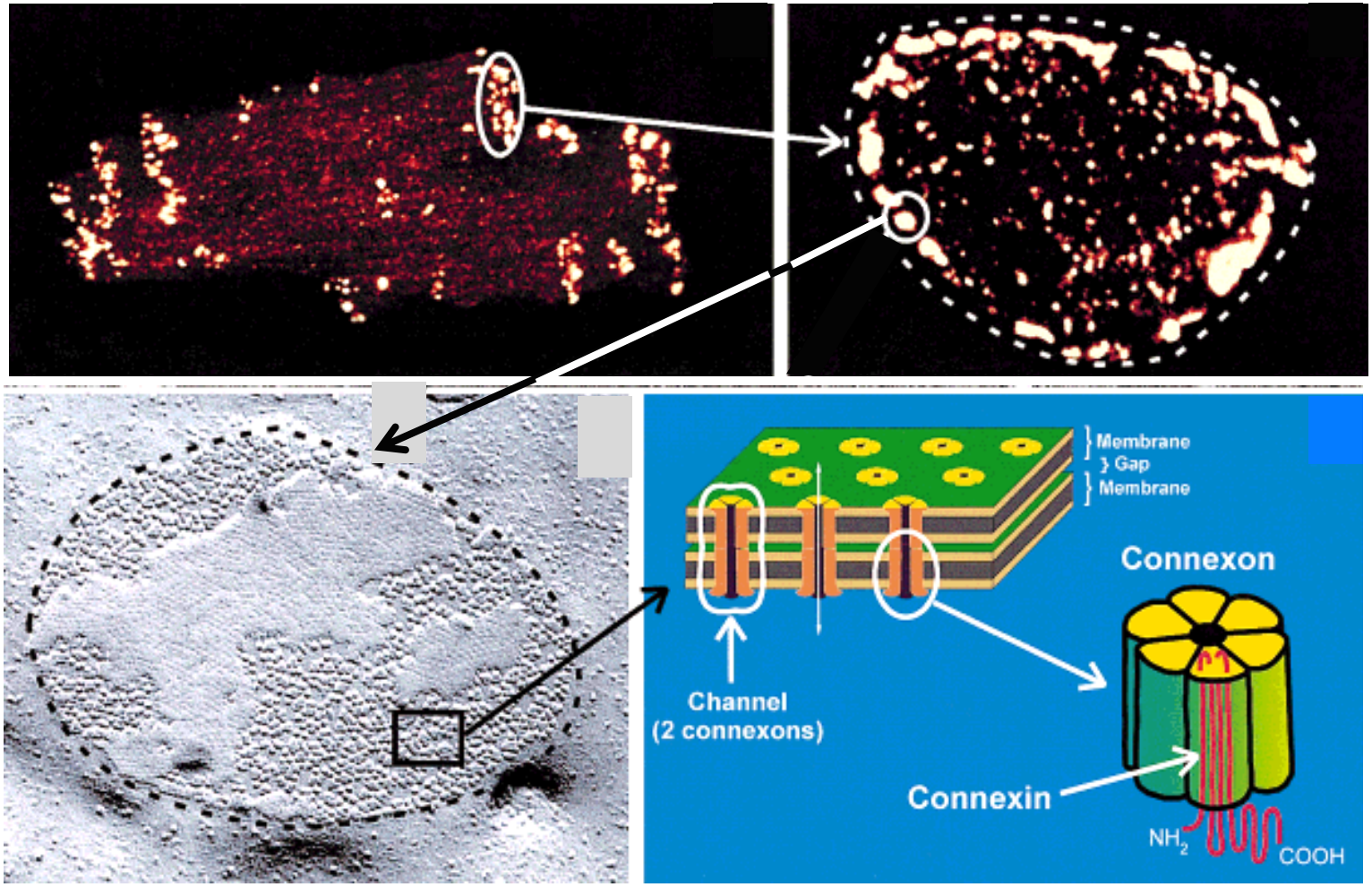
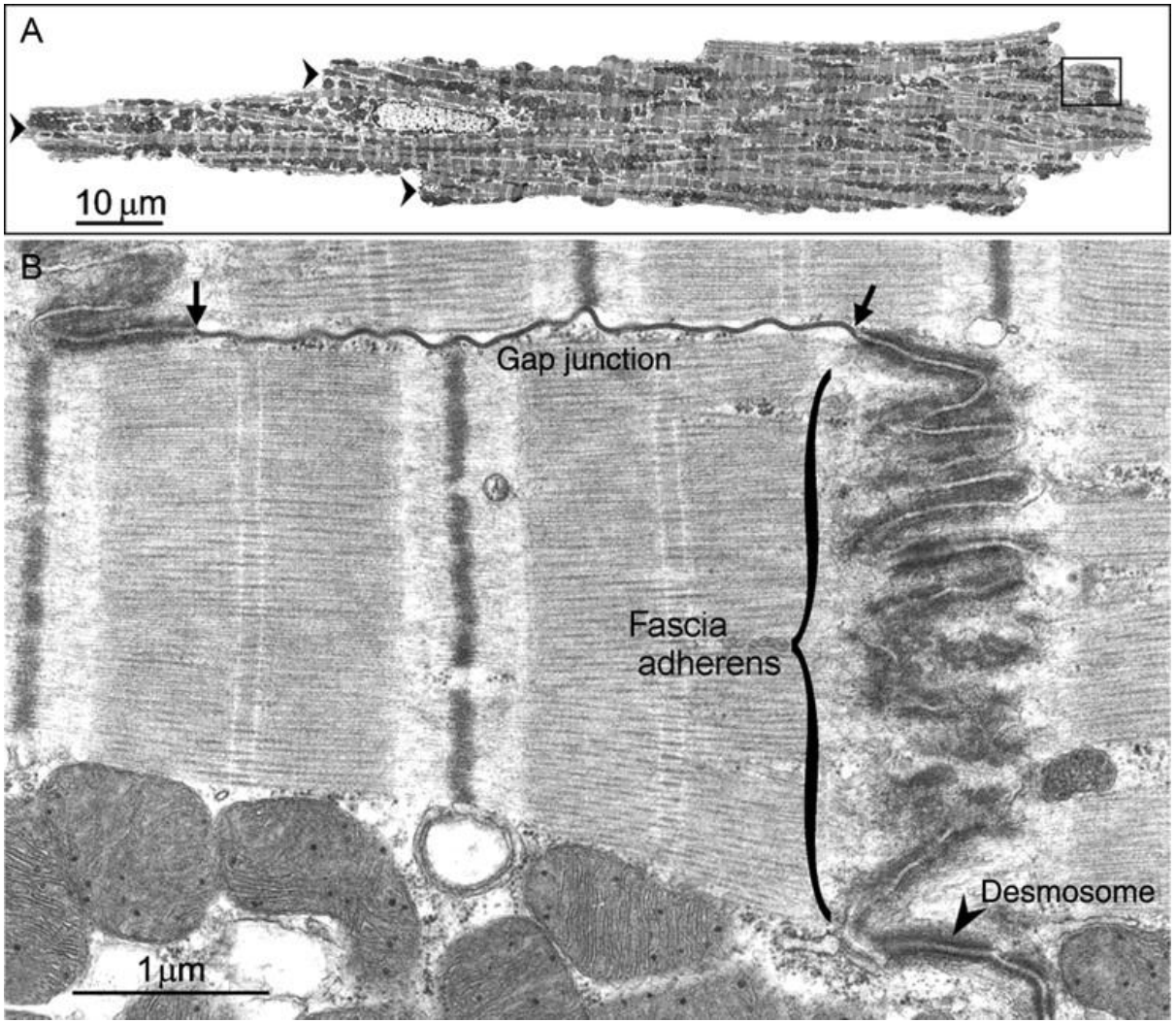
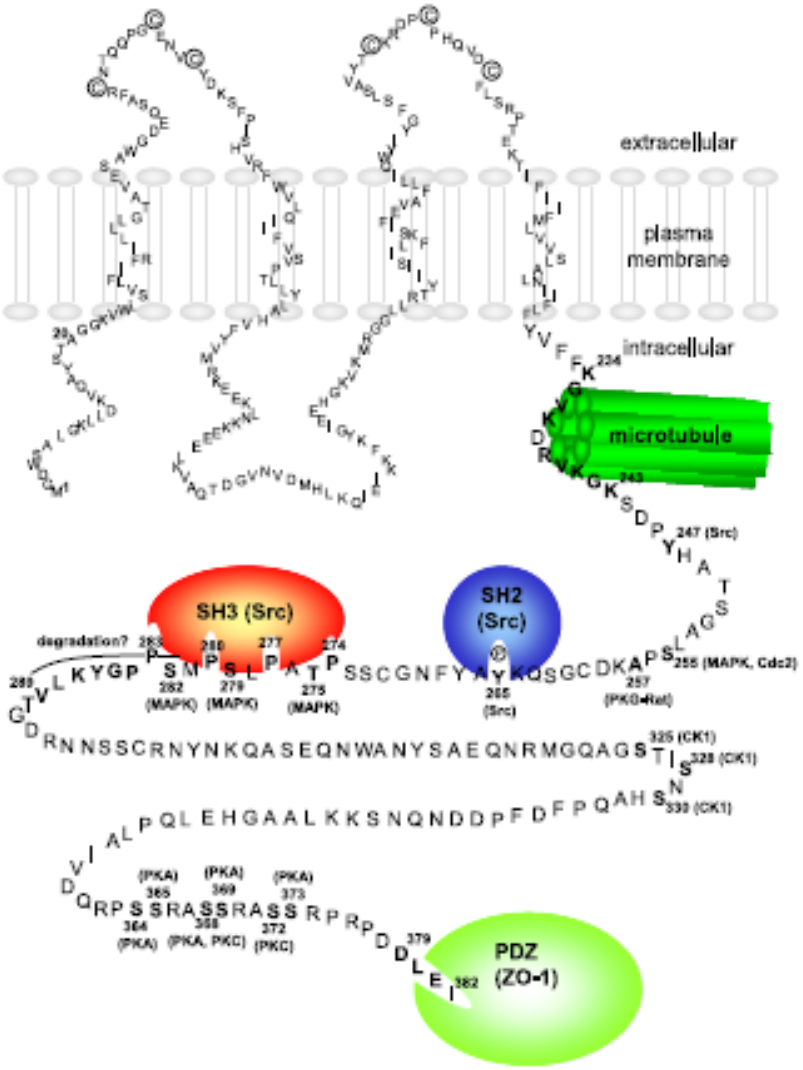


Severs NJ, Bioessays 2000

Intercellular Electrical Conduction
Intercalated Disc Structure

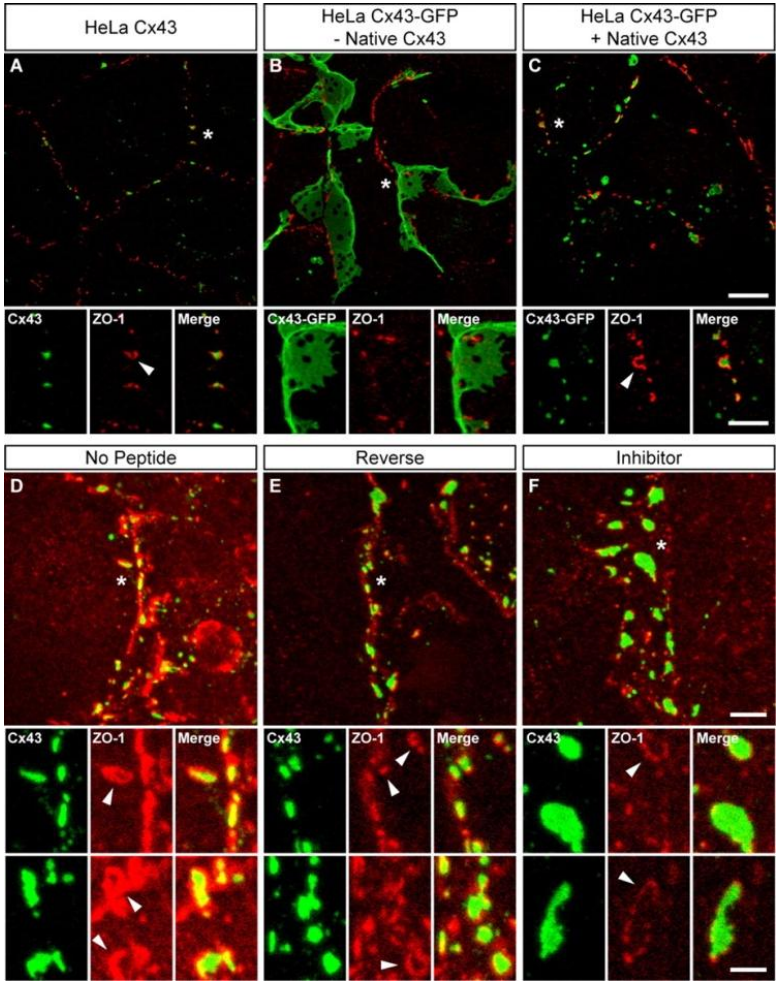


Intercellular Electrical Conduction
Connexin 43 structure and Posttranslational modification



