Vulnerability to Cardiac Arrhythmias

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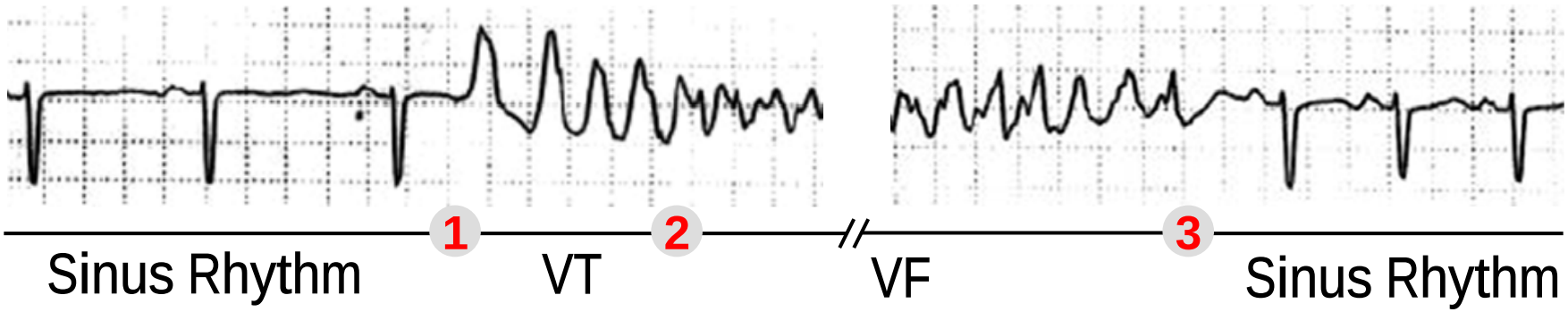
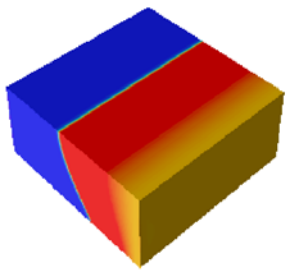
The transitions in cardiac arrhythmias

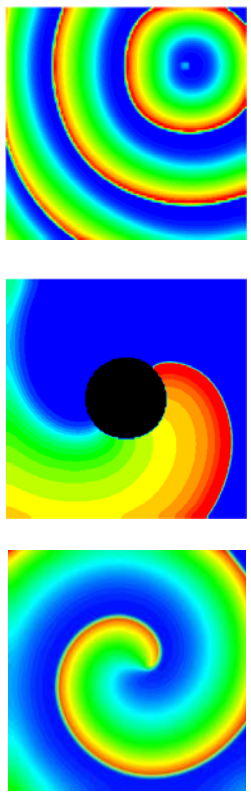


Suppress PVC, or reduce vulnerable window, or both.



