Intramural Virtual Electrodes

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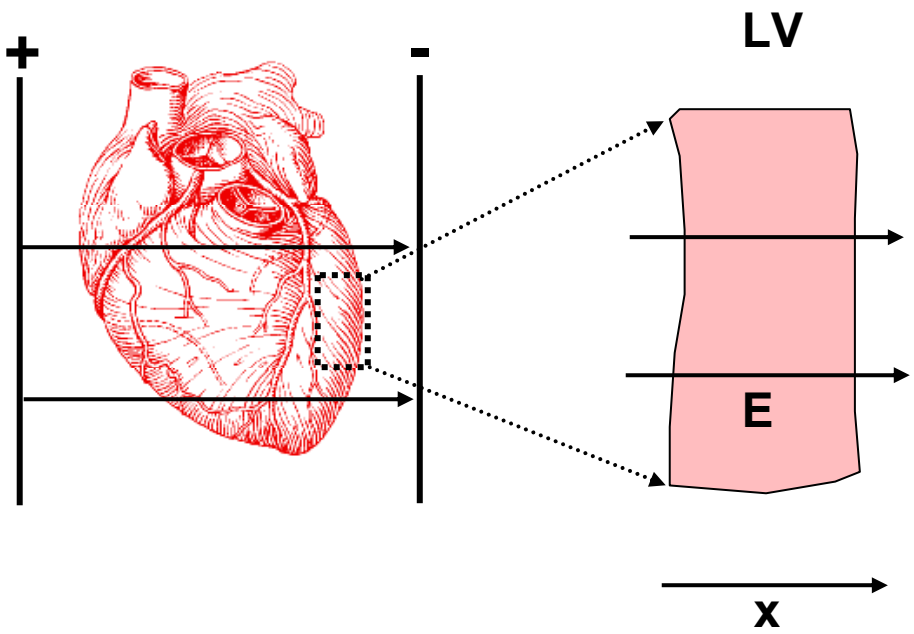
Mechanism of defibrillation

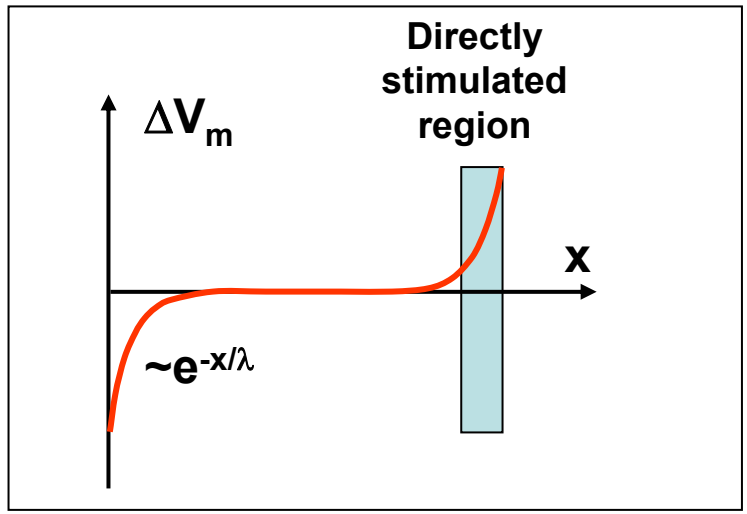
- "Defibrillation requires … ***depolarizing a large number of multiple asynchronous reentrant circuits***" (Hurst's The Heart, 10th edition, 2001, p.933)
- "The current penetrates most of the fibers of the ventricles at the same time, thus ***stimulating essentially all parts of the ventricles simultaneously***" (Textbook of Medical Physiology, Guyton AC & Hall JE,10th edition, 2000, p.140)

How does a shock depolarize and stimulate all parts of the ventricles simultaneously?

Shock stimulation

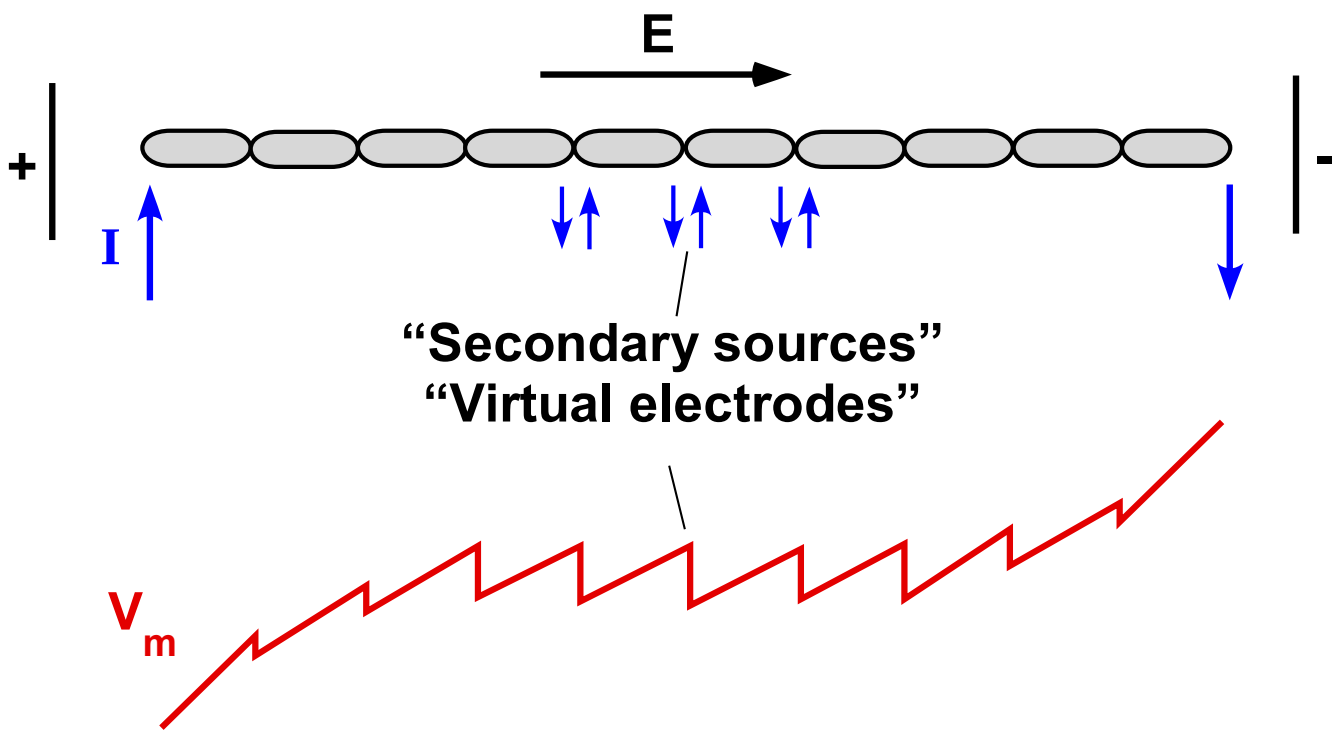


Cable model



1. **A shock does not only depolarize, it also hyperpolarizes**
2. **V_m is not changed in the majority of intramural tissue**
3. **A shock can stimulate only a narrow sub-surface region on the cathodal side of the wall**

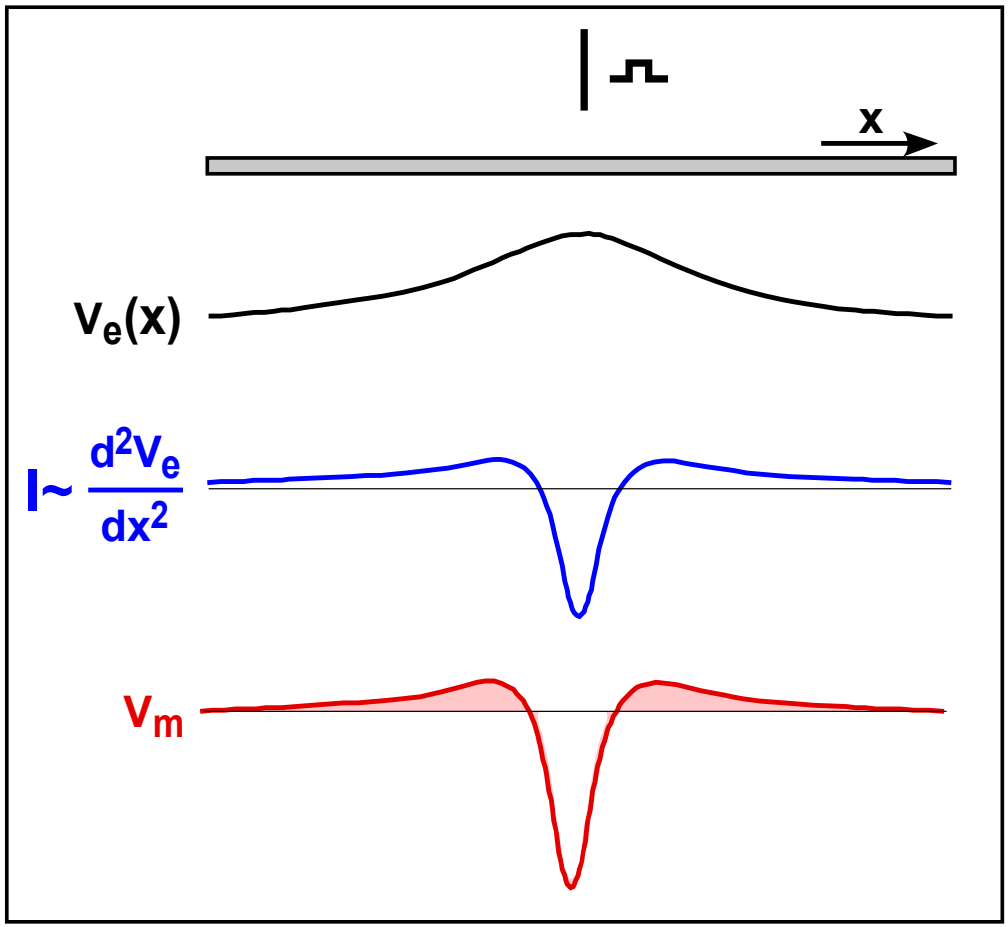
Mechanisms of Virtual Electrodes
1. Resistive barriers



Plonsey and Barr, Med Biol Eng Comput, 1986
Krassowska et al, IEEE Trans Biomed Eng, 1987

Mechanisms of Virtual Electrodes
2. Non-uniform shock field

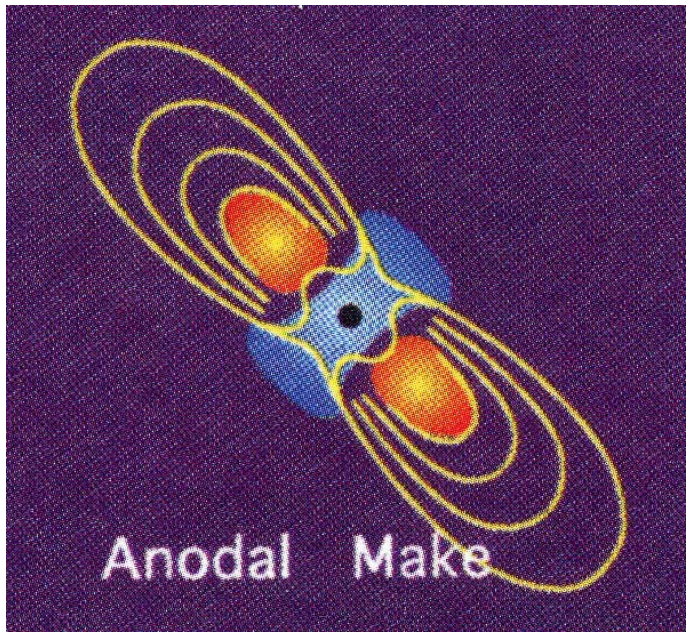
Local current application in 1D cable model