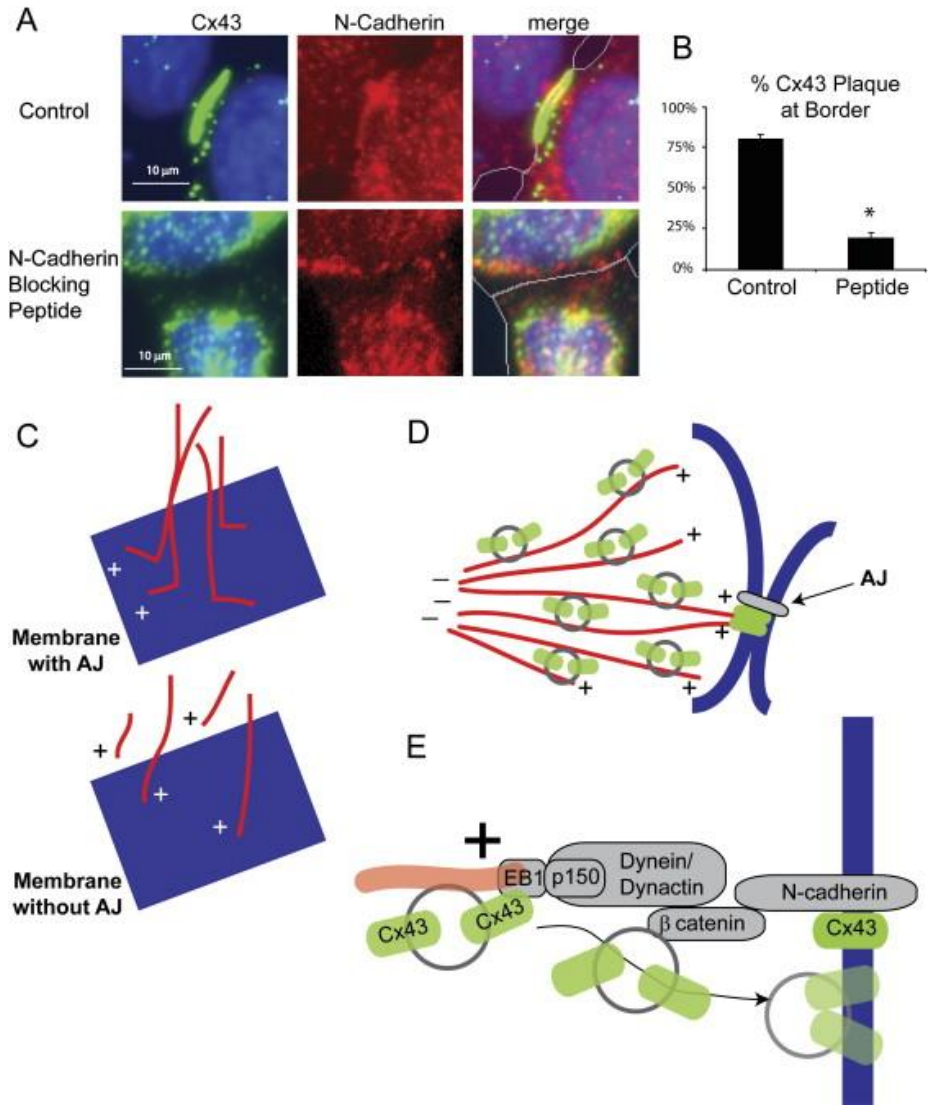
GJ Accessory Proteins

- 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) = αCT-1



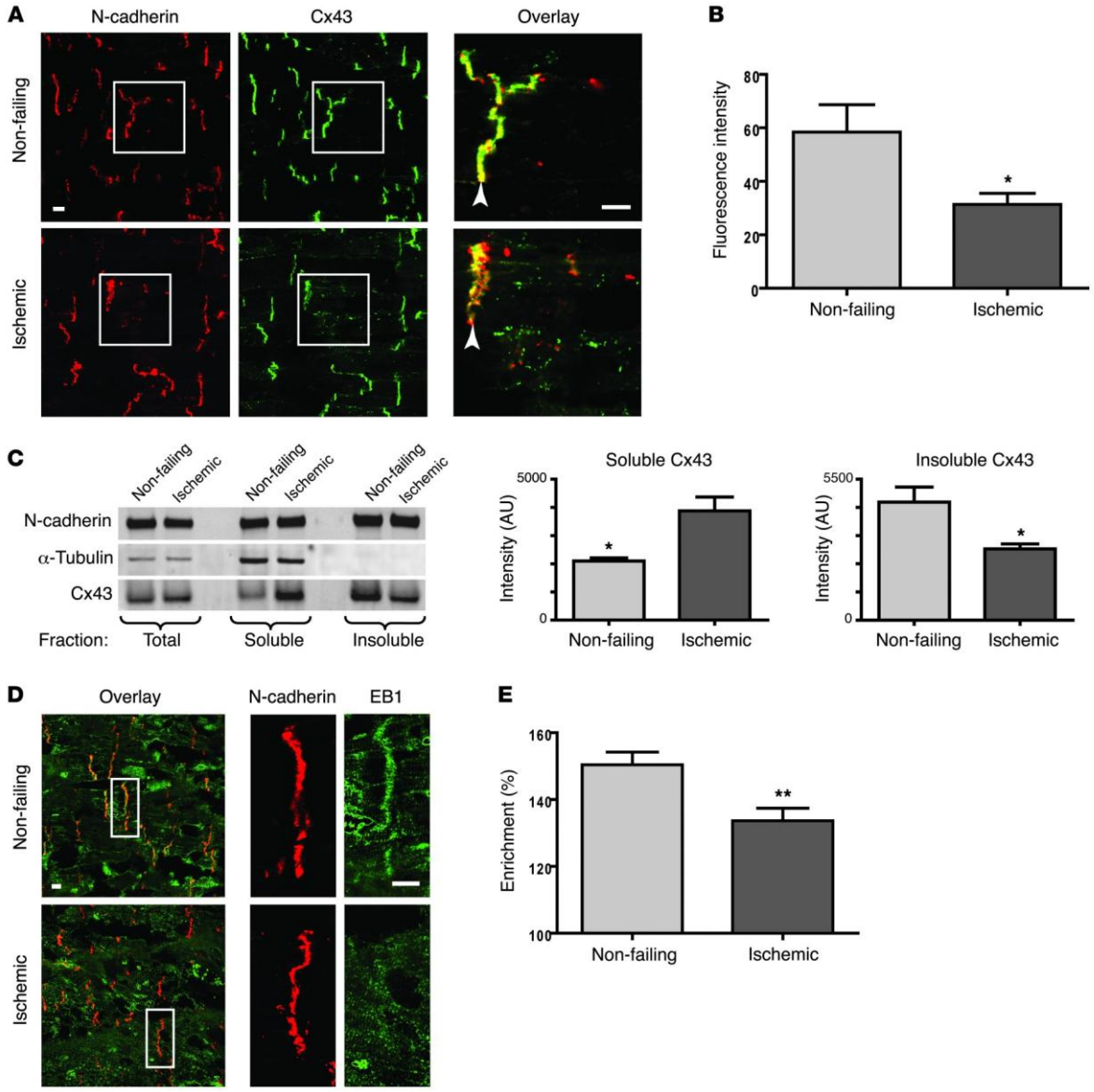
* Hunter et al Mol. Biol. Cell 2005 Vol. 16, Issue 12, 5686-5698

Connexin 43 Trafficking to Intercalated Disc



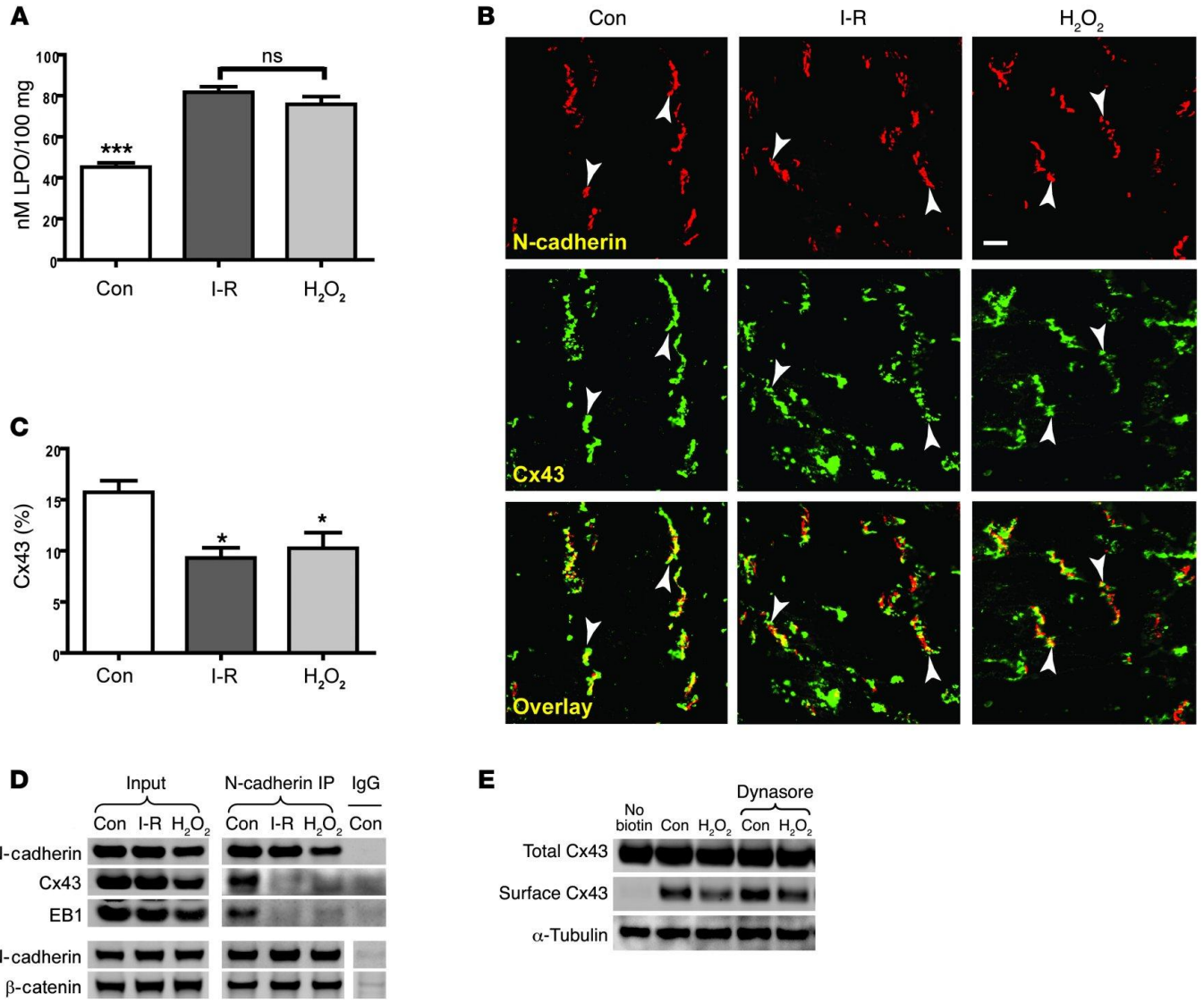
Reduced Cx43 at Gap Junctions in Human Failing Hearts