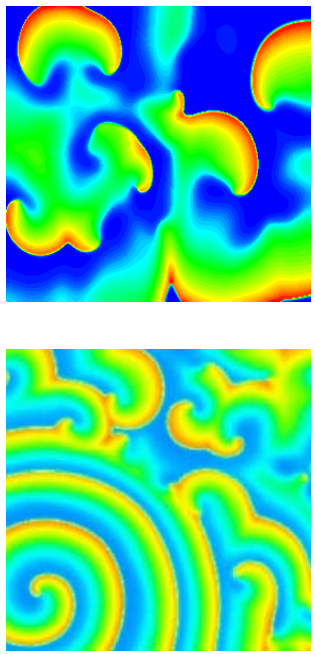
1

PVC in proper time & space



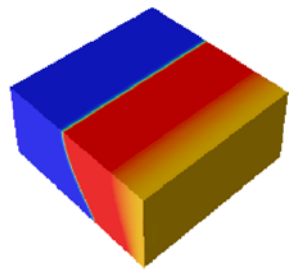
2

Dynamic instability
Heterogeneity

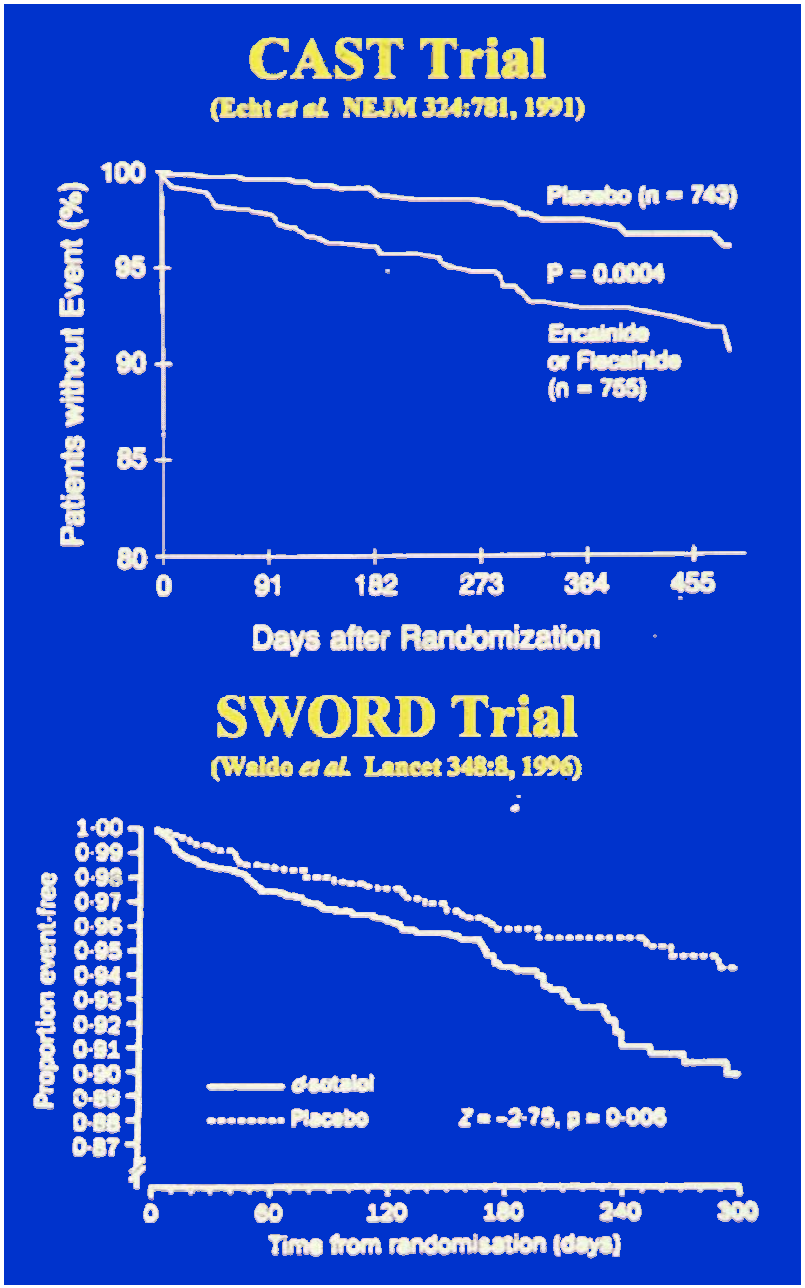


3

Electrical shock
AA Drug
Spontaneously



Clinical trials on arrhythmia prevention



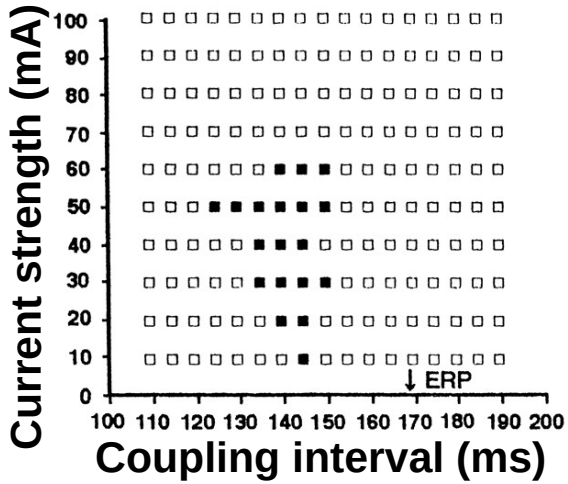
In the CAST trial, encainide and flecainide were used to suppress PVCs in patients of post-myocardial infarction, and were shown to be effective in suppressing PVCs, however, "During an average of 10 months of follow-up, the patients treated with active drug had a higher rate of death from arrhythmia than the patients assigned to placebo. Encainide and flecainide accounted for the excess of deaths from arrhythmia and nonfatal cardiac arrests (33 of 730 patients taking encainide or flecainide [4.5 percent]; 9 of 725 taking placebo [1.2 percent]; relative risk, 3.6." (NEJM 321, 1989)