“Activating function”
Rattay, IEEE Trans Biomed Eng,1989

Mechanisms of Virtual Electrodes
2. Non-uniform shock field

Local current application in 2D anisotropic bidomain model

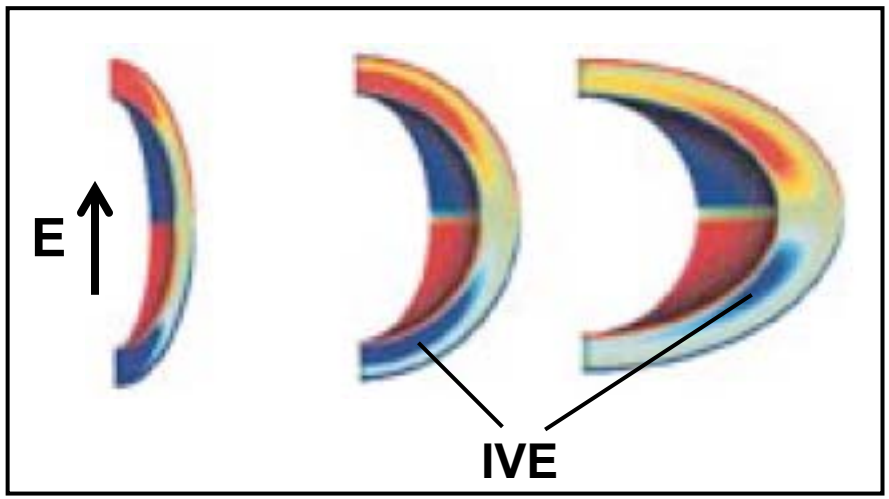


Wikswo et al, Biophys J, 1995

Sepulveda et al, Biophys J, 1989
Knisley et al, Biophys J, 1994
Wikswo et al, Biophys J, 1995

Mechanisms of Virtual Electrodes
3. Changing fiber orientation

Uniform field application in 3D anisotropic bidomain LV model



Entcheva et al, IEEE Trans Biomed Eng,1999

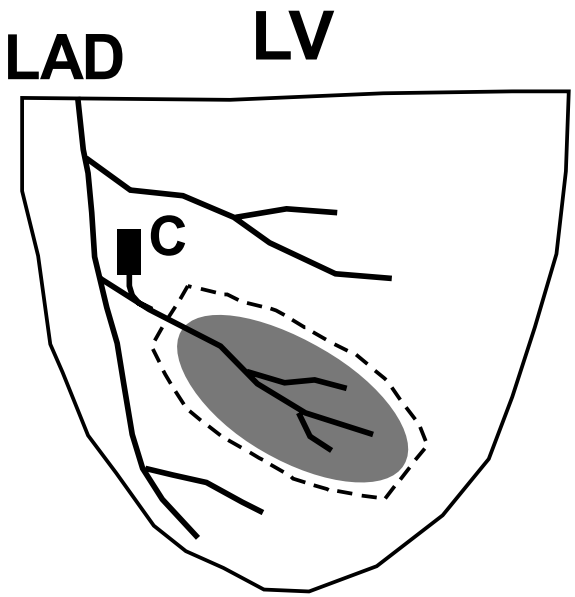
- Intramural virtual electrodes are formed where fiber orientation rapidly changes with respect to electric field

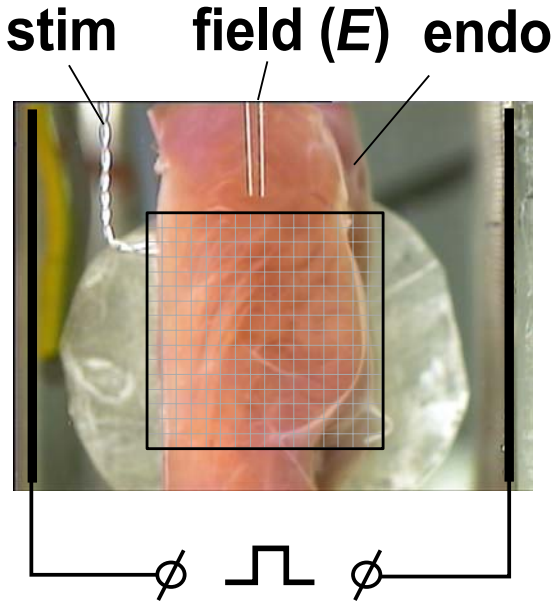
Trayanova et al, 1993; 1998; 2001
Roth, 1994
Entcheva et al, 1998; 1999
Efimov et al, 2000

Questions about IVE for experiments

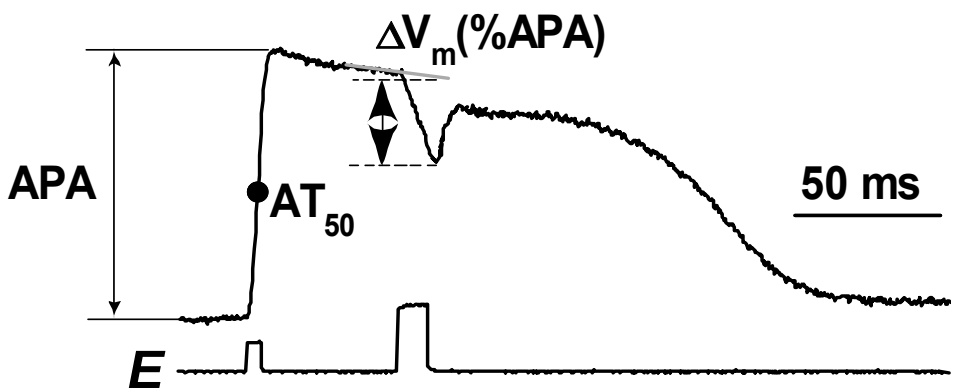
1. Do IVE really exist in the heart?
2. Can IVE cause simultaneous tissue activation?
3. What is the mechanism of IVE?