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

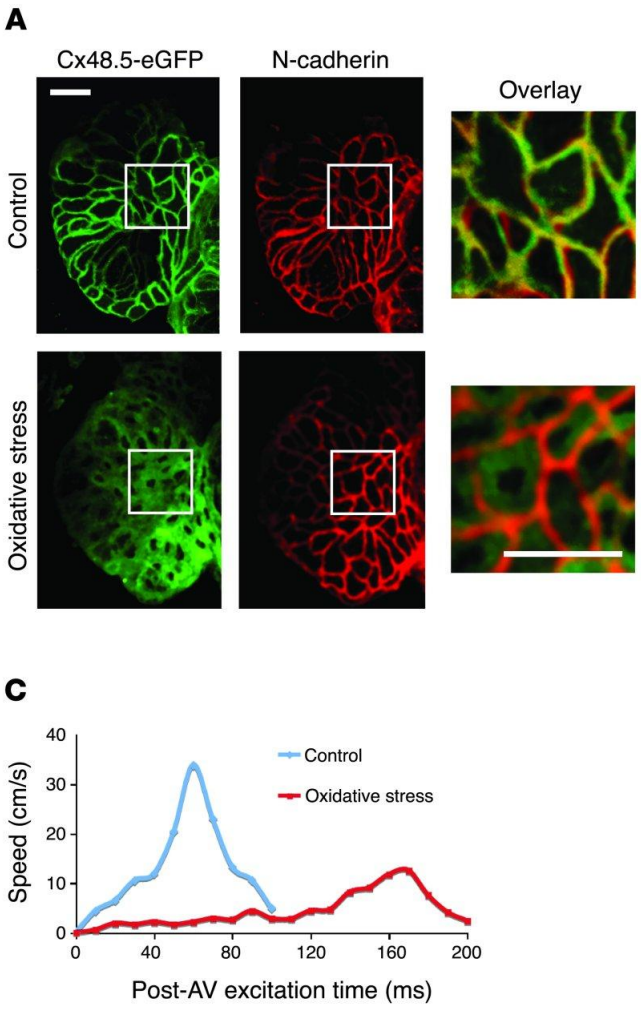


Oxidative Stress Reduces Cx43 delivery to Intercalated Discs

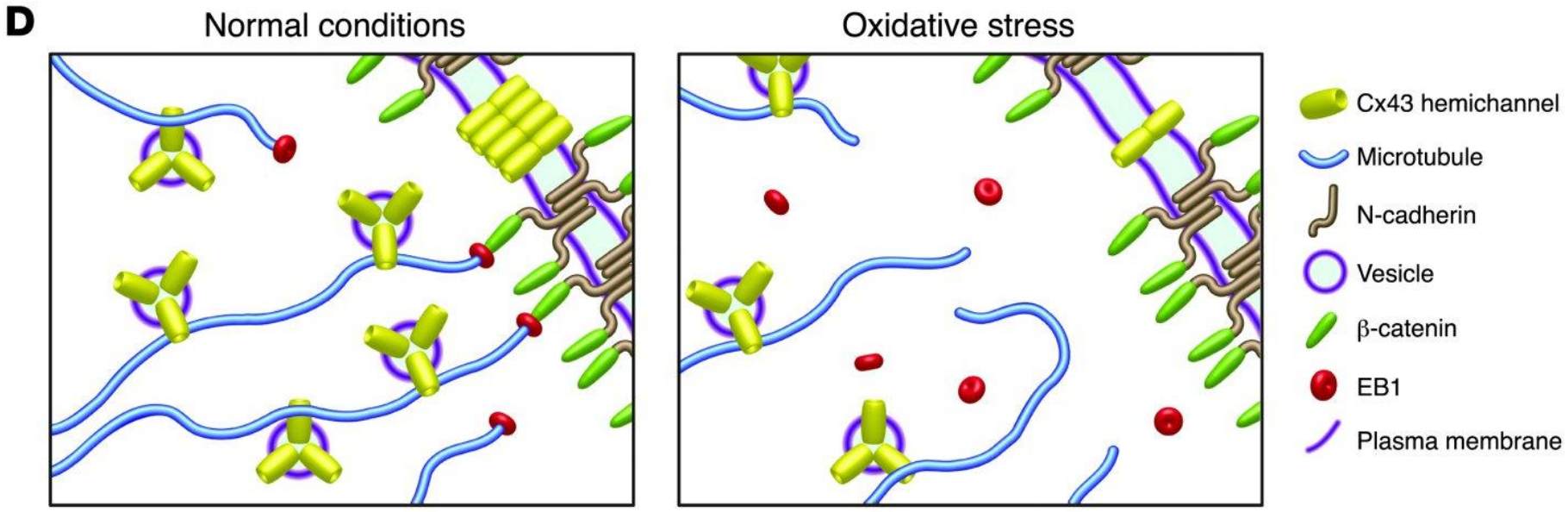
Smyth et al *J Clin Invest.* 2010; 120(1):266



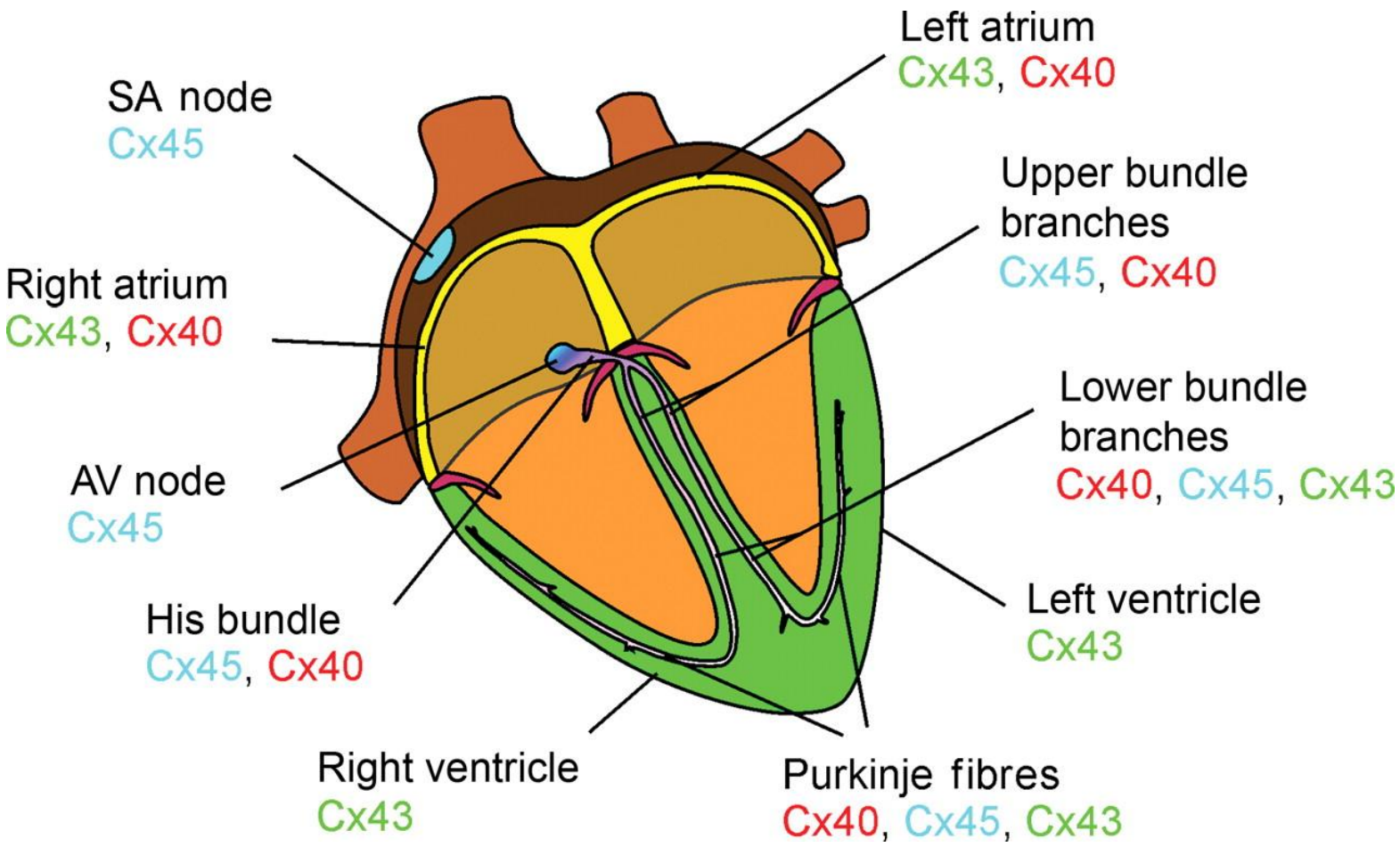
Oxidative Stress Reduces Conduction Velocity
Smyth et al *J Clin Invest.* 2010; 120(1):266



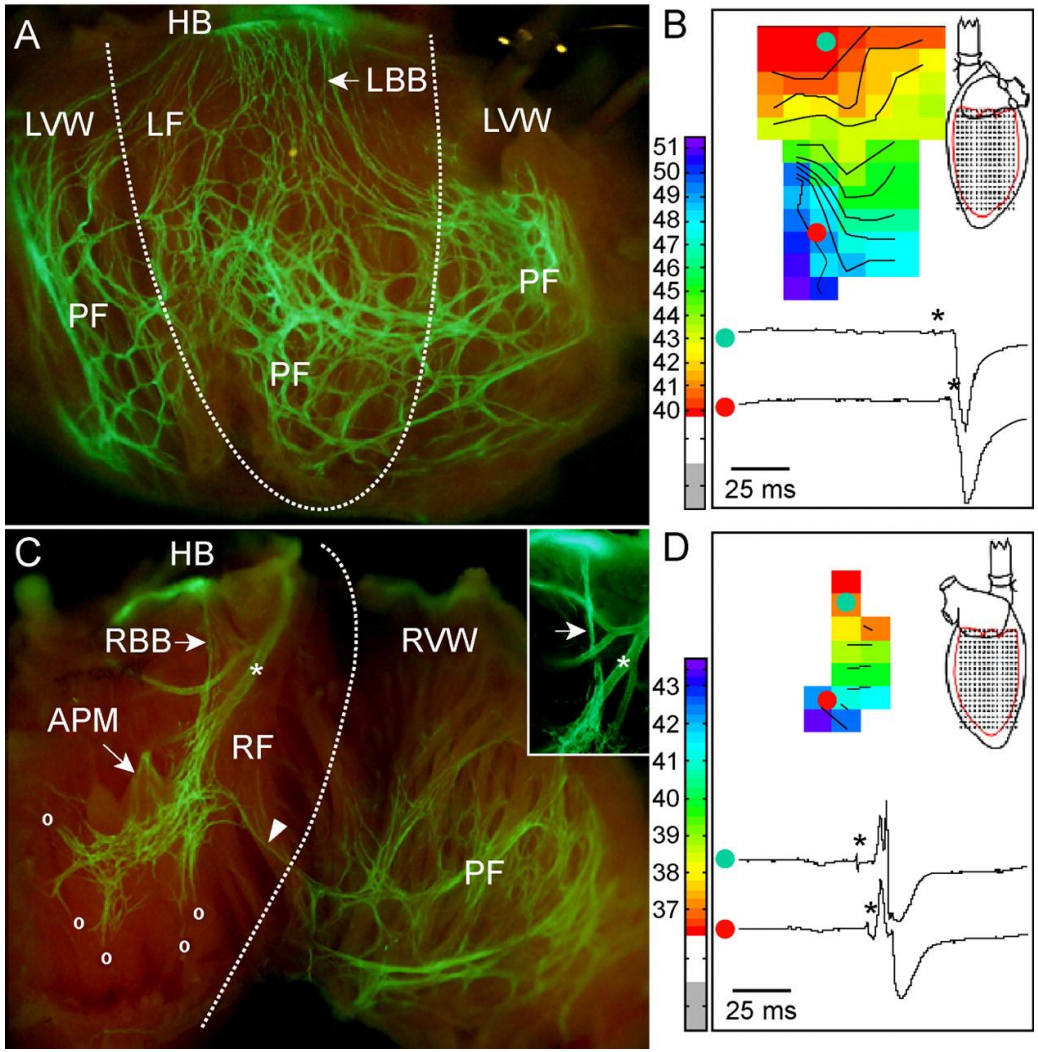
Schematic Model for Microtubule-mediated Cx43 delivery to Gap Junctions



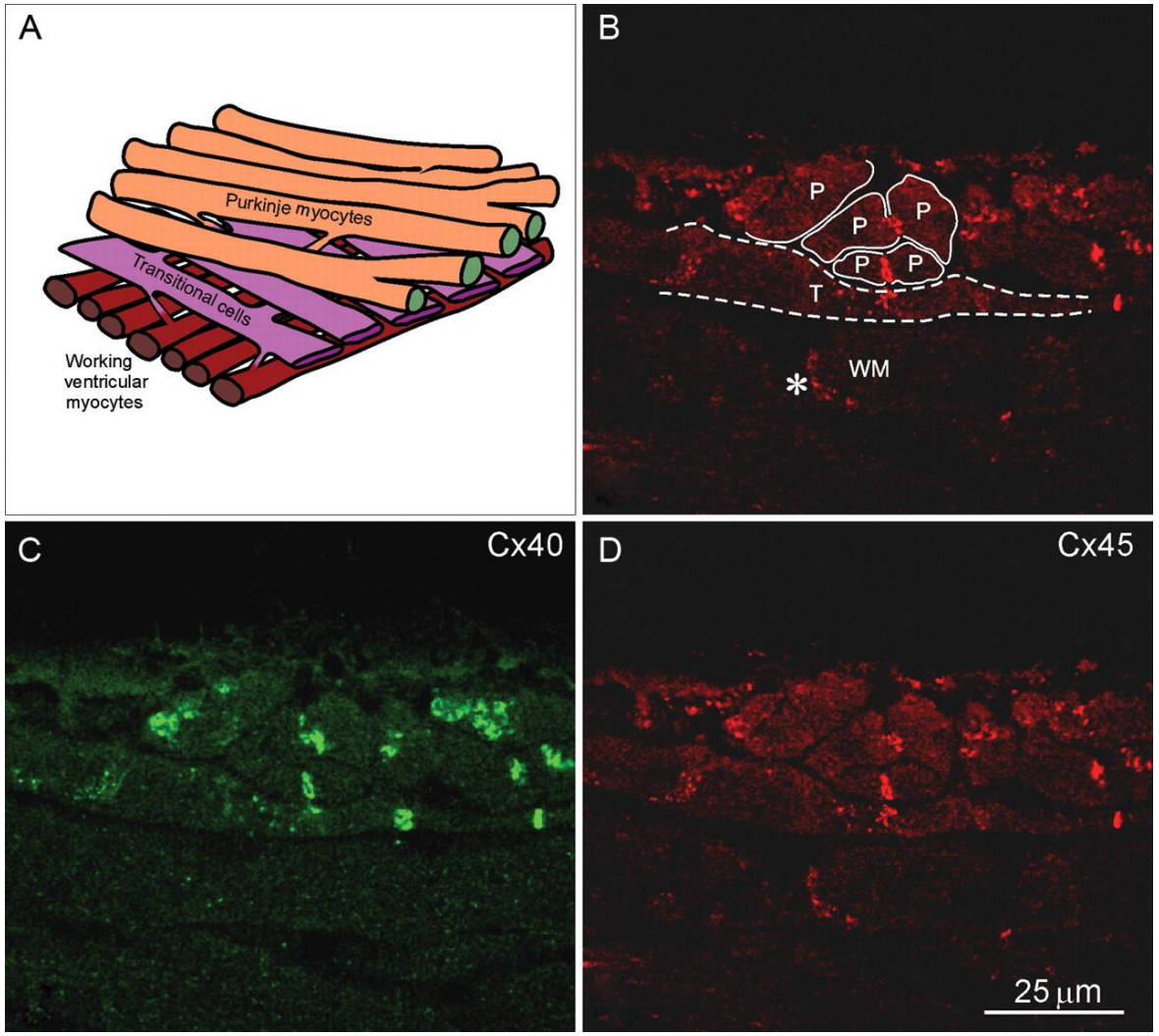
Cardiac Connexin Isoform Expression/Distribution