The SWORD trial "FINDINGS: After 3121 of the planned 6400 patients had been recruited, the trial was stopped. Among 1549 patients assigned d-sotalol, there were 78 deaths (5.0%) compared with 48 deaths (3.1%) among the 1572 patients assigned placebo (relative risk 1.65 [95% CI 1.15-2.36], p = 0.006). Presumed arrhythmic deaths (relative risk 1.77 [1.15-2.74], p = 0.008) accounted for the increased mortality." (Waldo et al, Lancet 348, 1996)

Induction of reentry by strong electrical stimuli

Single, strong electrical stimuli delivered through a relatively small electrode can, when properly timed, induce ventricular fibrillation in the normal heart, whereas stimuli of low intensity usually do not.[1–6] Even when two to five successive low-intensity premature stimuli (i.e., stimuli with shorter coupling intervals than that of the basic rhythm) are applied to the normal ventricle, ventricular fibrillation is rarely induced.[1,5–10]

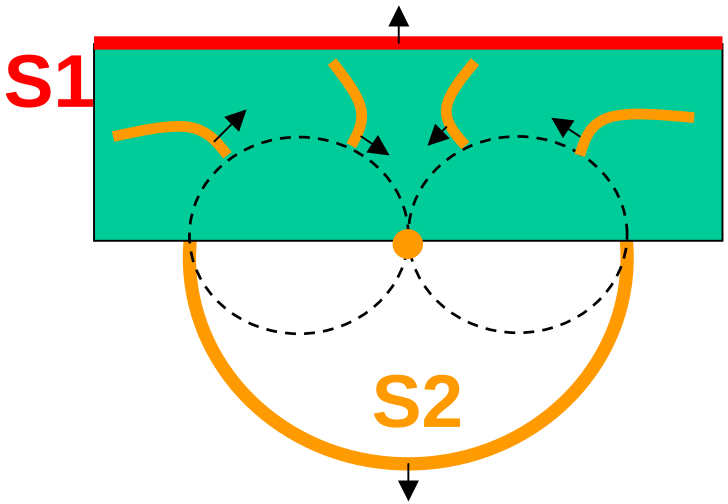
(Janse, Chaos 1998)