Optical Mapping of Intramural V_m in Wedge Preparations

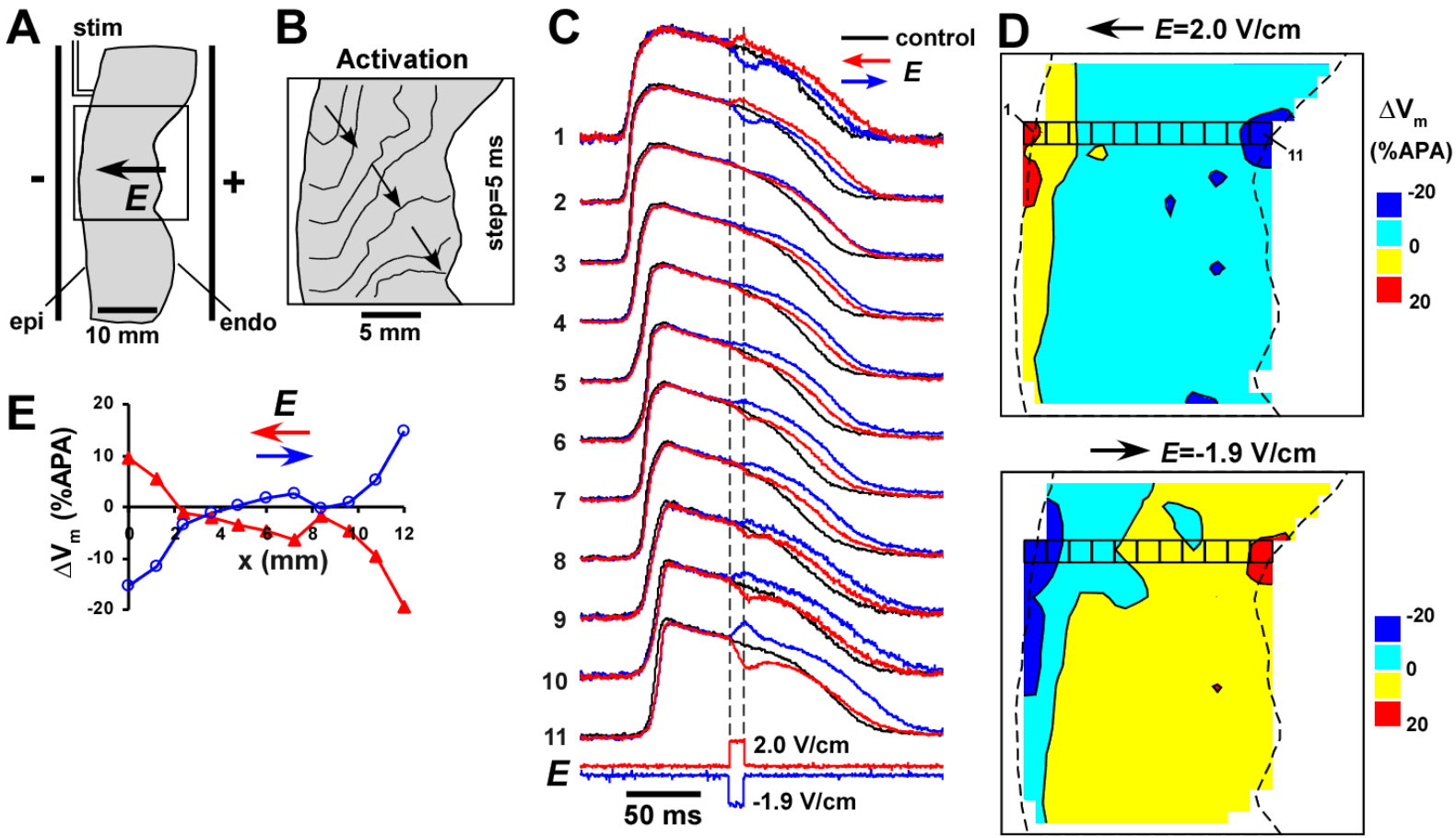




Δx=1.2 mm

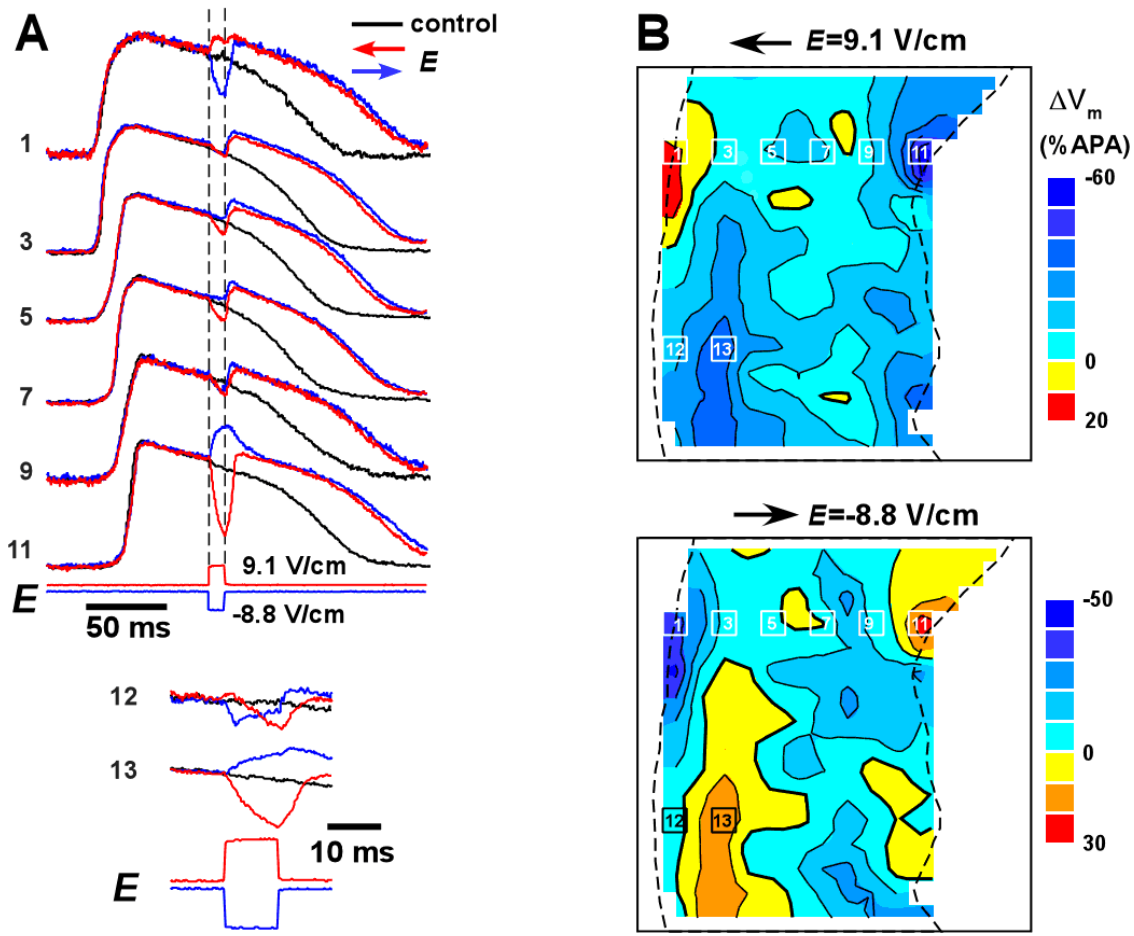


Intramural ΔV_m: Weak shocks



Fast et al, Circulation, 2002

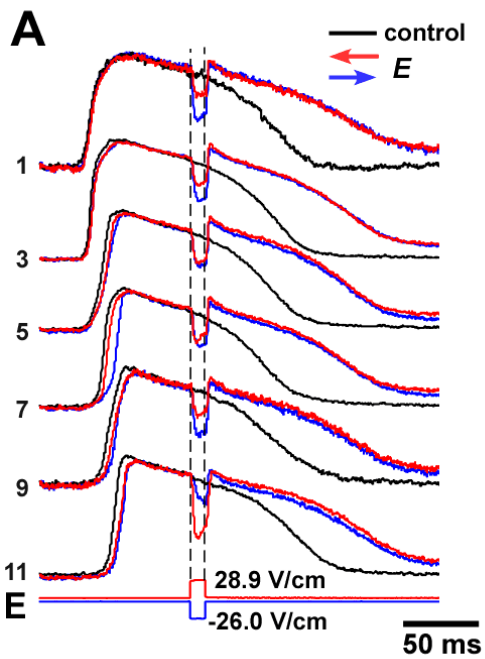
Intramural ΔV_m: Intermediate shocks

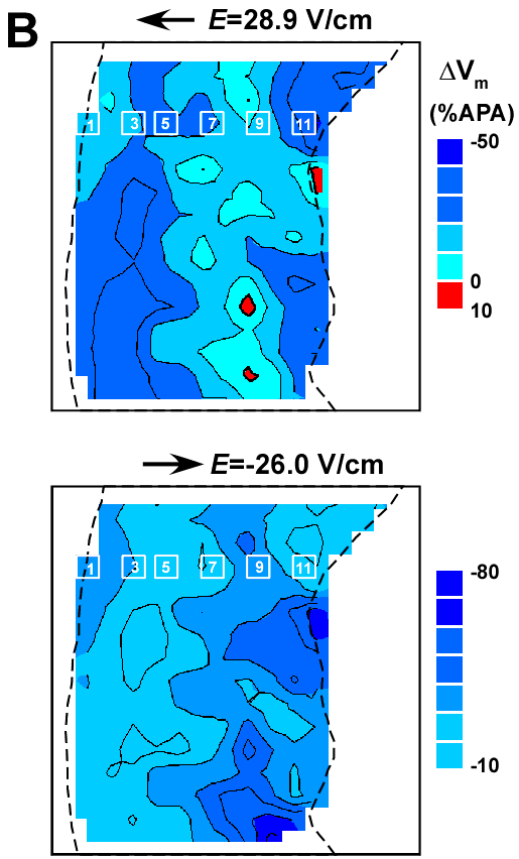


1. Significant non-uniform intramural ΔV_m
2. ΔV_m are asymmetric: $\Delta V^-_m > \Delta V^+_m$
3. ΔV^-_m extend to the cathodal side
4. APD is prolonged for both ΔV^+_m and ΔV^-_m

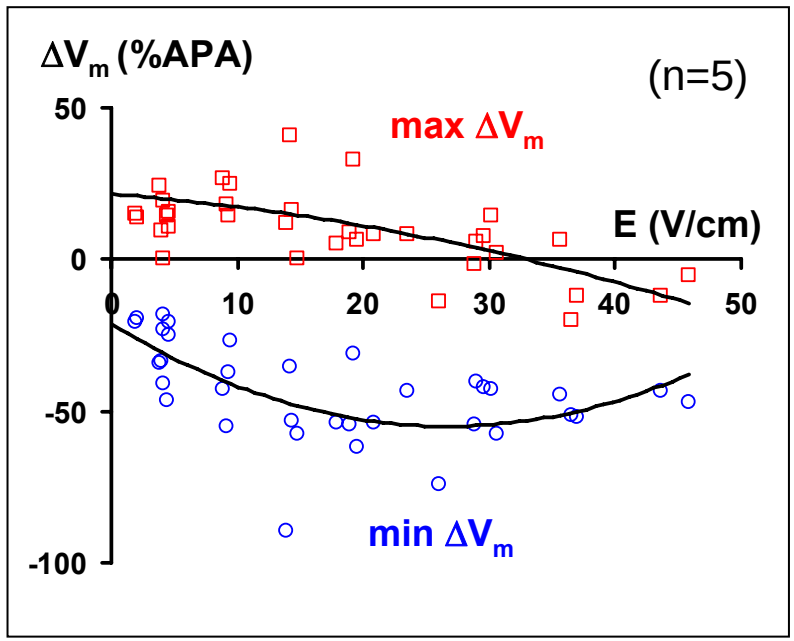
Fast et al, Circulation, 2002

Intramural ΔV_m: Strong shocks





Globally negative intramural ΔV_m for both shock polarities

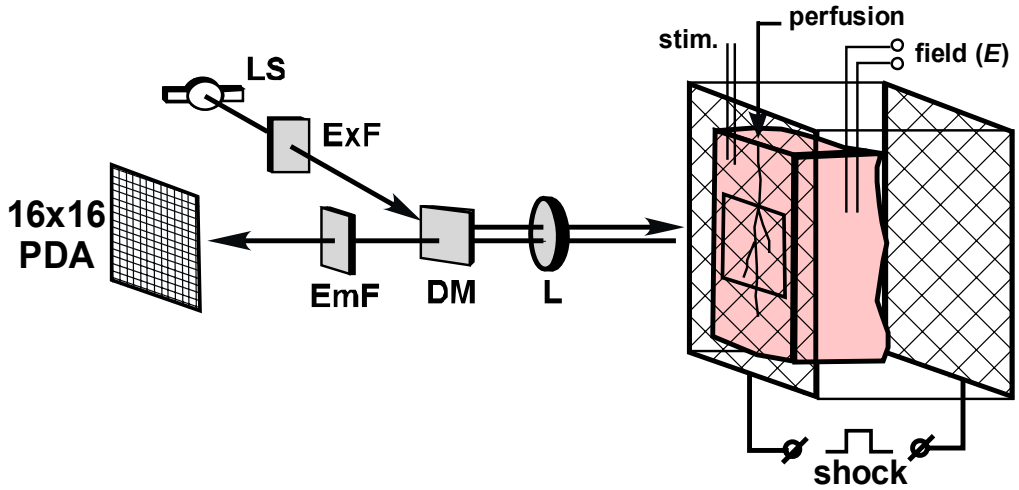


Fast et al, Circulation, 2002

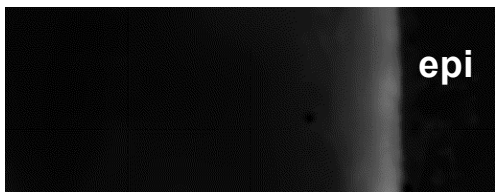
Limitations of the wedge preparation

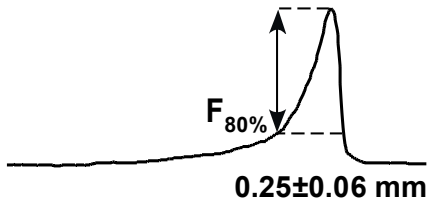
1. Cut transmural surface
2. Boundary conditions

Mapping of IVE from intact epicardial surface



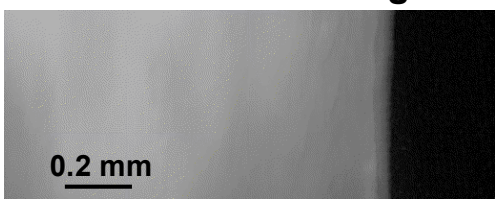
1. Surface Staining

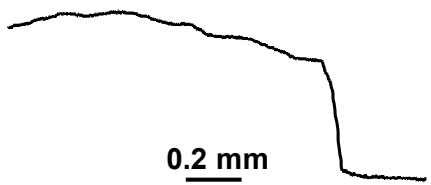




Signal collection depth < 0.25 mm

2. Global Staining

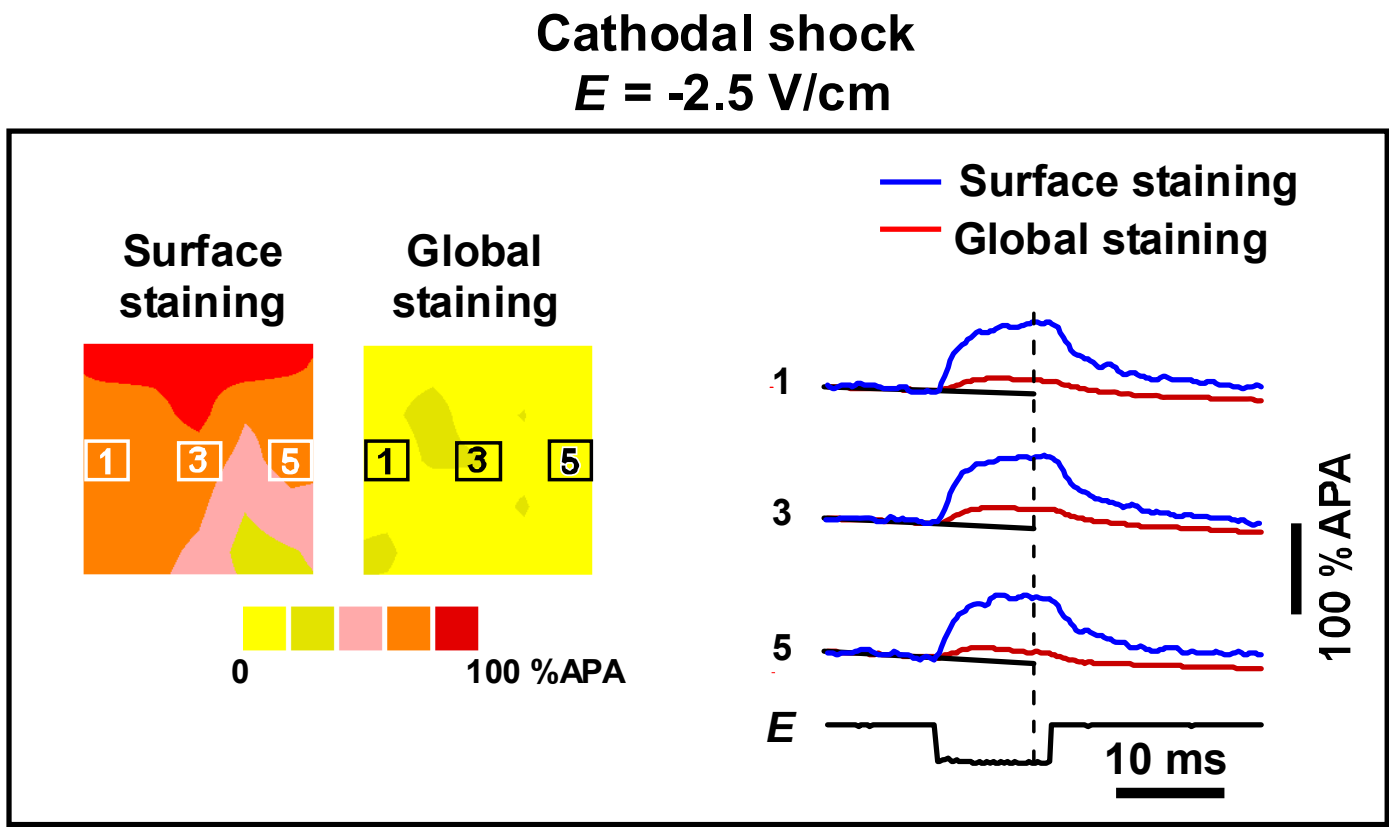




Signal collection depth ≈ 1.2 mm
(Ding et al, 2001)