Transgenic Cx40-GFP Mouse Cardiac Purkinje Fibre Network

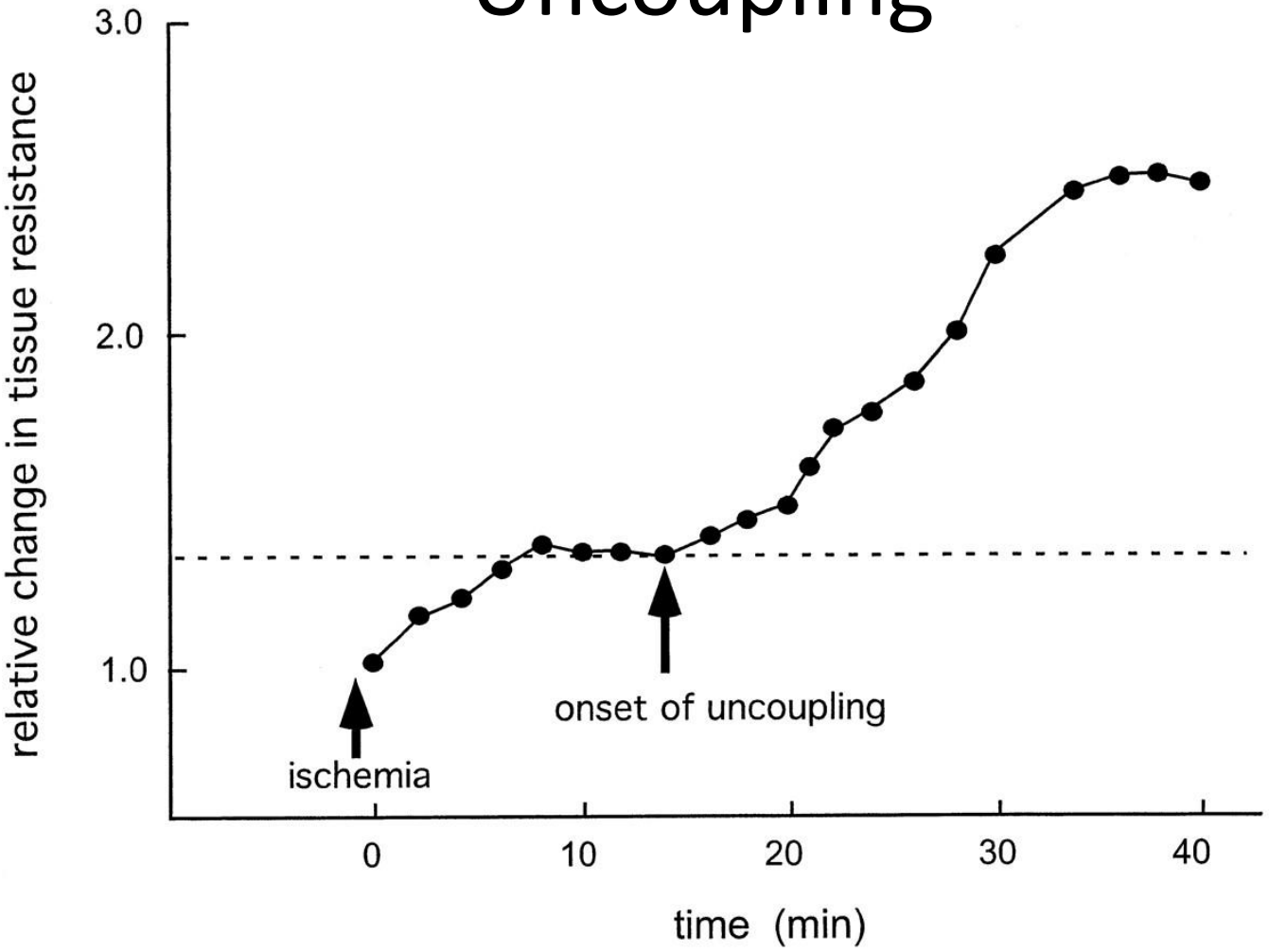


Purkinje Fibre-Cardiomyocyte Interface



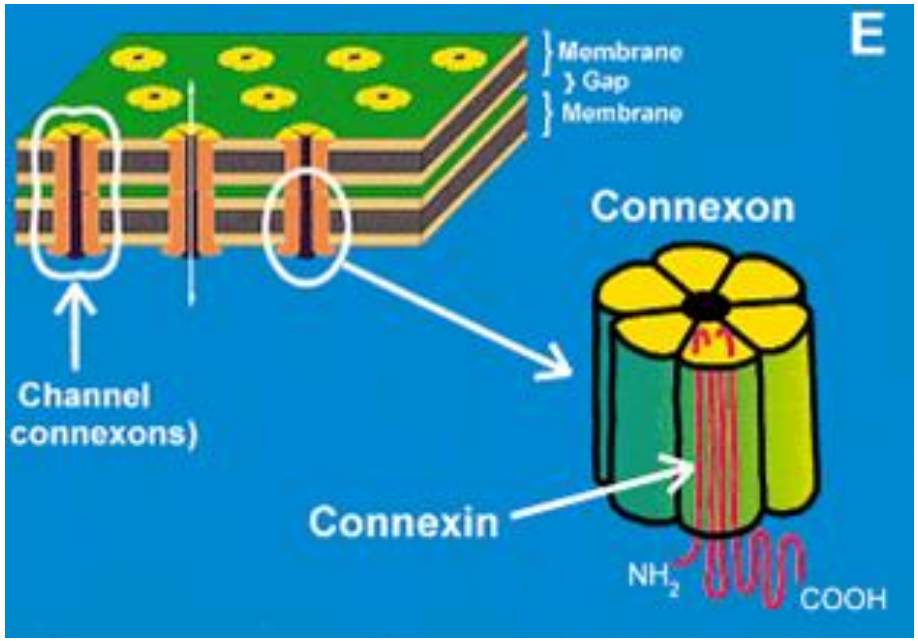
Gap Junction Function in Disease
1. Myocardial Ischaemia

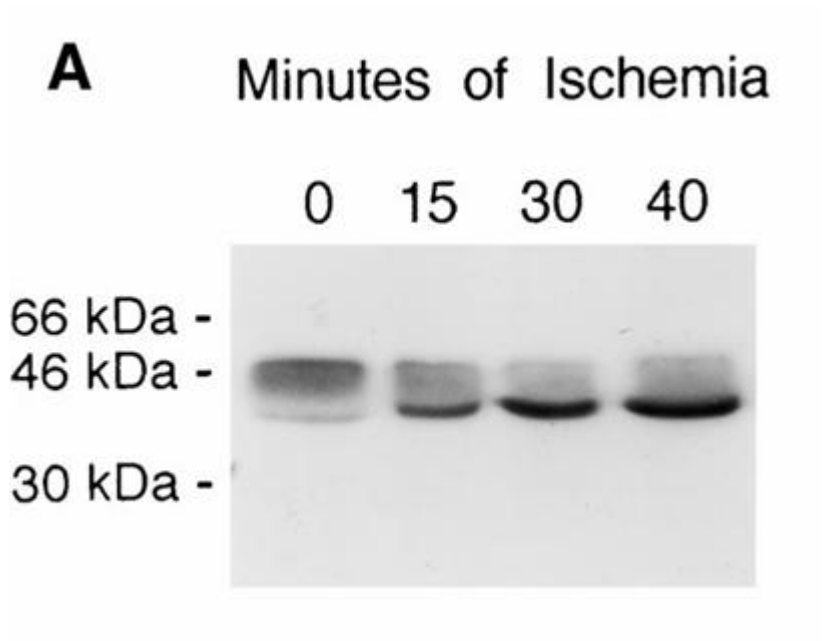
Background – Acute Ischaemia Associated with Gap Junctional Uncoupling



Beardslee, M. A. et al. Circ Res 2000;87:656-662

Background – Connexin43 Dephosphorylation in Ischaemia

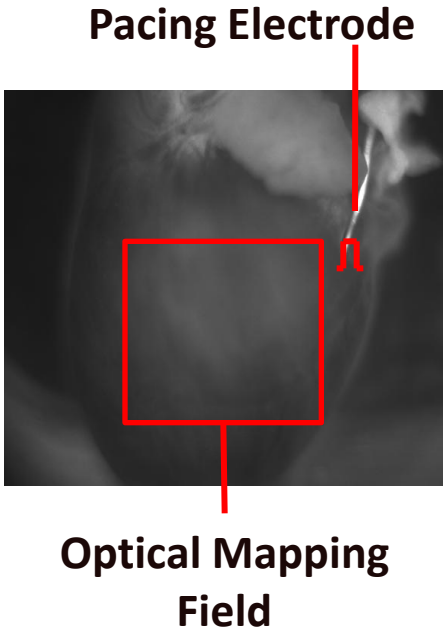


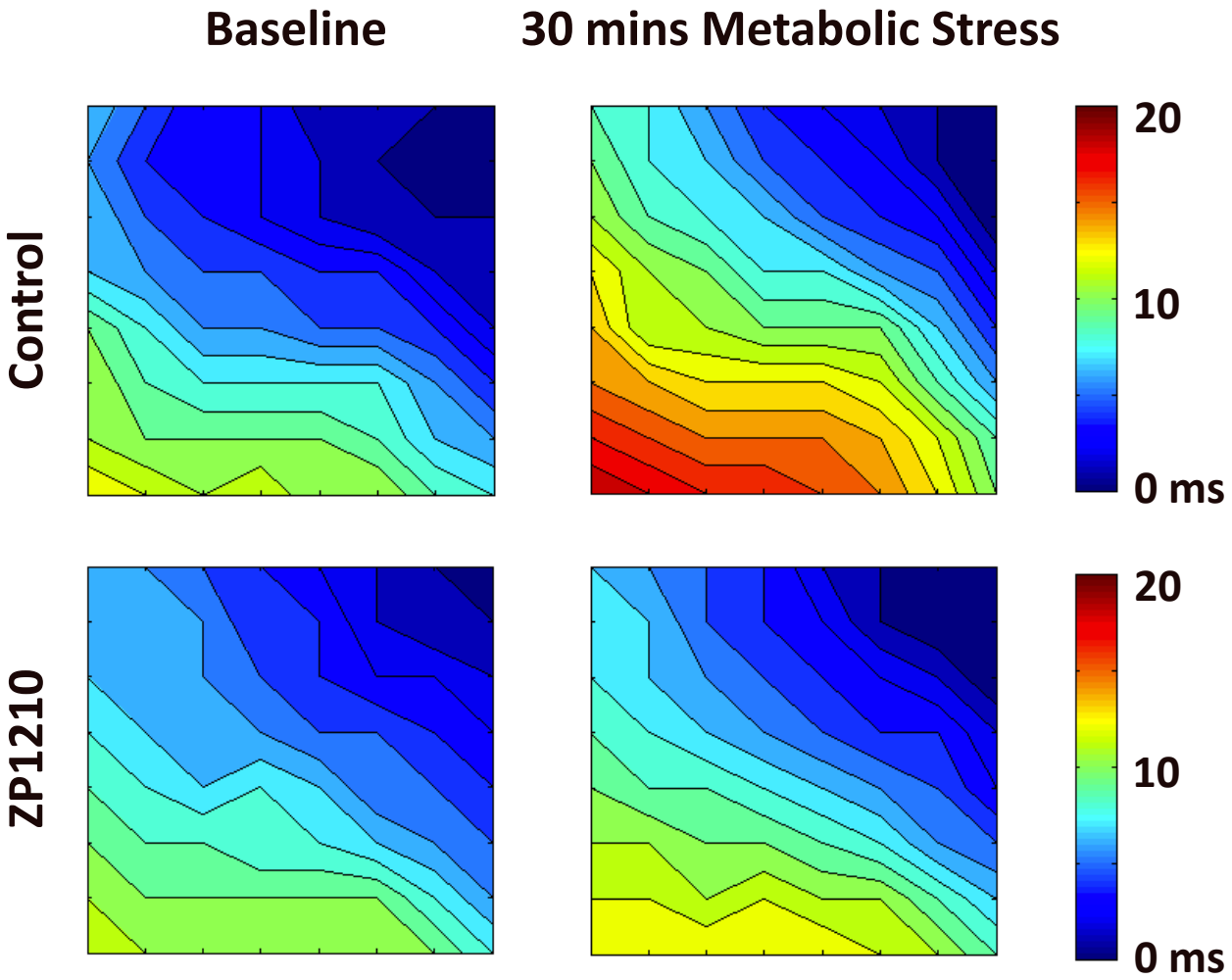


Severs NJ. Bioessays. 2000 Feb;22(2):188-99.