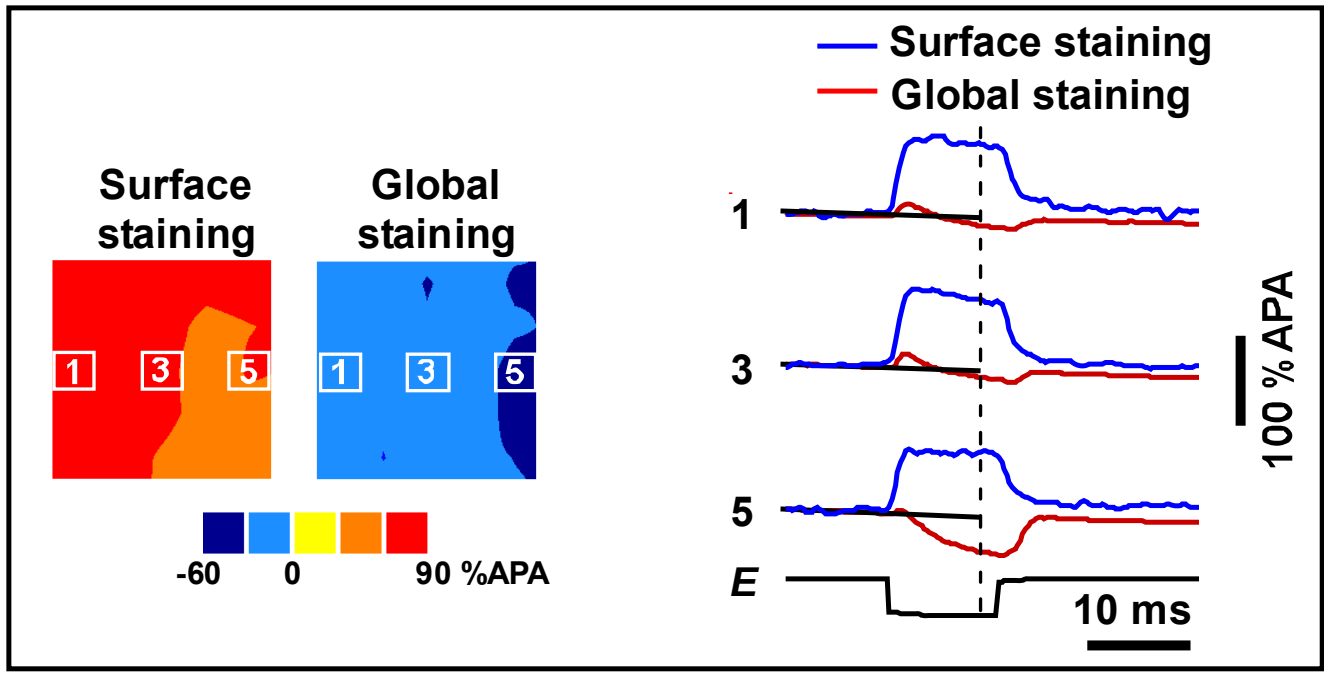
Sharifov & Fast, Circulation, 2004
Sharifov & Fast, Heart Rhythm, 2006

Epicardial SS vs GS ΔV_m
Weak shocks



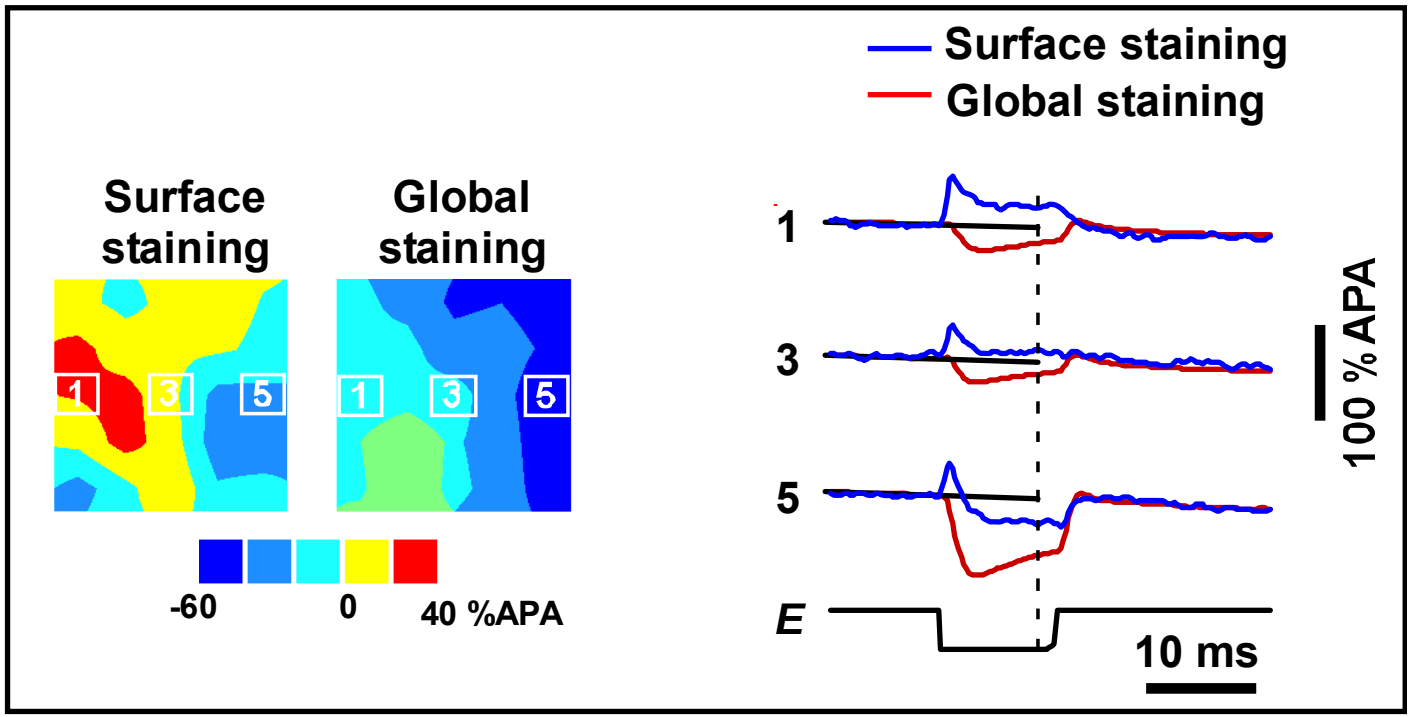
Epicardial SS vs GS ΔV_m
Intermediate shocks

Cathodal shock
***E* = -12 V/cm**

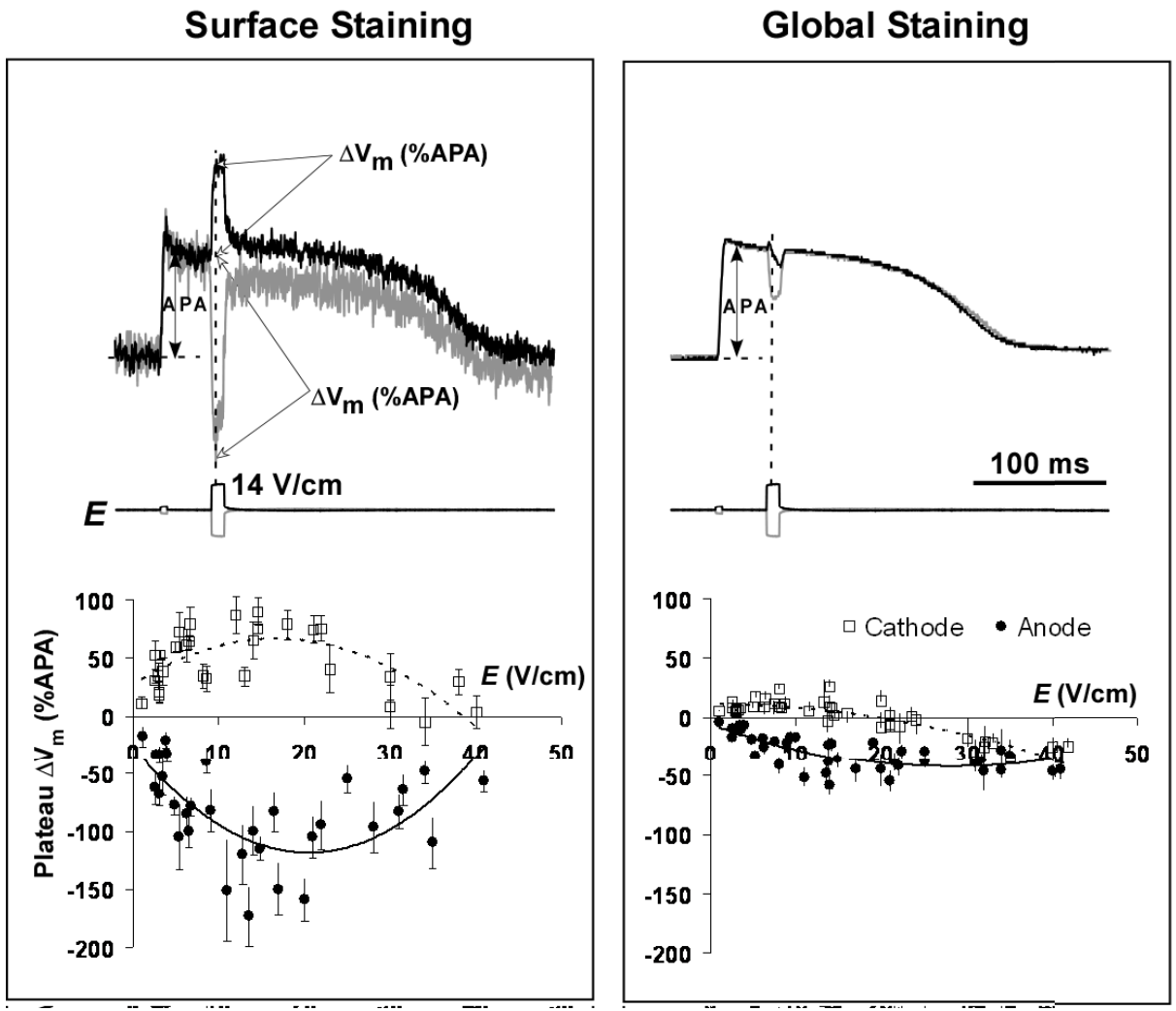


Epicardial SS vs GS ΔV_m
Strong shocks

Cathodal shock
***E* = -30 V/cm**



Epicardial SS vs GS ΔV_m



Sharifov & Fast, Heart Rhythm, 2006

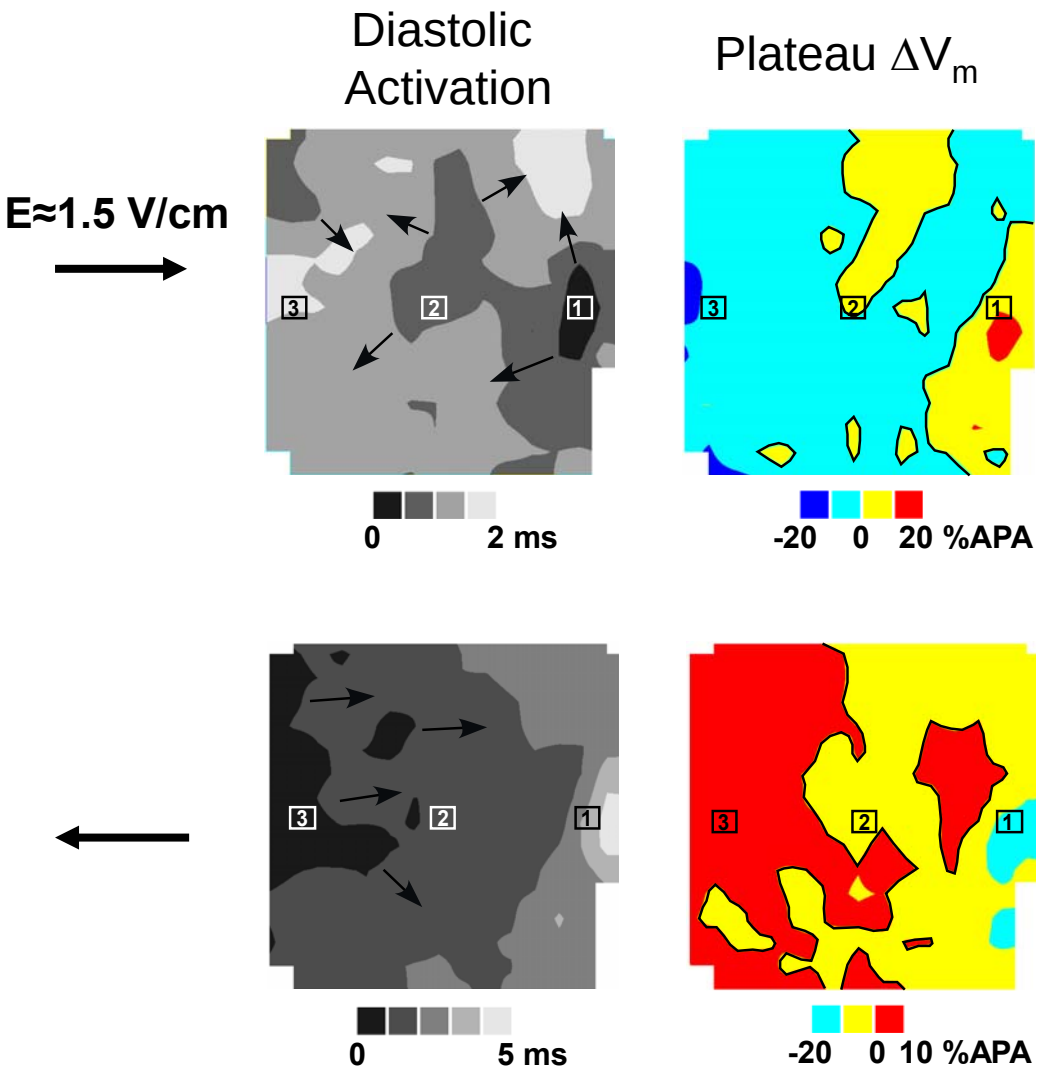
Conclusion 1

Results of both transmural and epicardial mapping experiments indicate that shocks produce intramural virtual electrodes

Questions

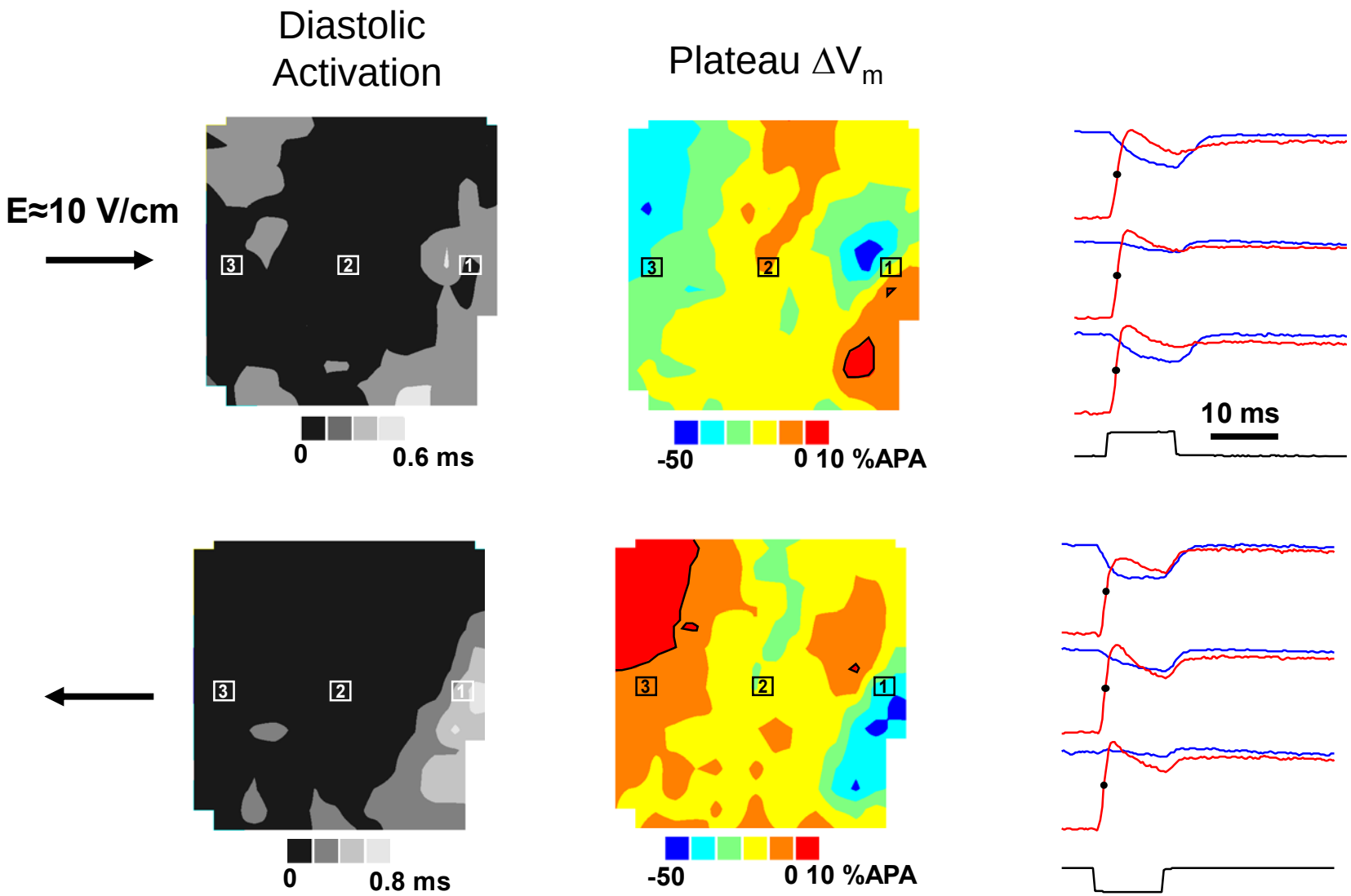
1. Do IVE really exist in the heart?
2. **Can IVE cause simultaneous tissue activation?**
3. What is the mechanism of IVE?

Intramural activation: Weak shocks



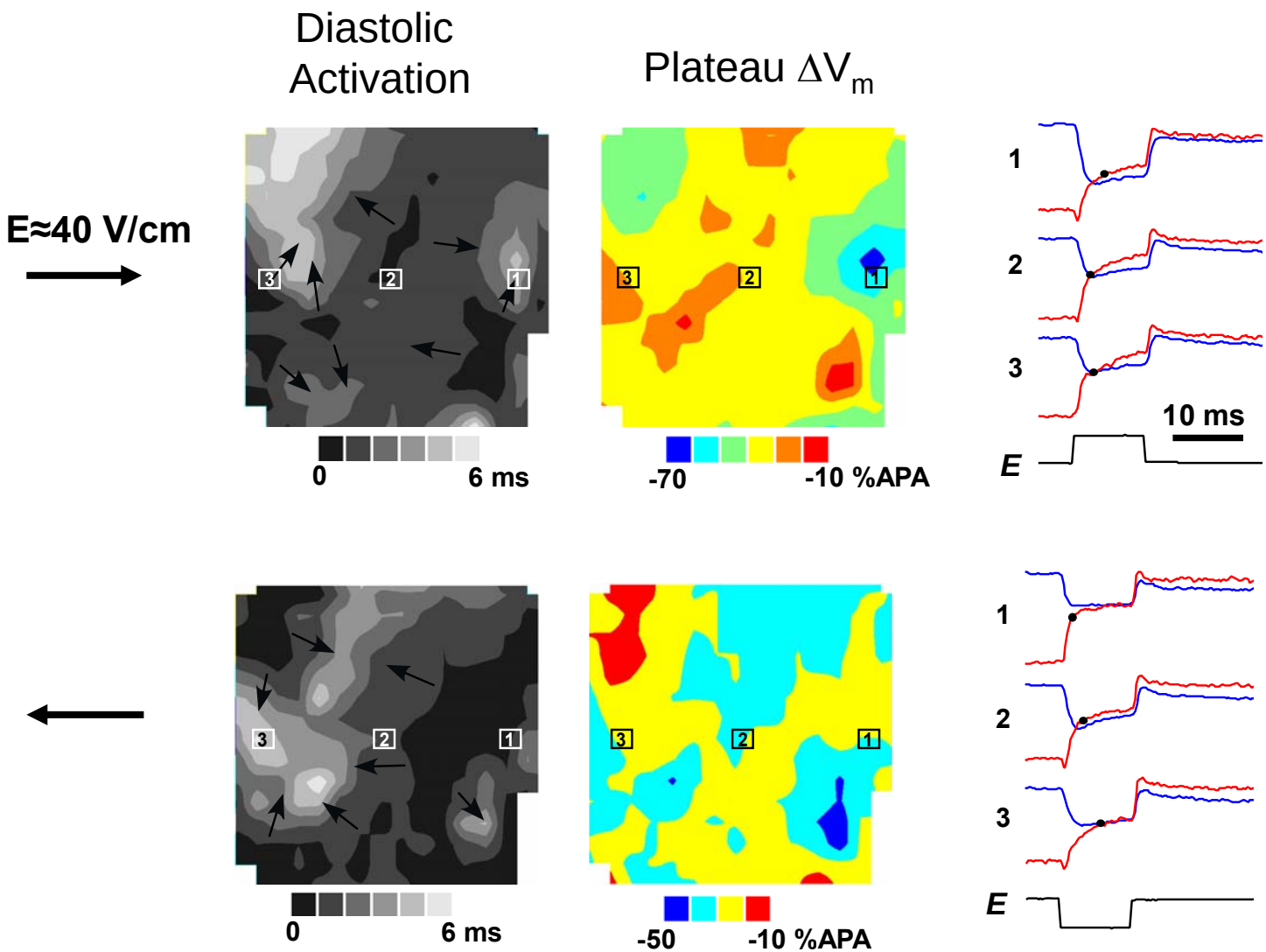
Sharifov & Fast, JCE, 2003

Intramural activation: Intermediate shocks



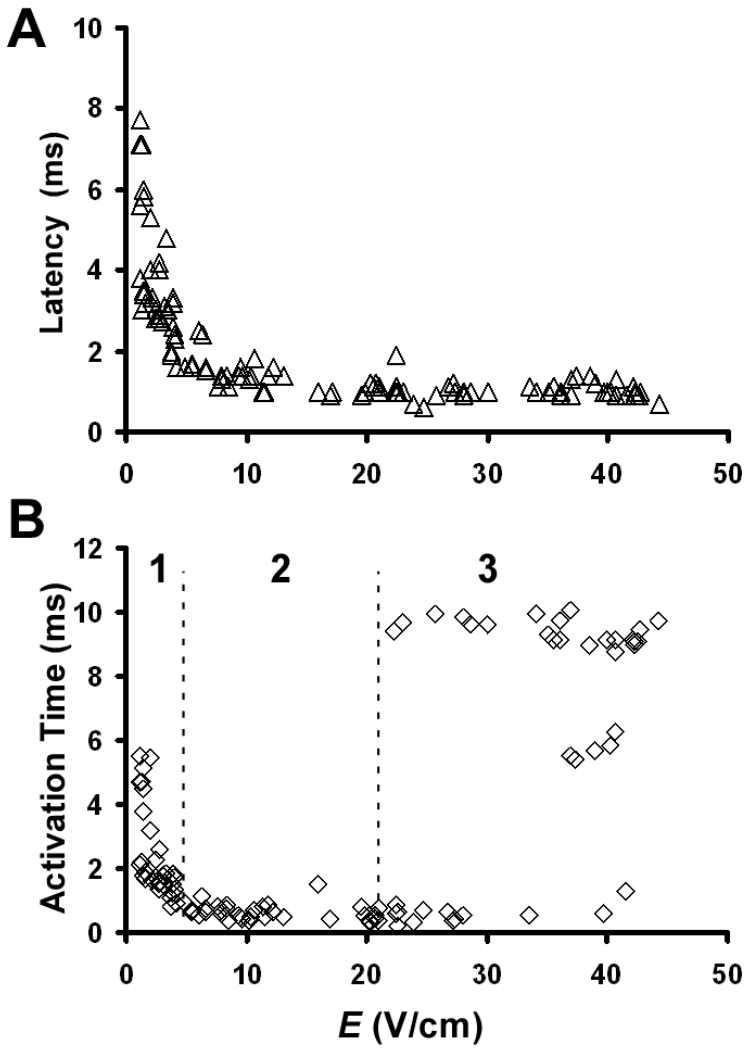
Sharifov & Fast, JCE, 2003

Intramural activation: Strong shocks



Sharifov & Fast, JCE, 2003

Latency and time of intramural activation



Sharifov & Fast, JCE, 2003

Conclusion 2

Shocks applied during diastole cause direct and rapid activation of the intramural myocardium over a wide range of shock strength due to formation of lVE