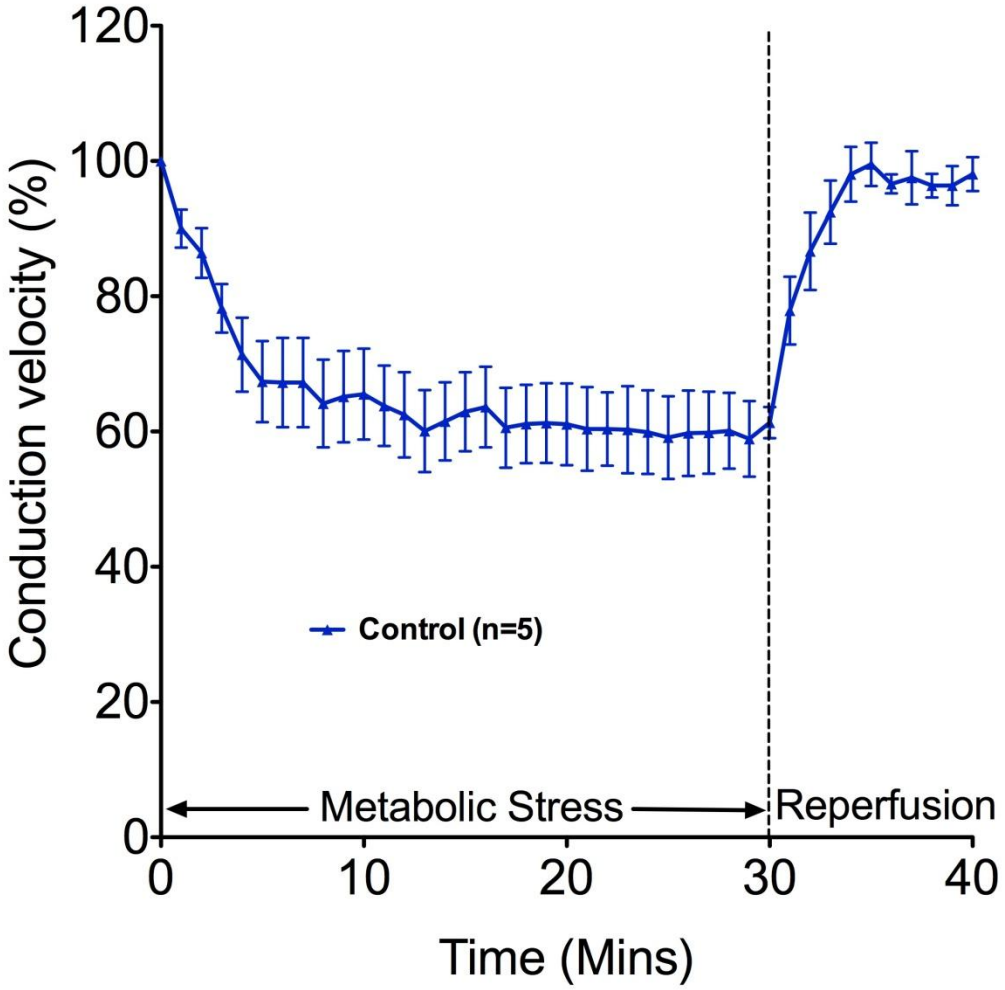
Beardslee MA et al. Circ Res. 2000 Oct 13;87(8):656-62

Epicardial Activation Maps





Conduction slowing with Metabolic Stress



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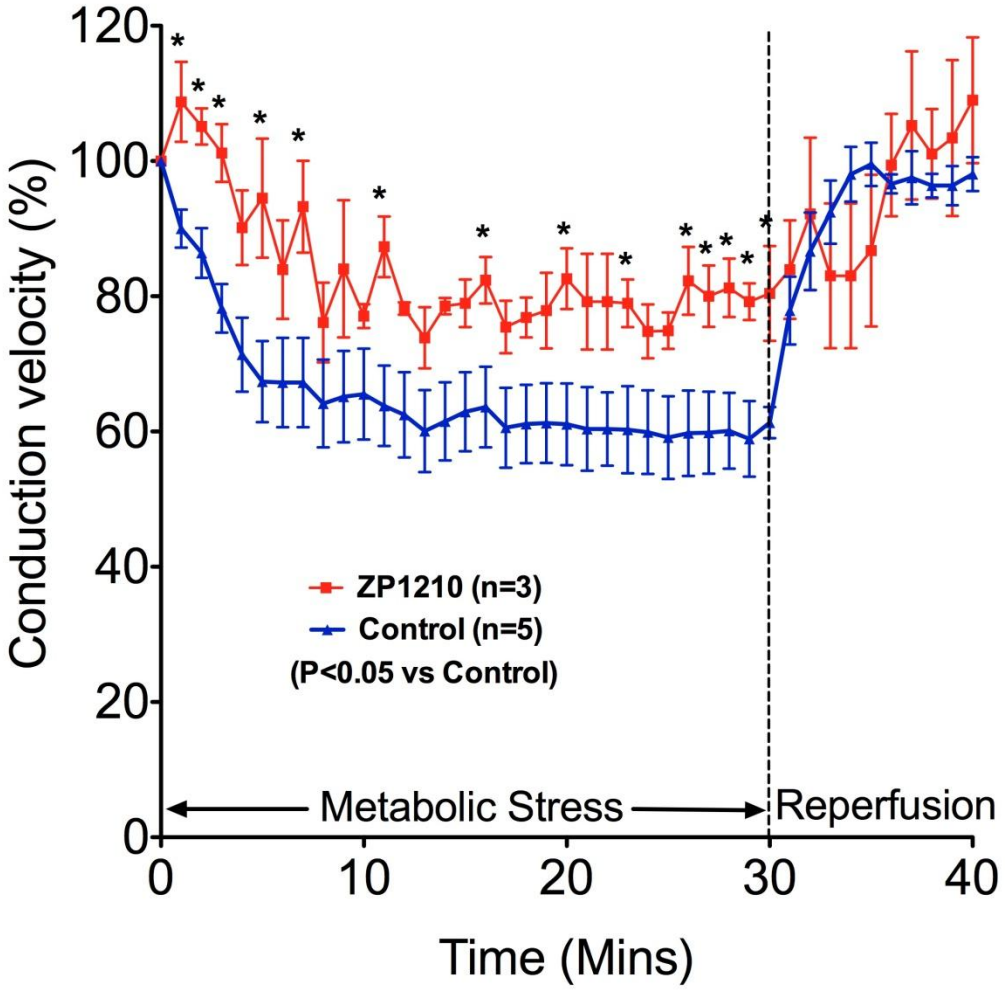
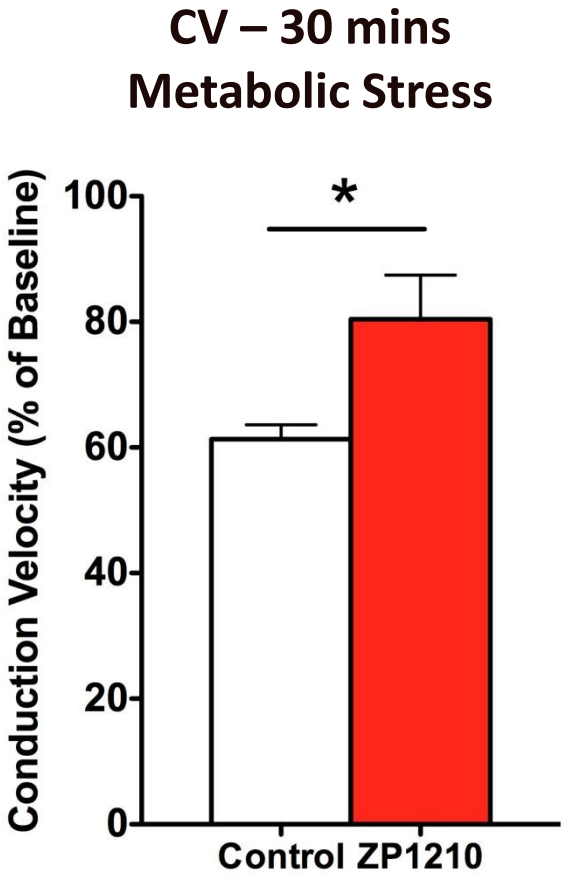
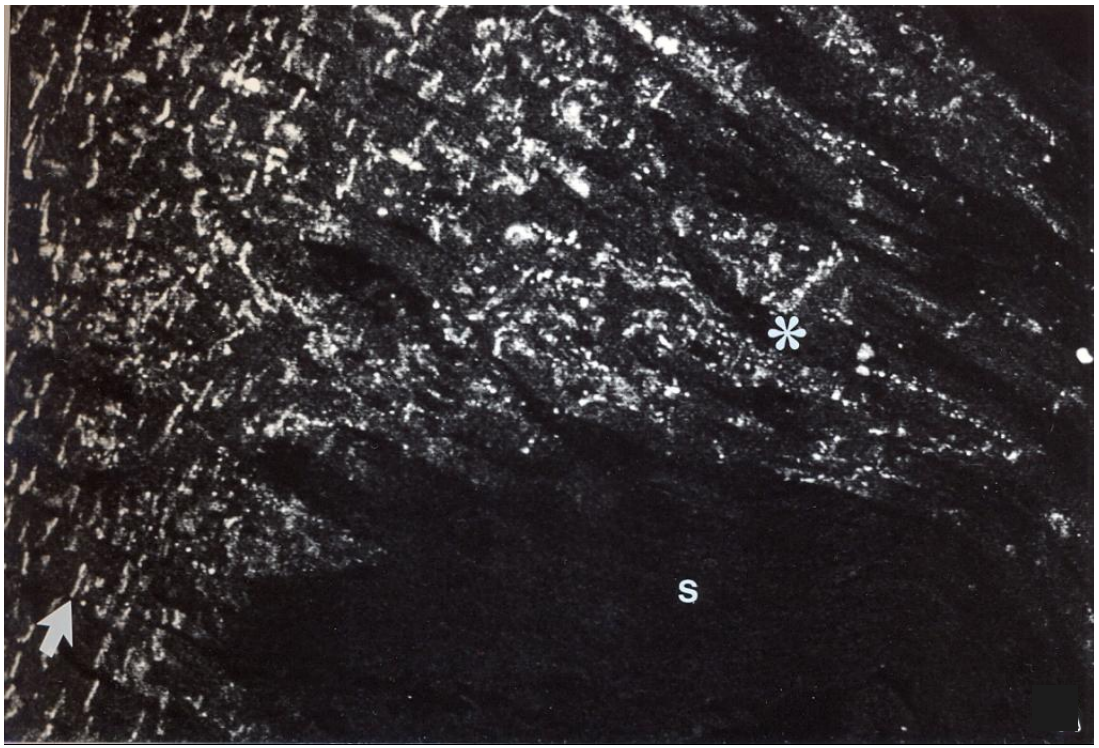
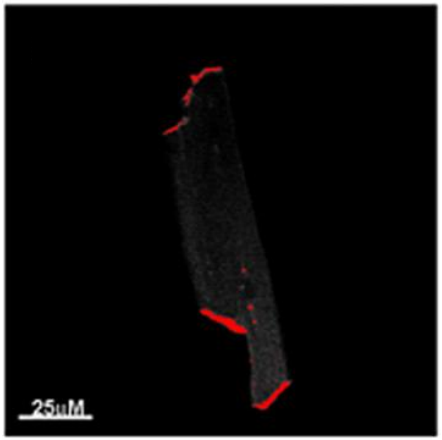
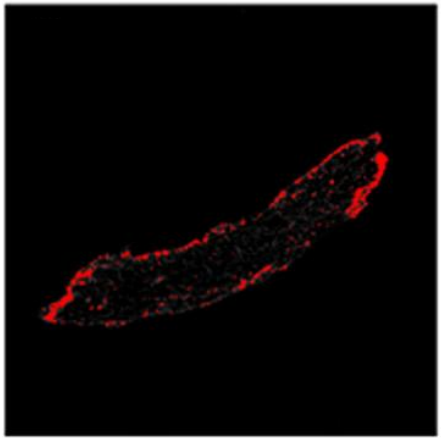




Substrate – Gap junction lateralisation







Peters *et al.* J Cardiovasc Electrophysiol.

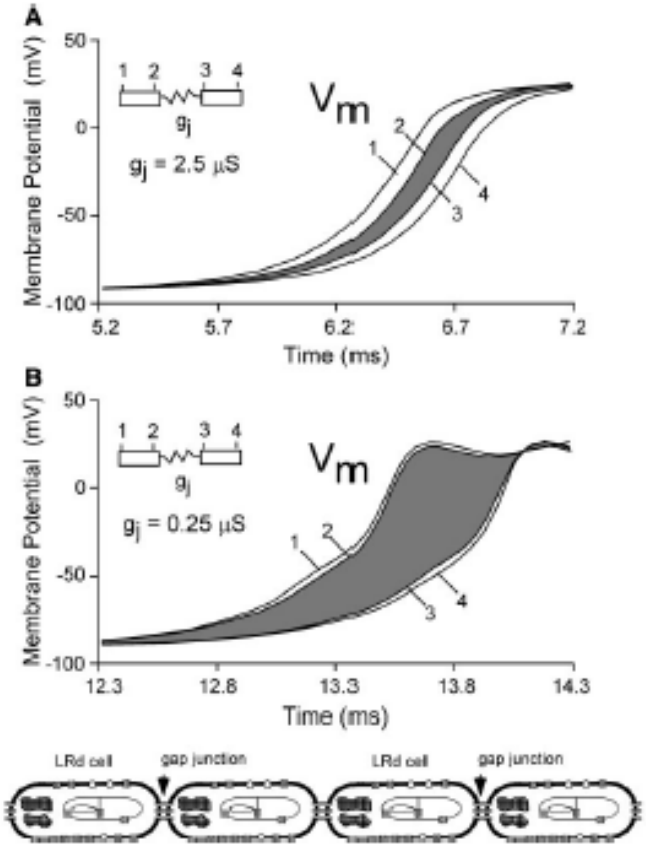
Cabo *et al.* Cardiovasc. Res. 200

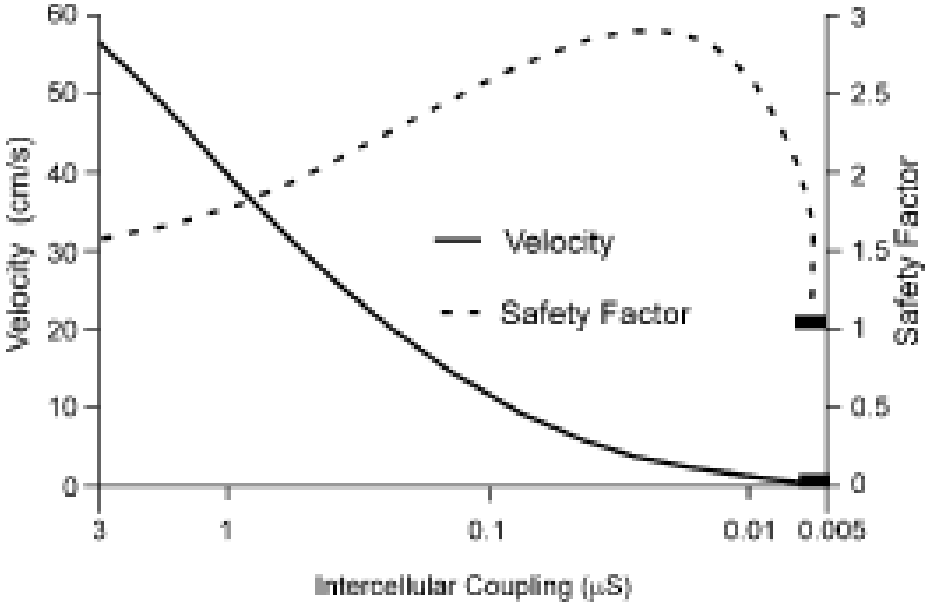
Gap Junction Function in Disease
2. Myocardial Infarction

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





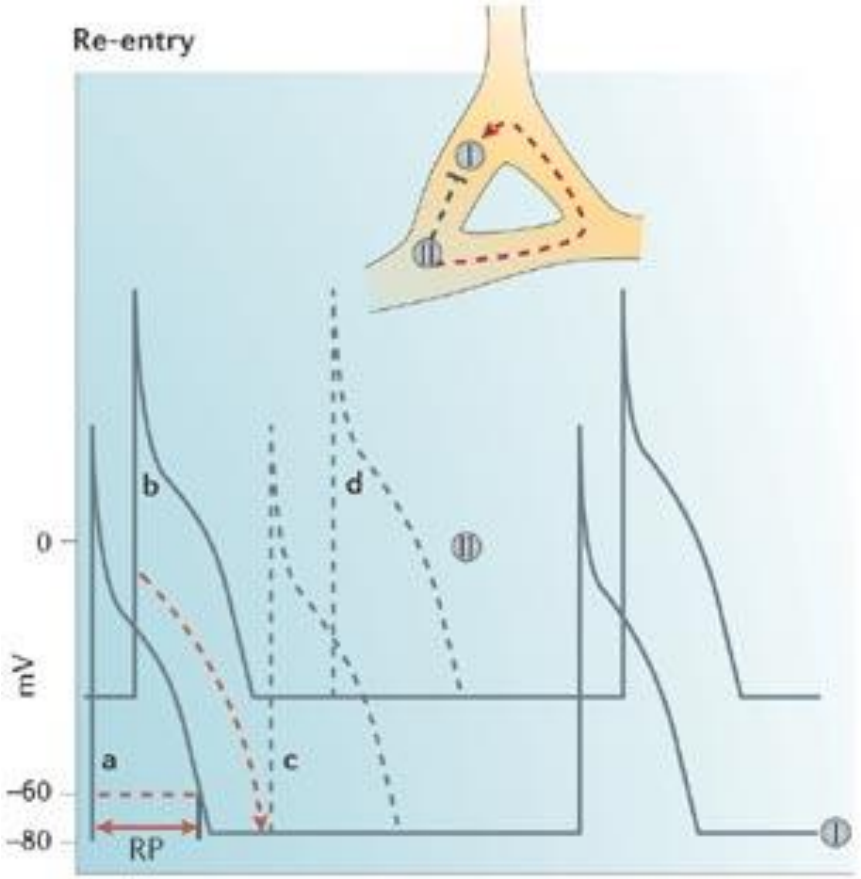
Kleber and Rudy 2004 Physiological Reviews 84 431-488

Reentry

- Excitable gap

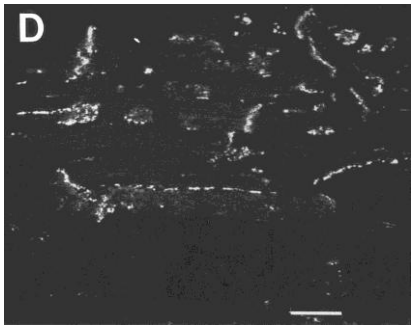
- Anatomical
  - Infarction scar / fibrosis
  - Purkinje fibres / bundle branches
  - Inexcitability
    - Metabolic sink / block
- Functional
  - Conduction Slowing
  - Repolarisation heterogeneity
    - APD prolongation e.g. long QT
    - Ca^{2+} Alternans = T wave alternans