Questions

1. Do IVE really exist in the heart?
2. Can IVE cause simultaneous tissue activation?
3. **What is the mechanism of IVE?**

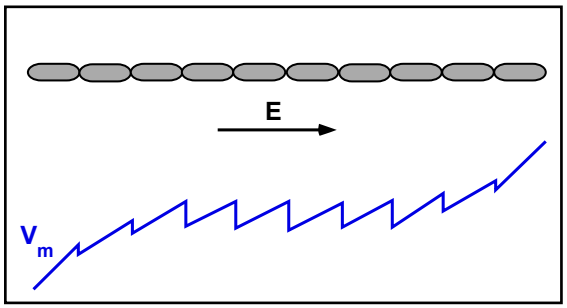
Why are all plateau ΔV_m negative during strong shocks?

Hypothesis

- Shocks produce both positive and negative ΔV_m on a ***microscopic scale***
- Because of the negative asymmetry of V_m response, positive ΔV_m are averaged out in macroscopic optical recordings

The role of cell boundaries in IVE

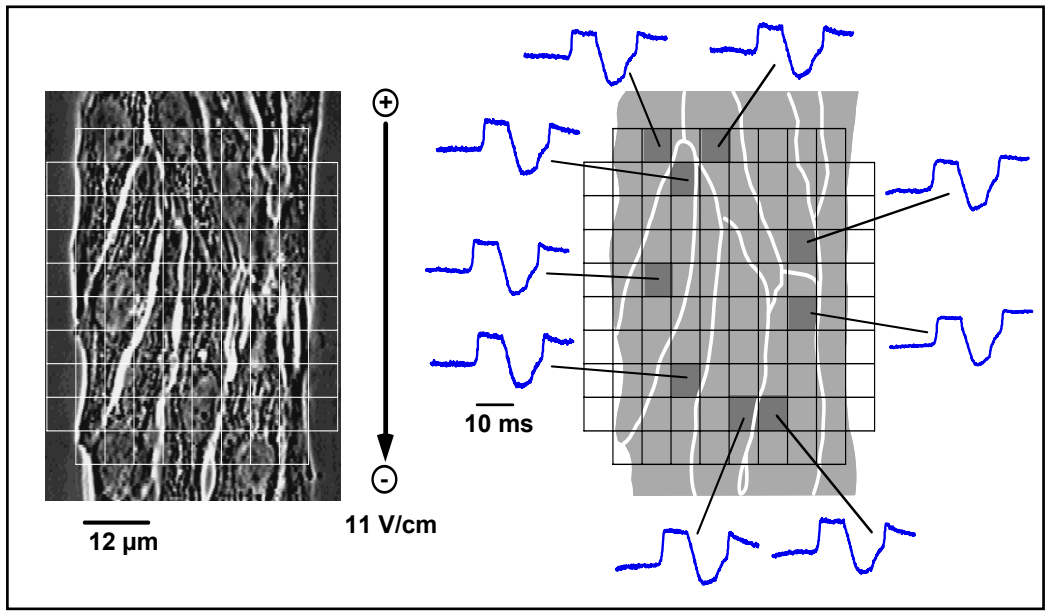
Model



Plonsey and Barr, 1986
Krassowska et al, 1987

Experiments

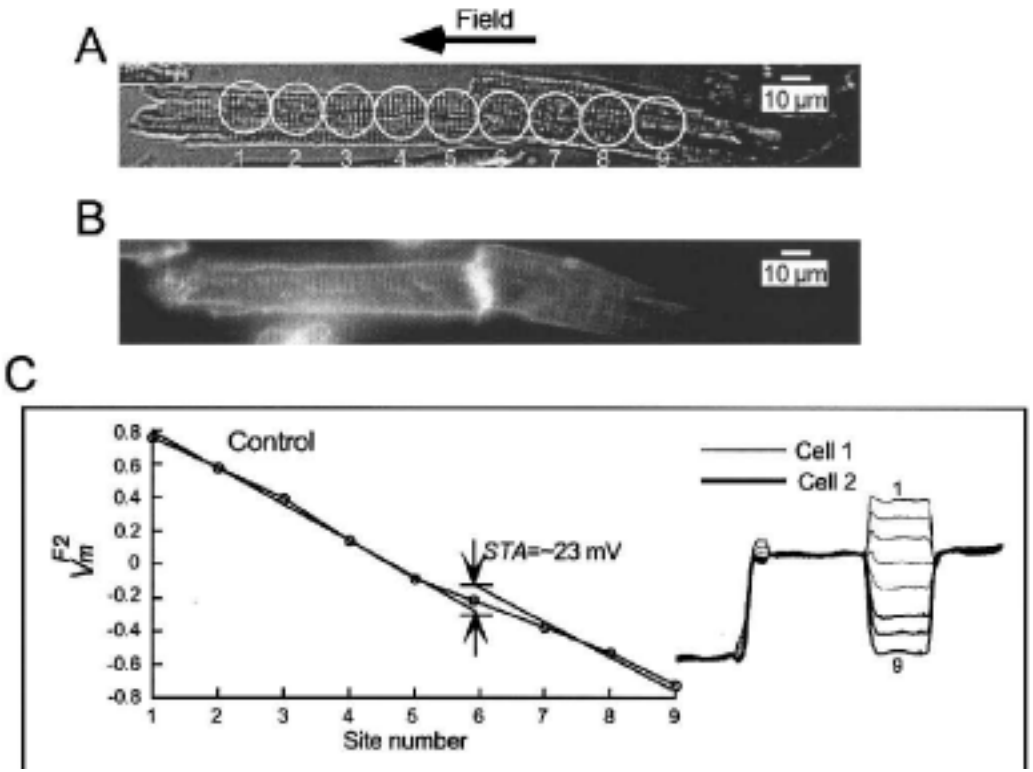
1. Cellular "saw-tooth" ΔV_m were not observed in cell cultures (Gillis et al, Circ Res, 1996)



2. "Saw-tooth" ΔV_m were not found in microelectrode measurements (20-µm steps) from porcine LV (Zhou et al, 1998)