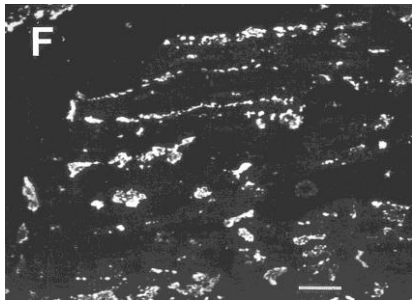
Anatomical Reentry 1

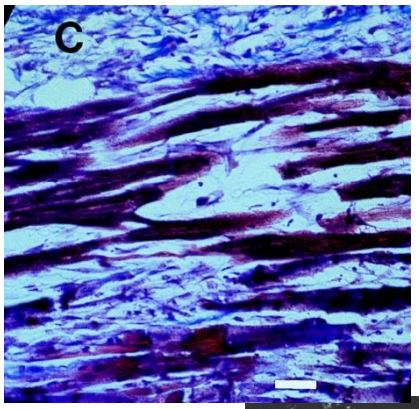


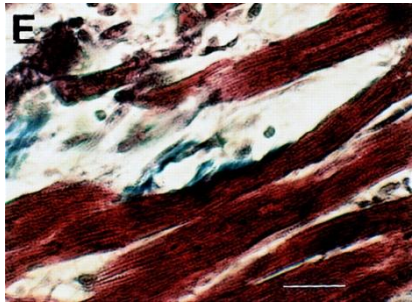
Anatomical Reentry 2

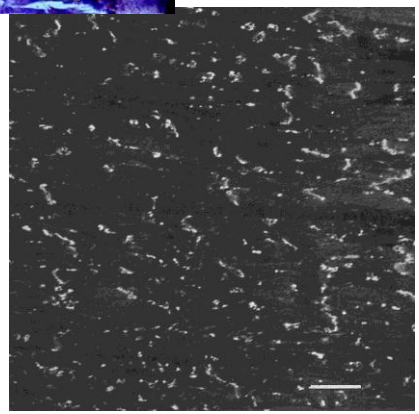
Myocardial Infarction Scar

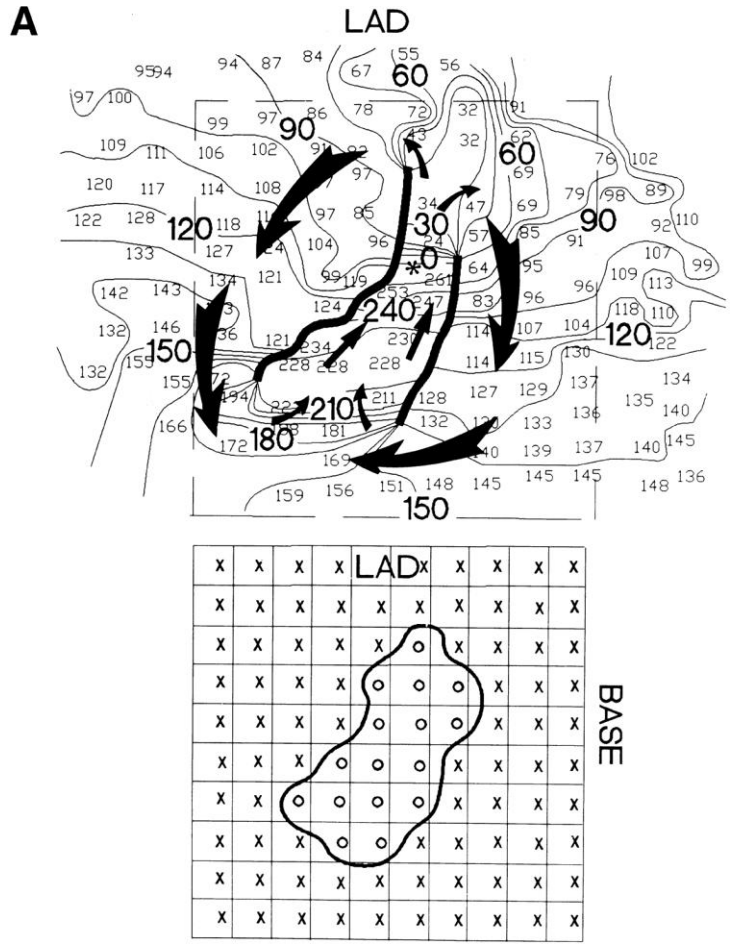










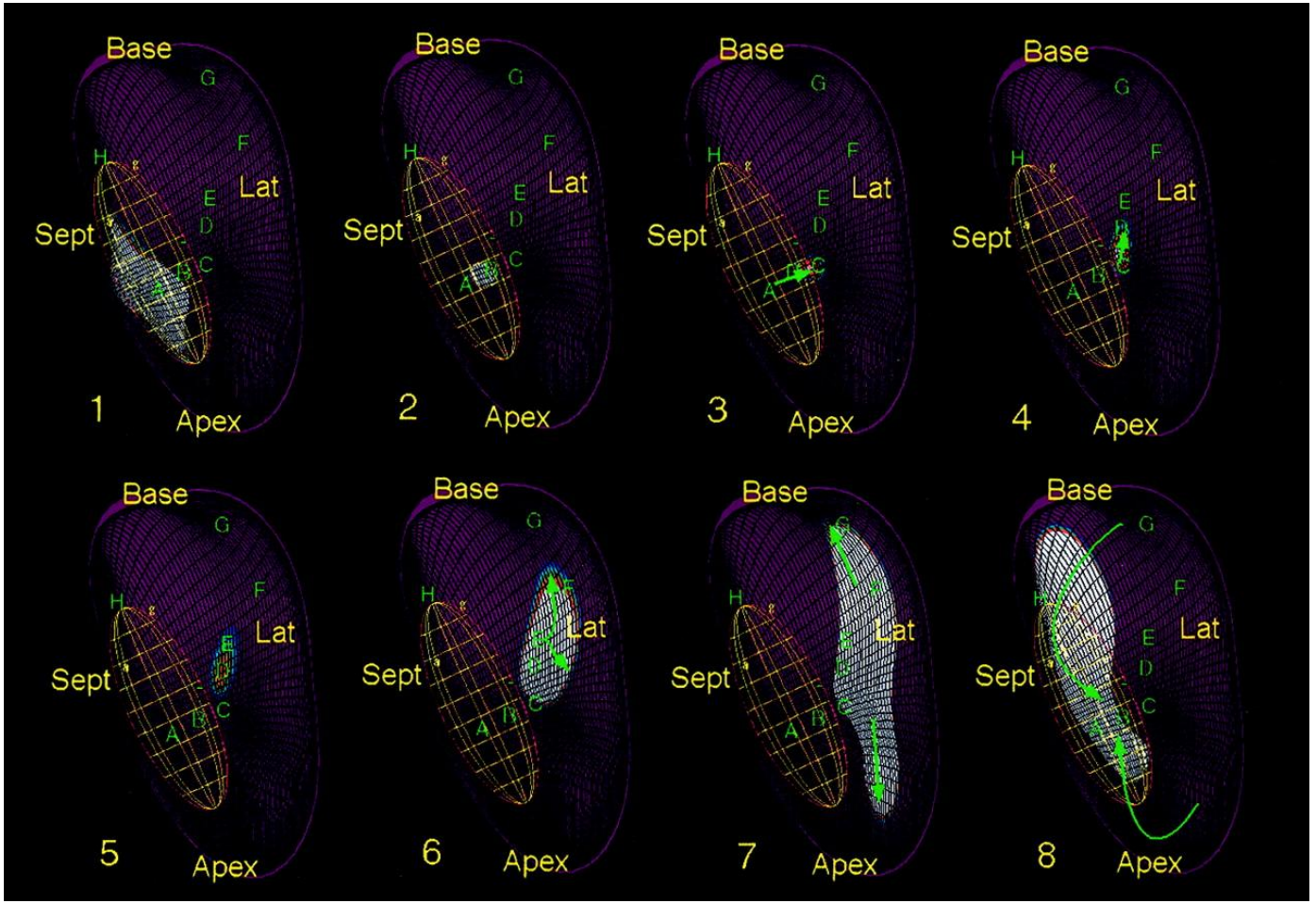


Peters, N. S. et al. Circulation 1997;95:988-996

Anatomical Reentry 2

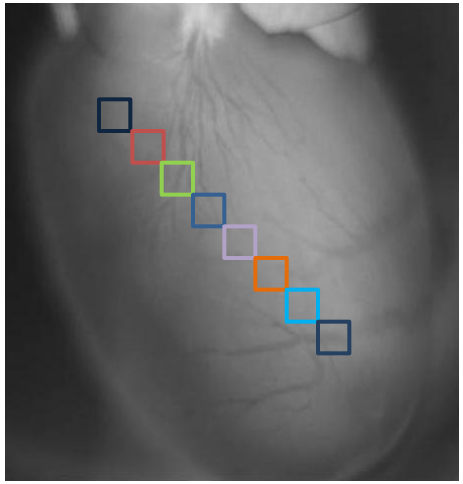
Myocardial Infarction Scar

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

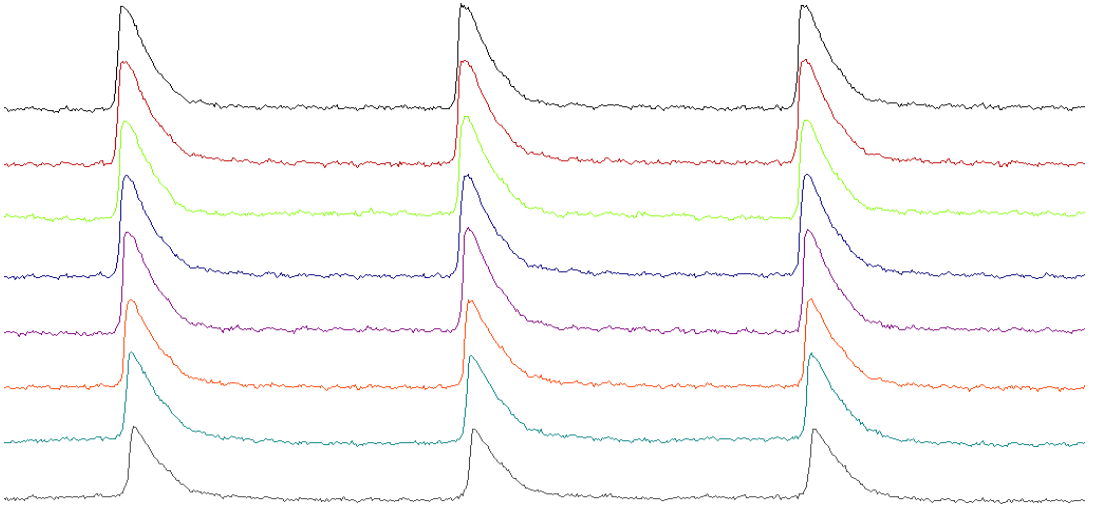


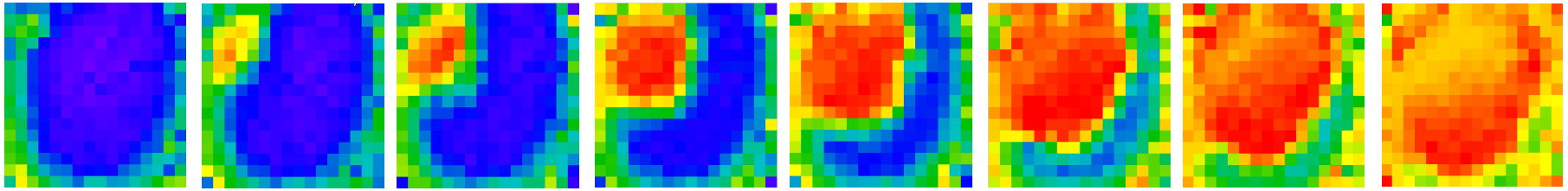
Chow, A. W.C. et al. Circulation 2002;105:2172-2178

Methods - Optical mapping



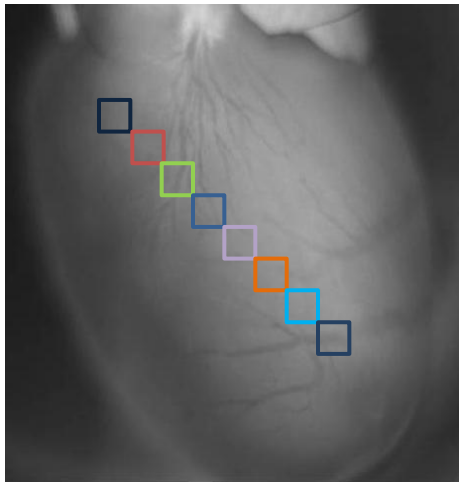
Optical Action Potentials for selected pixels

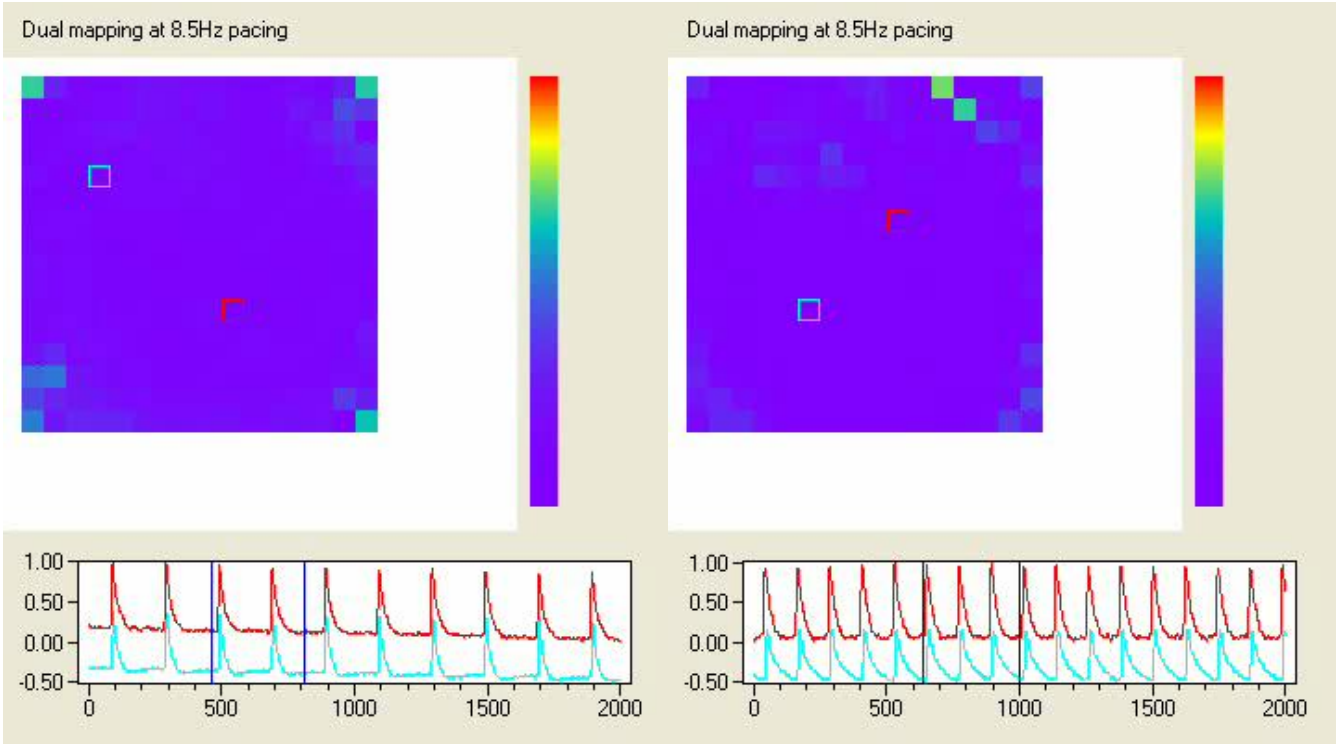




0 ms 2 ms 4 ms 6 ms 8 ms 10 ms 12 ms 14 ms

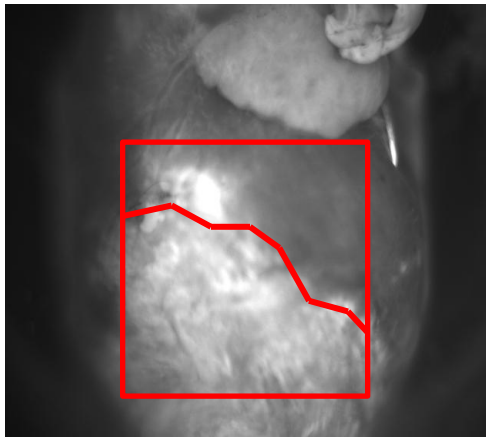
Optical mapping
Voltage-Sensitive Fluorescent Dyes



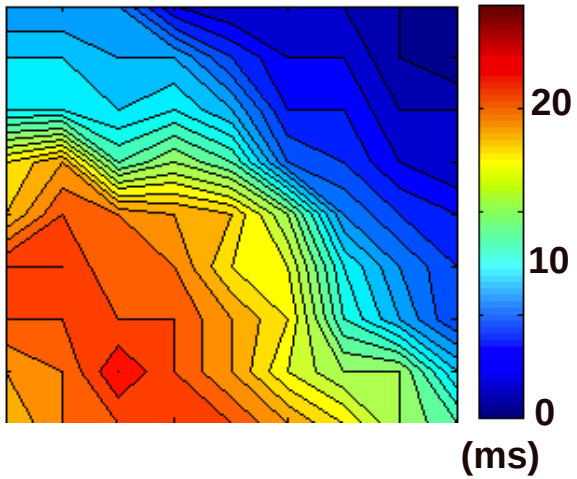


Optical Mapping of Chronically Infarcted Hearts

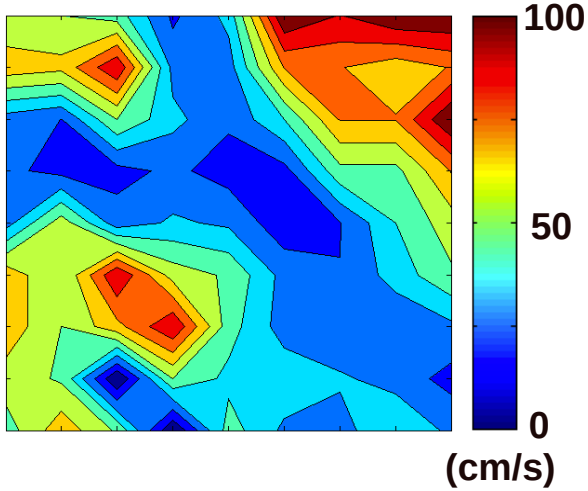
Heart in mapping chamber



Local Activation Map (Isochronal Map)

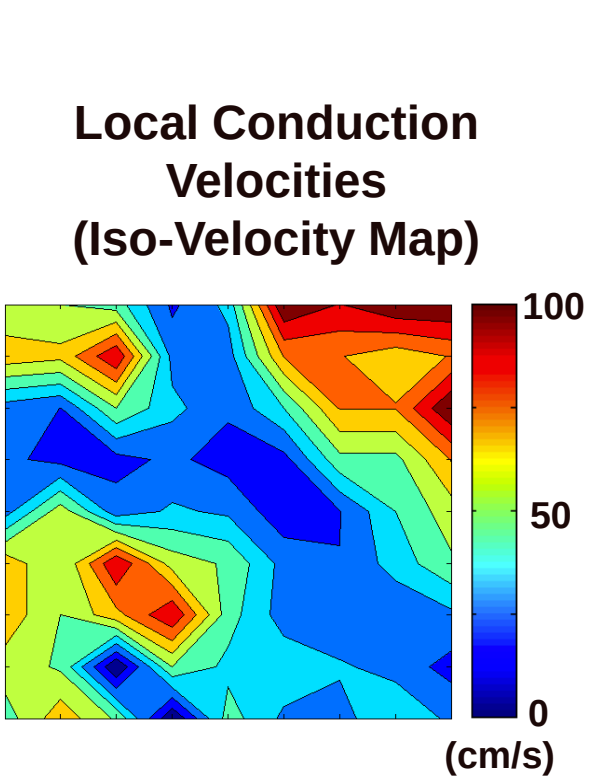


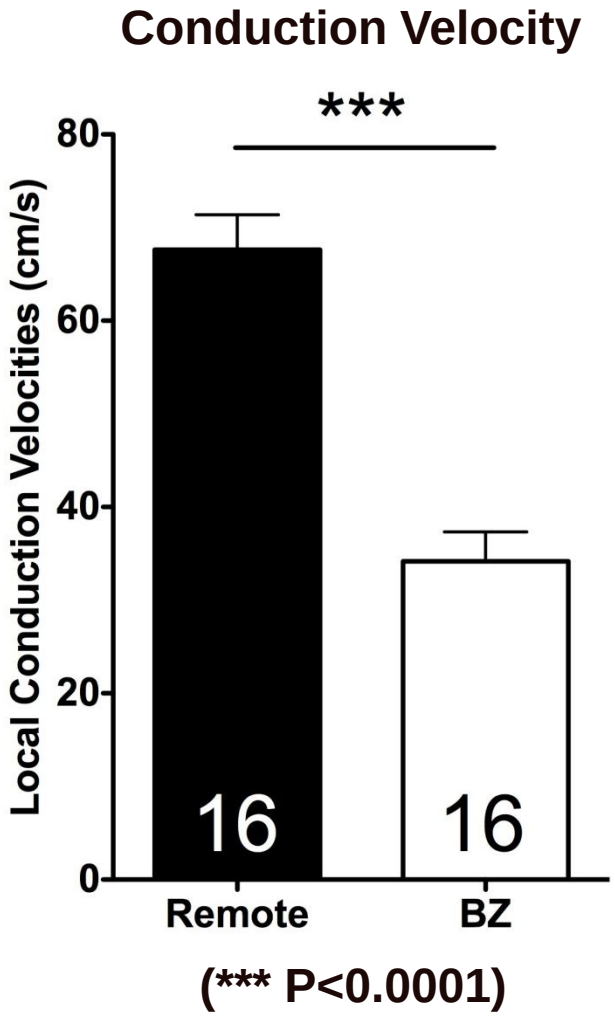
Local Conduction Velocities (Iso-Velocity Map)