The role of cell boundaries in IVE

3. Only small "saw-tooth" ΔV_m were measured in isolated cell pairs (Sharma & Tung, JCE, 2001)

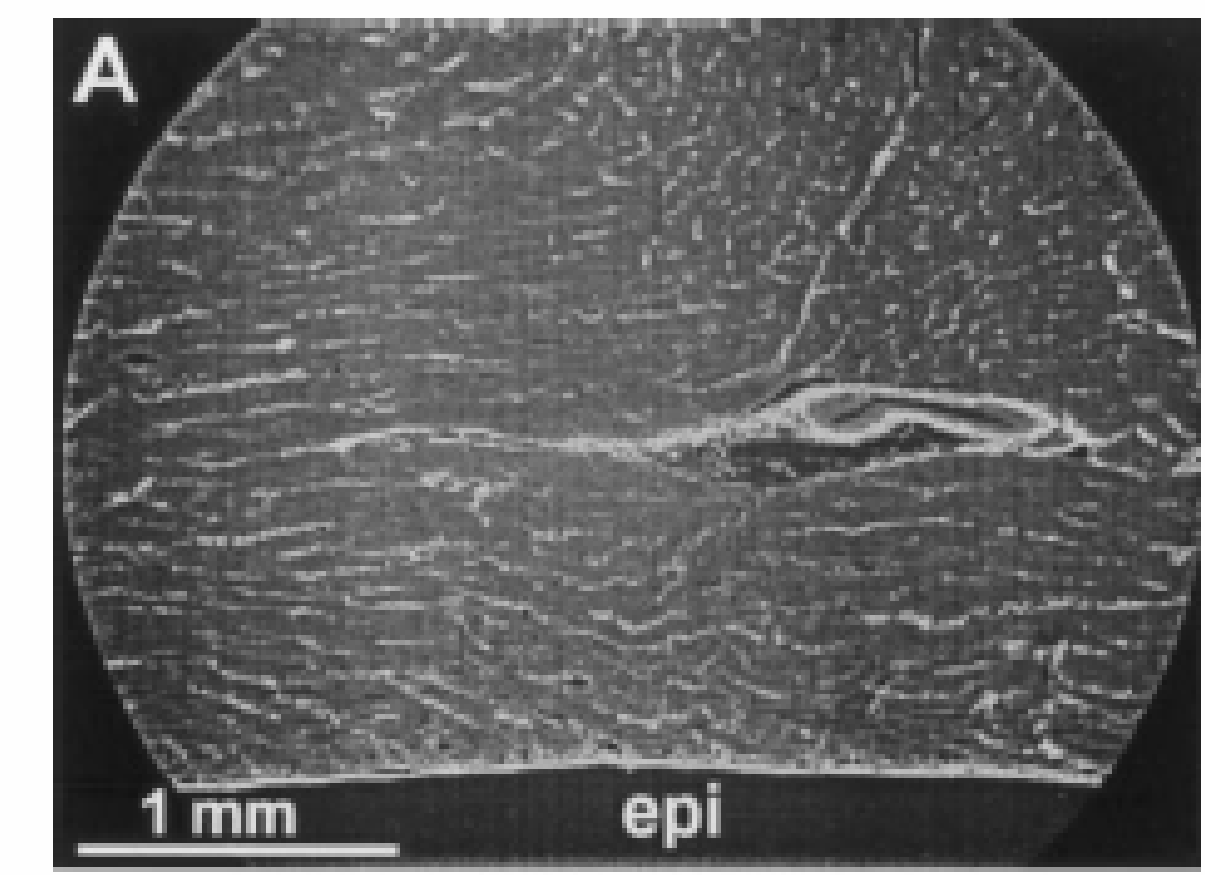


ΔV_m~11 mV

per 10 V/cm

Possible anatomic substrate for IVE

Collagen staining



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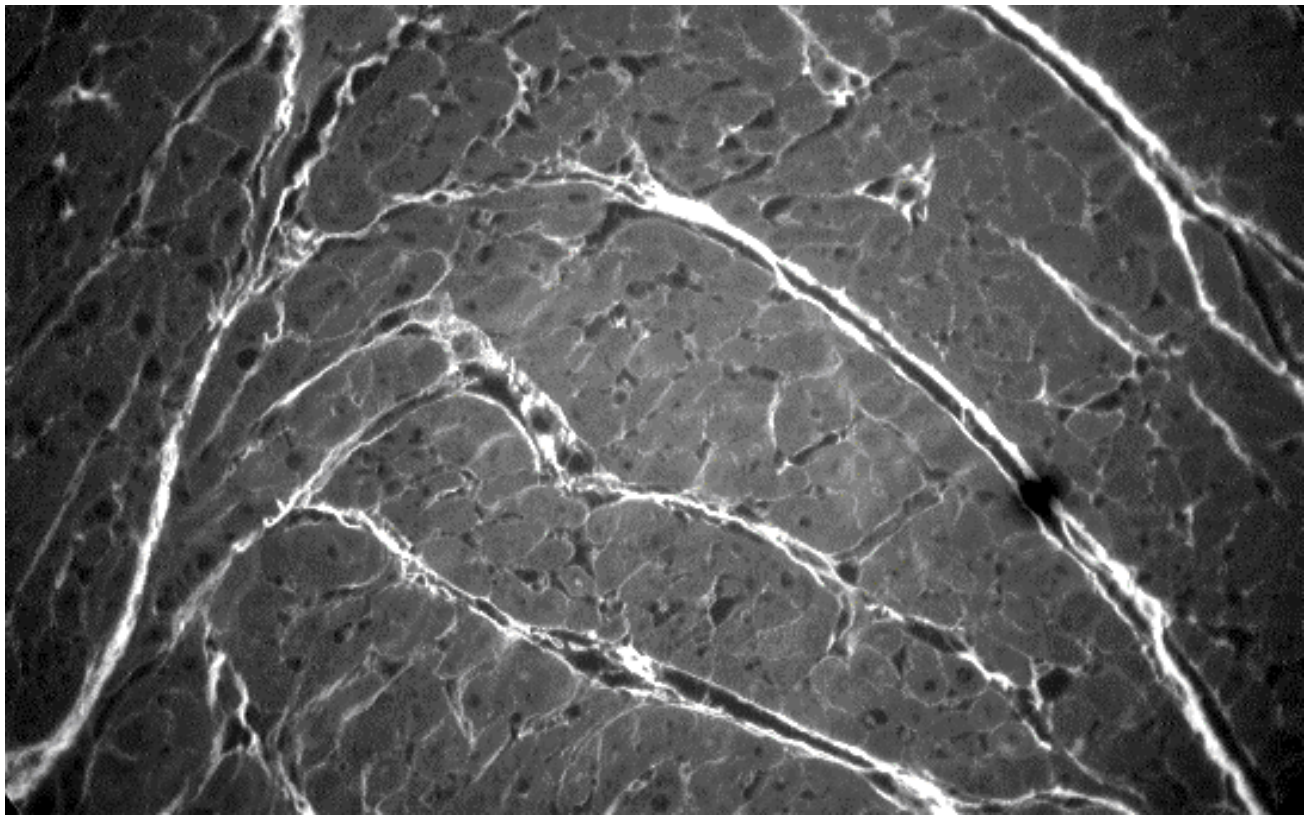
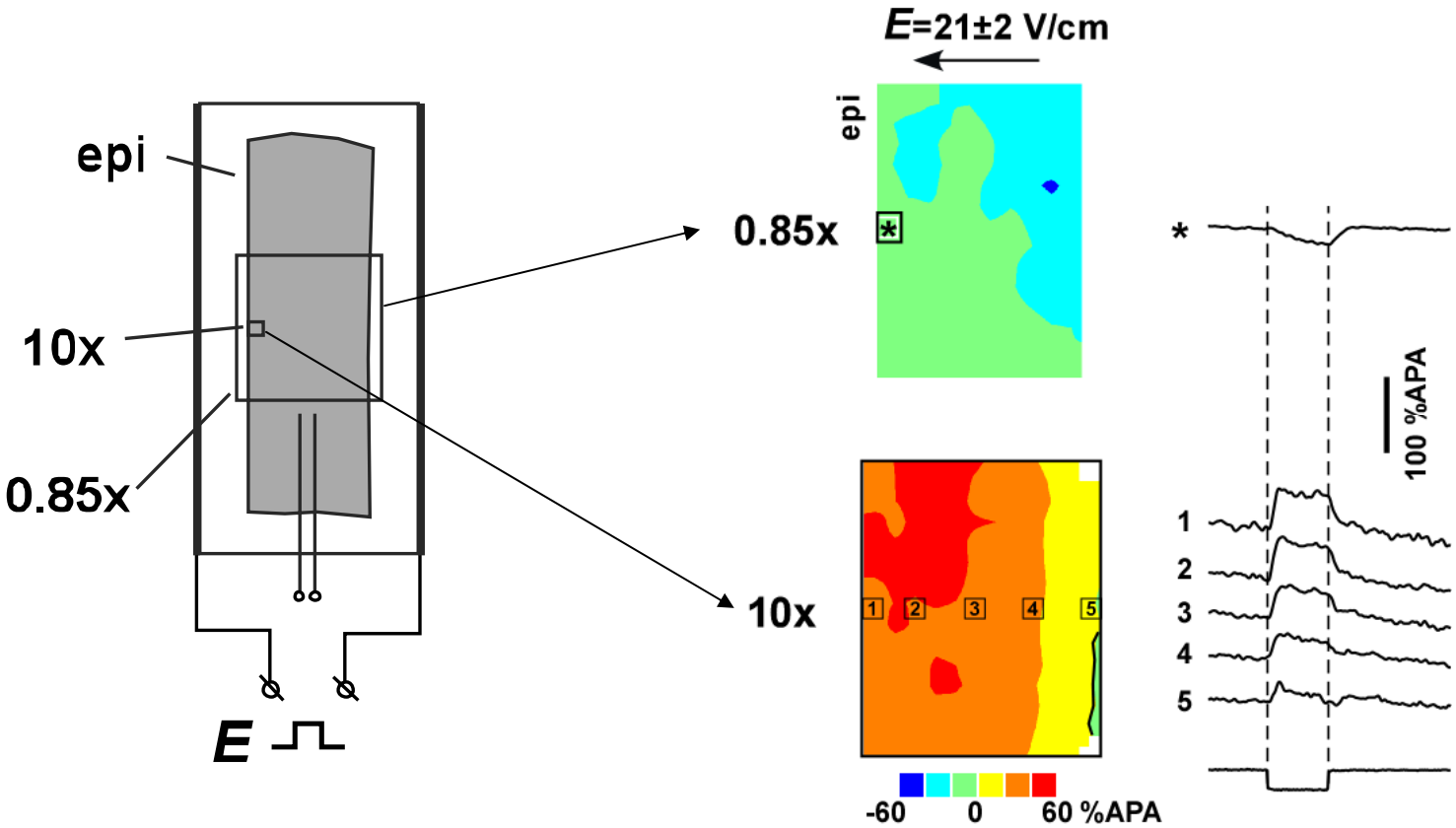


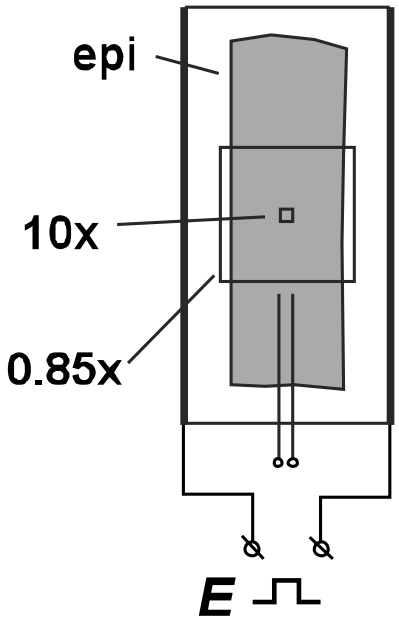
0.25 mm

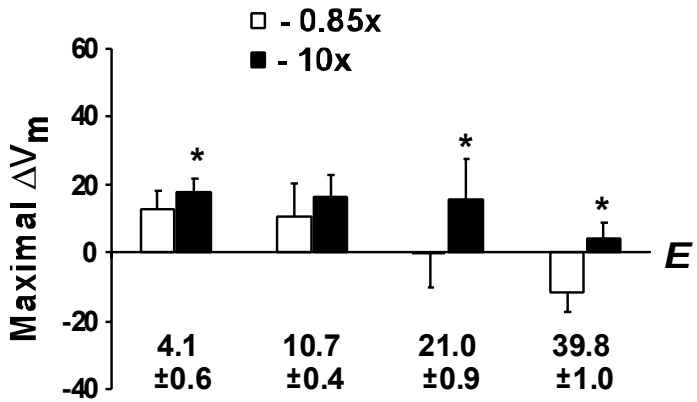
High-resolution mapping of intramural ΔV_m
Sub-epicardial ΔV_m