Non-infarcted: >50cm/s
BZ: 15-25 cm/s
Infarct: Variable

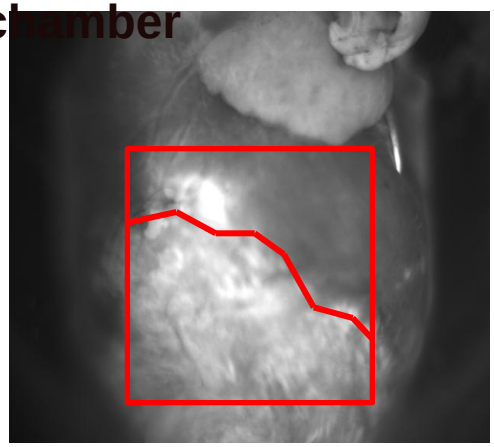
Slower Conduction Velocities at Infarct Border Zone



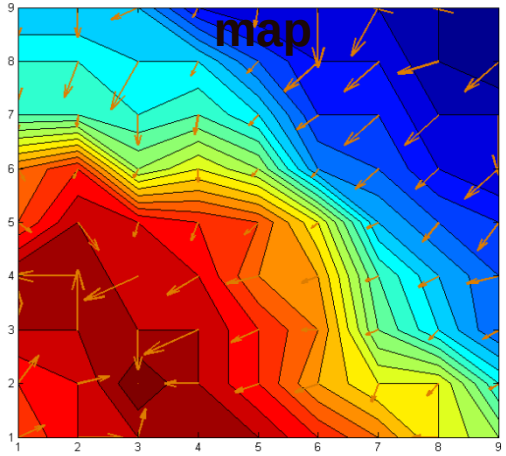


Local Activation Vectors and Conduction Velocities

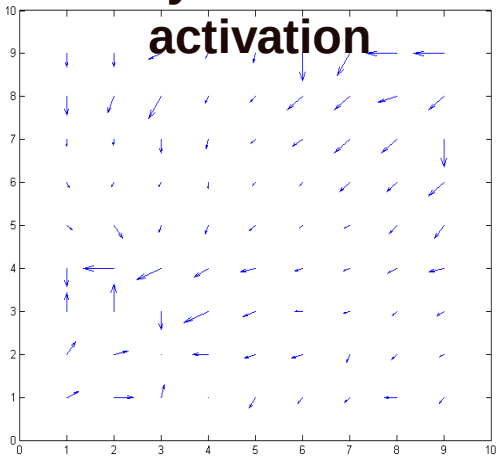
Heart in mapping chamber



CV Vectors superimposed on isochronal activation map



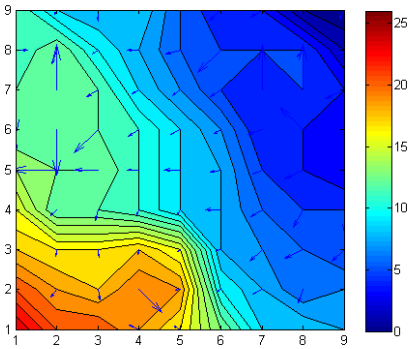
Local Conduction Velocity and vector of activation



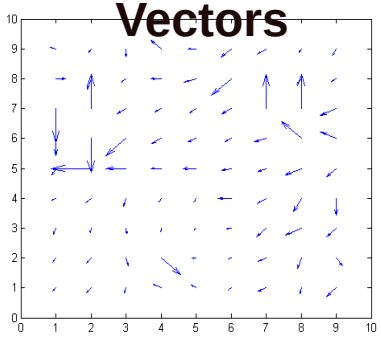
- Length of arrow proportional to CV
- Direction of arrow denotes direction of activation

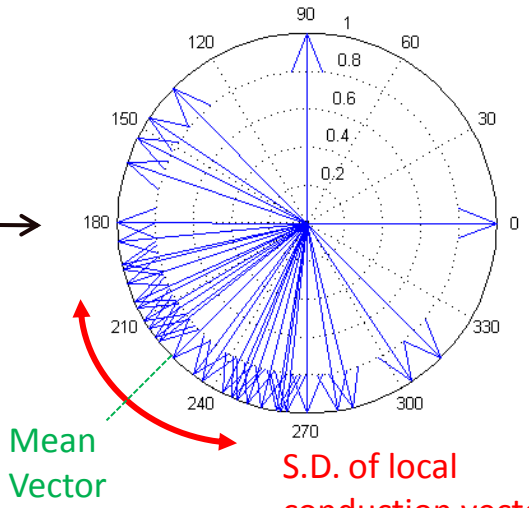
Assessing Dispersion of Local Conduction Velocities

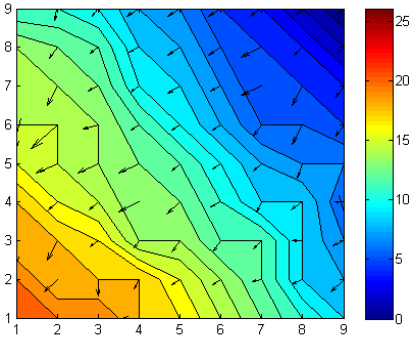
Activation Maps (Isochronal Map)

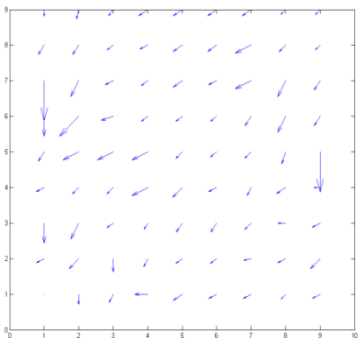


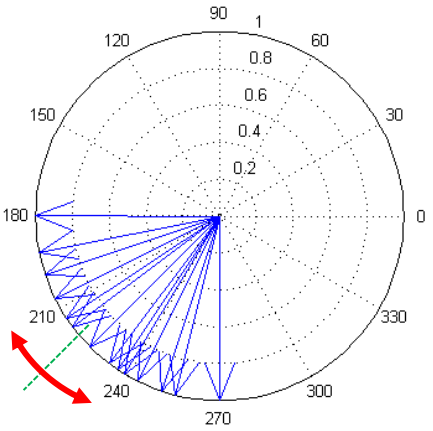
Local Conduction Vectors



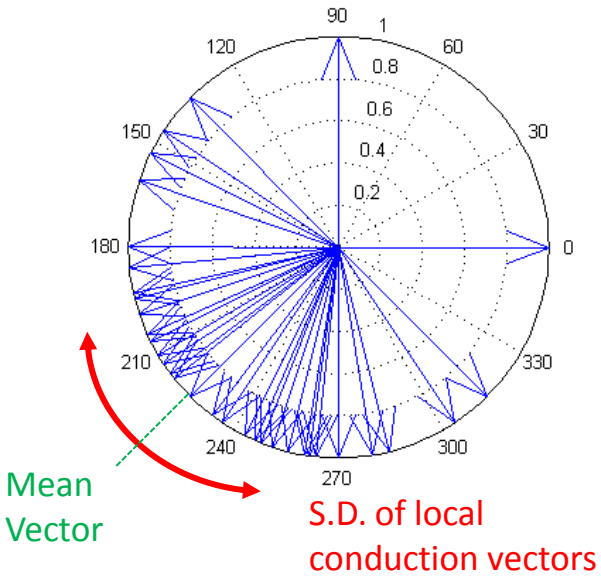


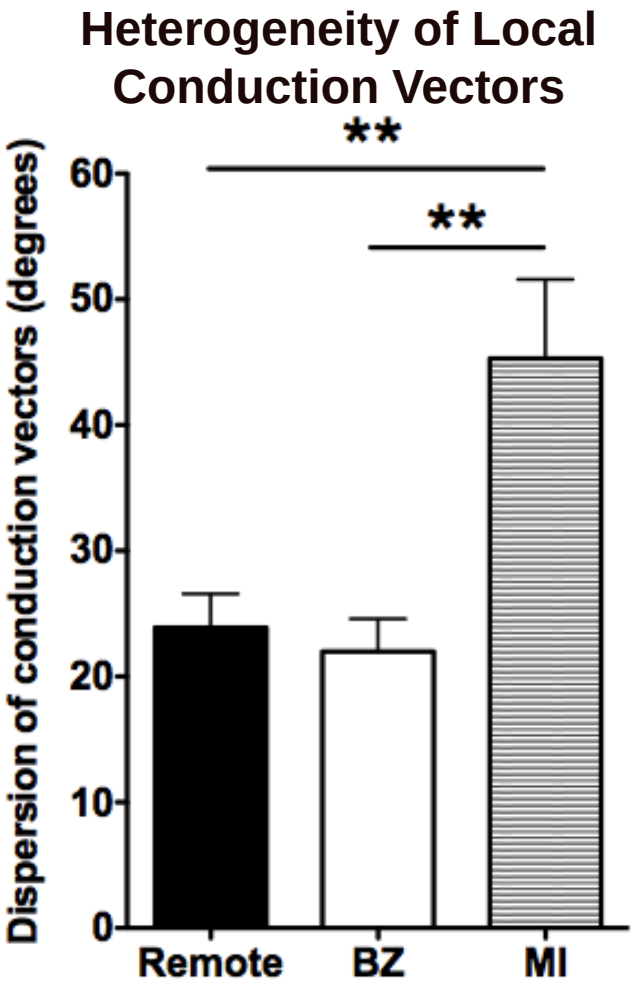






Heterogeneous Conduction Vectors in Infarct Zone





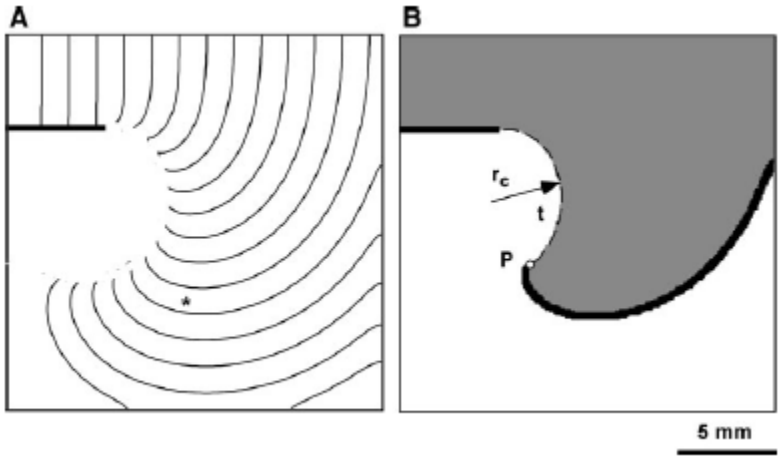
(ANOVA P<0.001, Post-hoc t-test ** P<0.01)

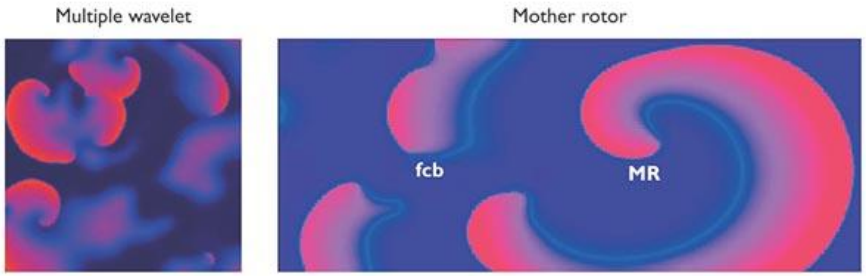
Action Potential Propagation in Cardiac cellular networks-Structure Function Relationships

- 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

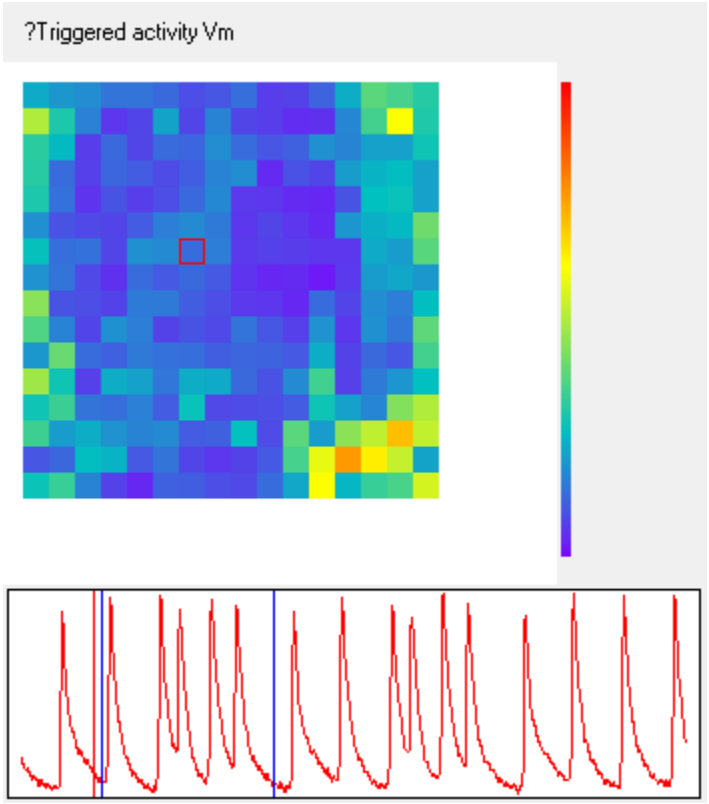
- Wavebreak occurs at points of functional conduction slowing/block
- Occurs at highest curvature, where greatest source-sink mismatch
- Resulting wave forms a rotor
  - 2D = spiral wave
  - 3D = scroll wave
- Short cycle length with resulting fast tachycardia





Optical Mapping Arrhythmias

Triggered Activity



Ventricular Fibrillation