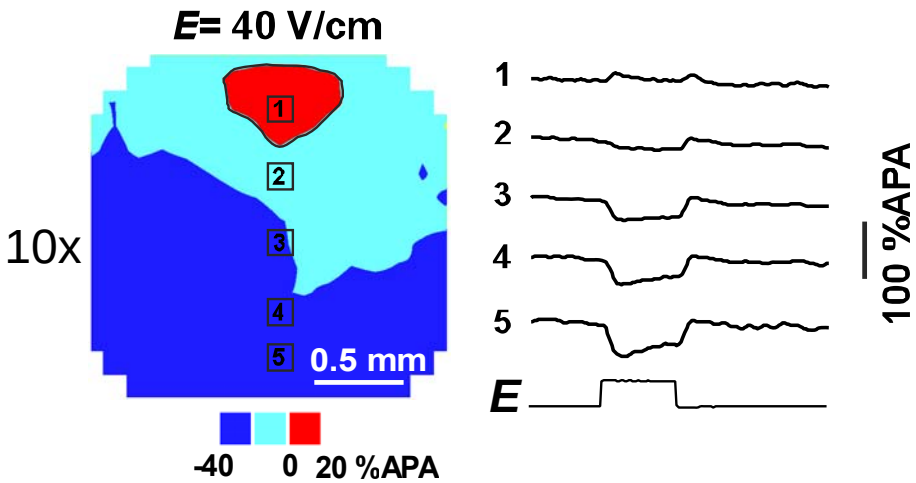


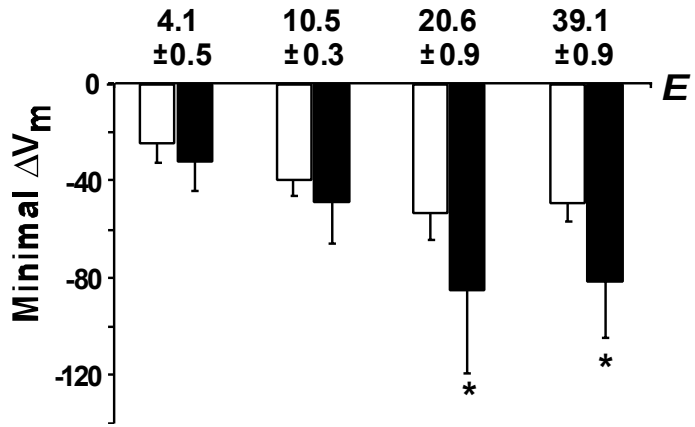
Sharifov et al, Cardiovasc Res, 2004

High-resolution mapping of intramural ΔV_m
Mid-wall ΔV_m







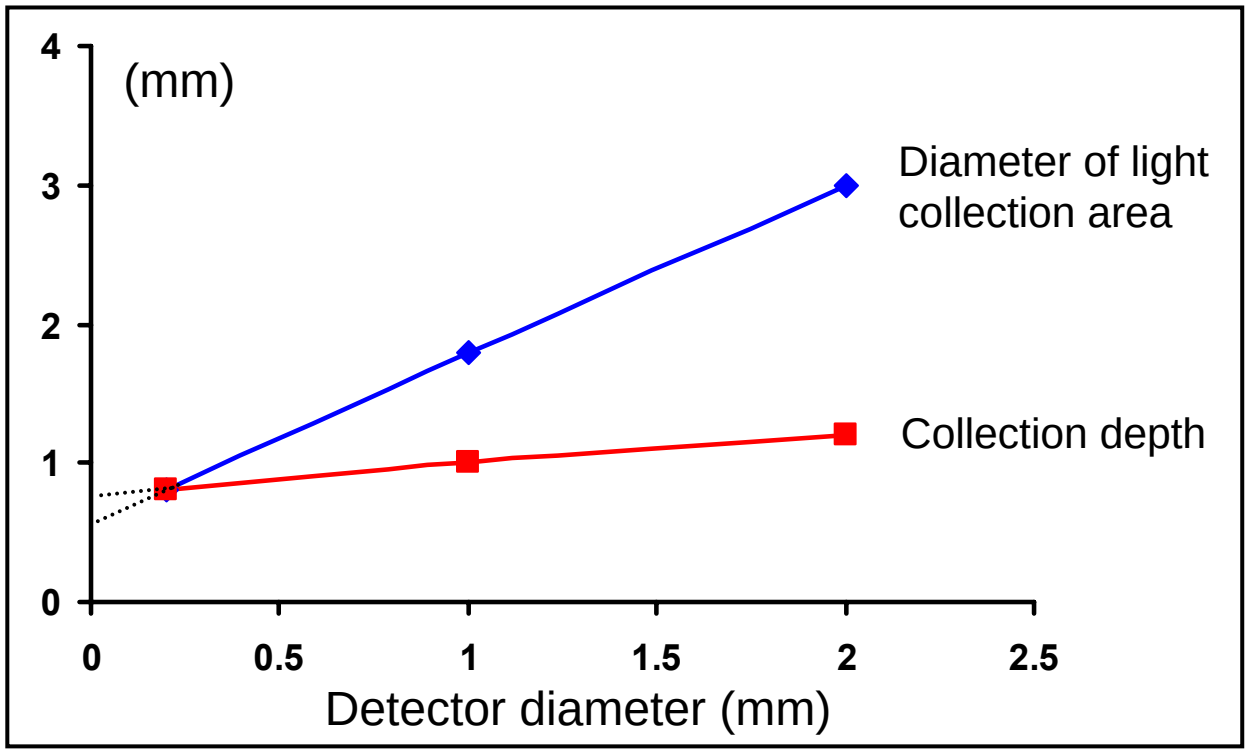


Sharifov et al, Cardiovasc Res, 2004

Resolution limit of optical mapping

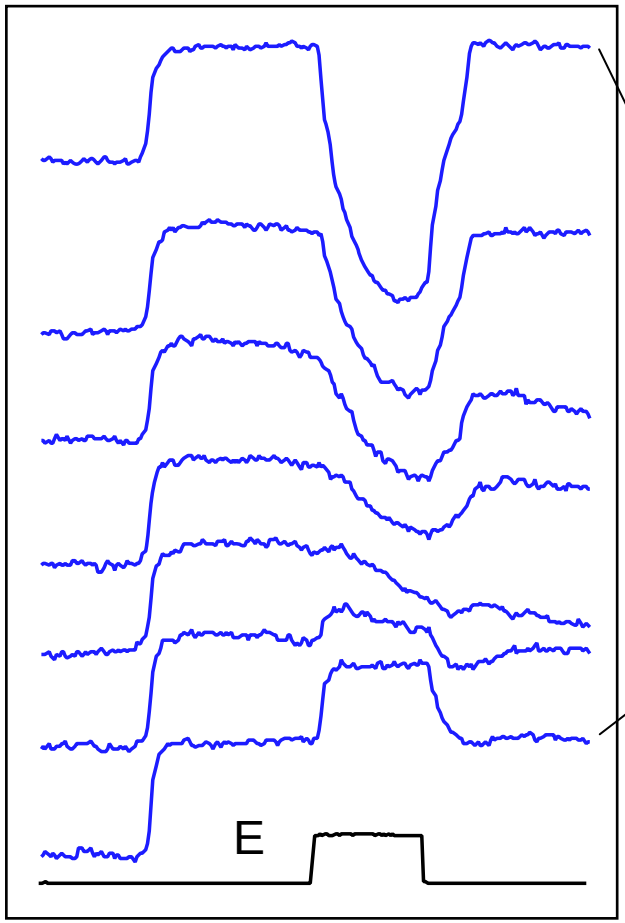
• On microscopic scale, optical resolution is limited not by detector dimensions but by light scattering and light integration from tissue depth (Ding et al, 2001; Hyatt et al, 2003)

Estimation of 80% light collection area and depth using Monte-Carlo model of light propagation (Ding et al, IEEE Trans Biomed Eng, 2001)

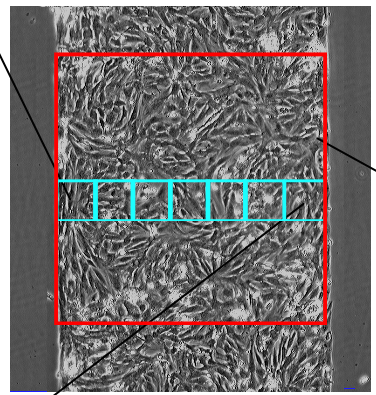


Microscopic ΔV_m in cultured cell strands
Effect of spatial averaging

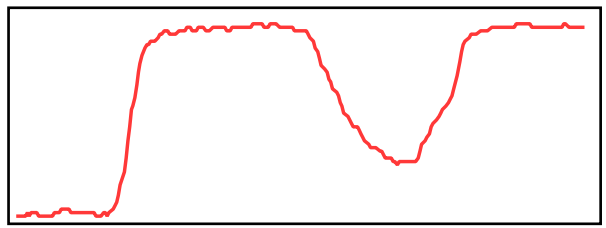
High resolution (dx=0.1 mm)



Cultured
cell strand



Low resolution (dx=0.7 mm)

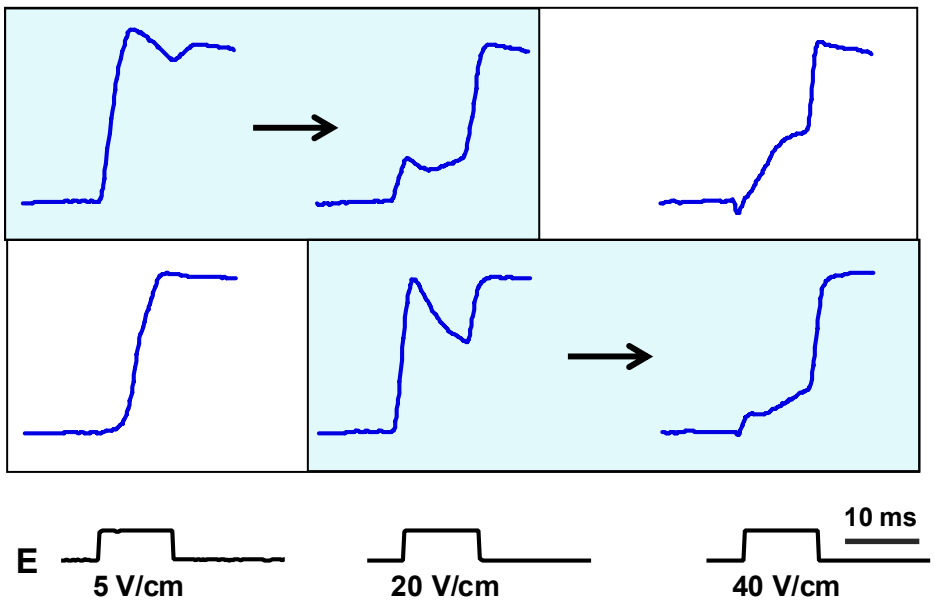


Transition of AP upstroke shape

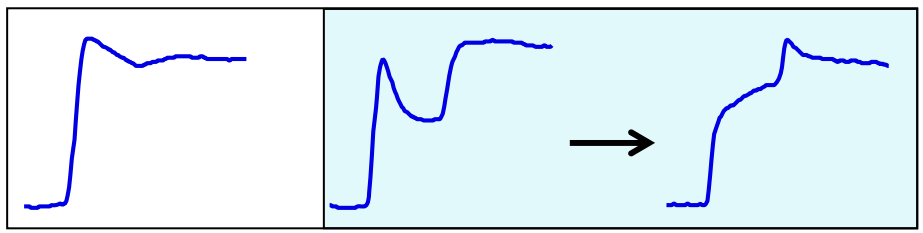
Averaged upstrokes in cell strands

Strand width=0.8 mm

Strand width=0.1 mm



Upstrokes in LV wedge preparations

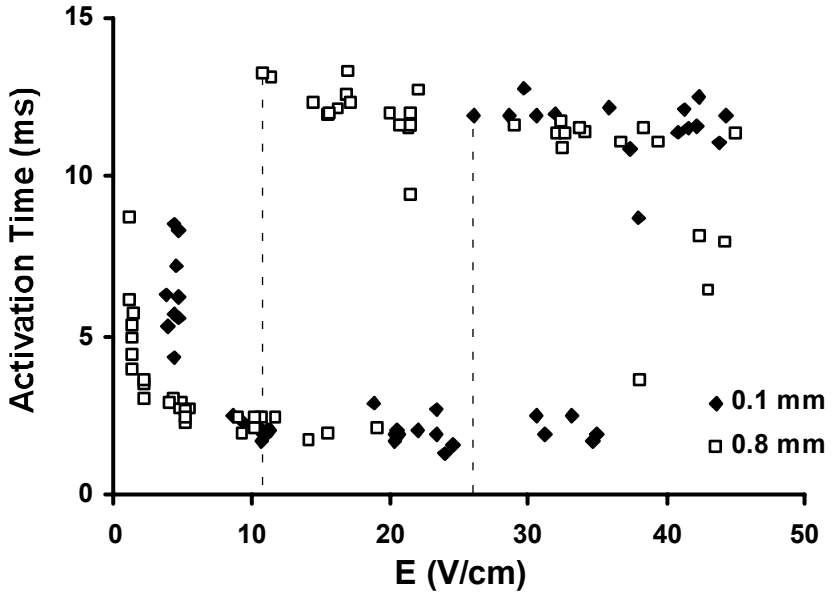


Cheek et al, JCE, 2005

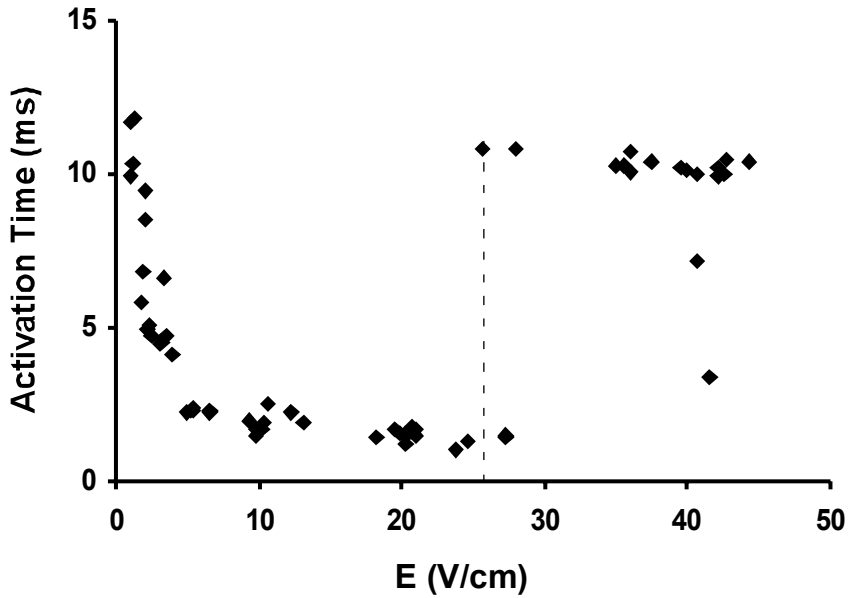
Transition to delayed activation

Cultured cell strands

□ Width=0.8 mm
◆ Width=0.1 mm



LV wedge preparations



Cheek et al, JCE, 2005

Conclusions

1. Shocks produce intramural virtual electrodes
2. When shocks are applied during diastole, IVE cause nearly simultaneous activation of the intramural myocardium over a wide range of shock strength
3. Intramural virtual electrodes produced by strong shocks have microscopic origin
4. The likely mechanism of such IVE is discontinuous tissue structure with dimensions of discontinuities on the order of 100 μm

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