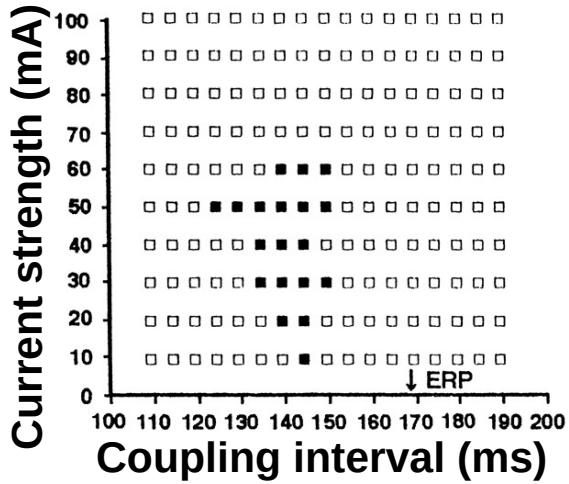


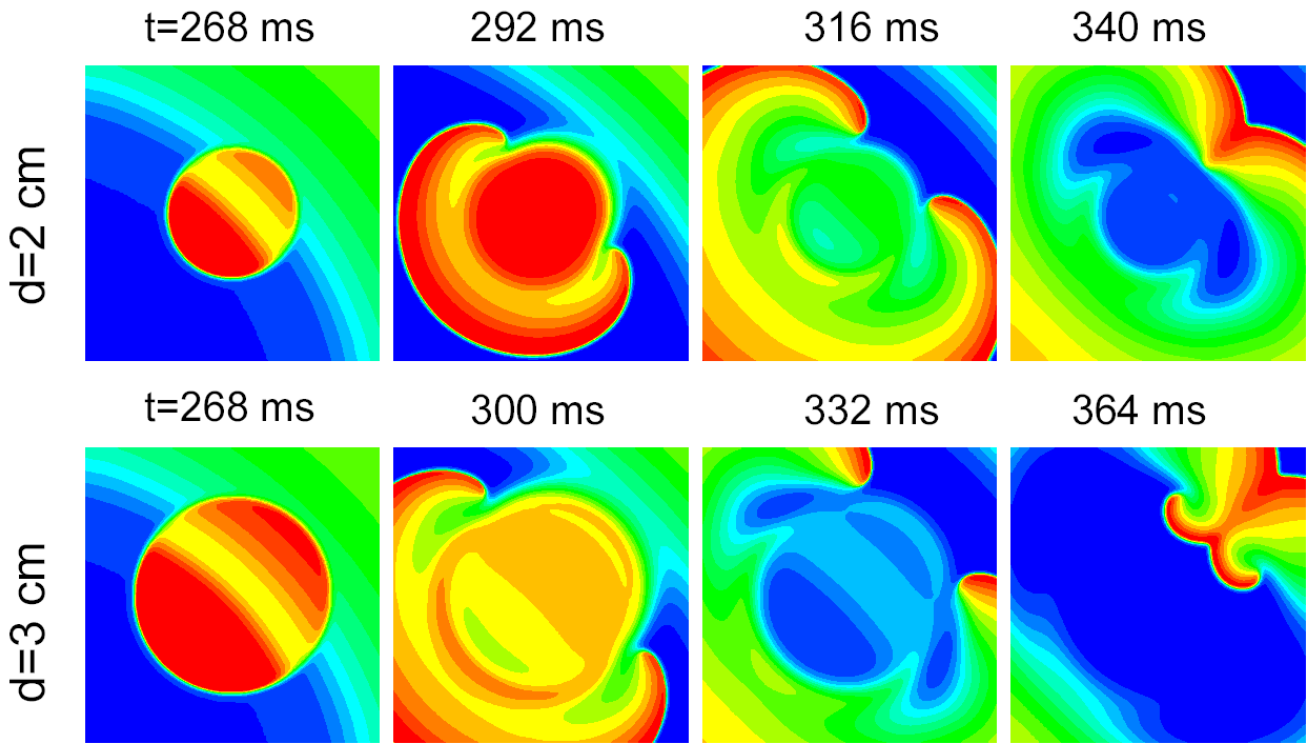
(Gotoh et al, circulation 1997)

Programmed electrical stimulation was performed in eight normal dogs using a stimulator and endocardial electrode catheters identical to those used in human studies. The right and left ventricular apex were paced at a drive cycle length of 400 ms and, in some cases, 500 ms, with a pacing sequence of single (S1S2), double (S1S2S3) and triple (S1S2S3S4) premature impulses introduced after eight paced complexes. Pacing sequences were performed using combinations of pulse width (1, 2 and 4 ms) and current strengths of 2, 5 and 10 times diastolic threshold, and in three dogs, 15 times diastolic threshold. Twenty-two episodes of ventricular fibrillation were initiated in five dogs in 170 pacing sequences using current strengths up to 10 times diastolic threshold, and six episodes of ventricular fibrillation in the two of three remaining dogs tested at 15 times diastolic threshold. Ventricular fibrillation was reproducible on seven of nine occasions. Ventricular fibrillation was never induced by S1S2 at up to 15 times diastolic threshold; it was induced by S1S2S3 in 3 (1.8%) of 170 sequences, but only at 10 times diastolic threshold. It was induced by S1S2S3S4 in 19 (11.4%) of 167 sequences using 2 to 10 times diastolic threshold, although 20 of 28 episodes only occurred with S1S2S3S4 at 10 or more times diastolic threshold. (Hamer et al, JACC 1984)

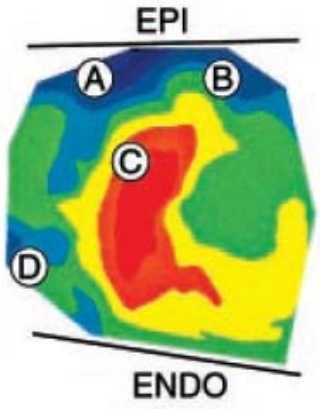
The pinwheel experiment (Coined by A. T. Winfree)



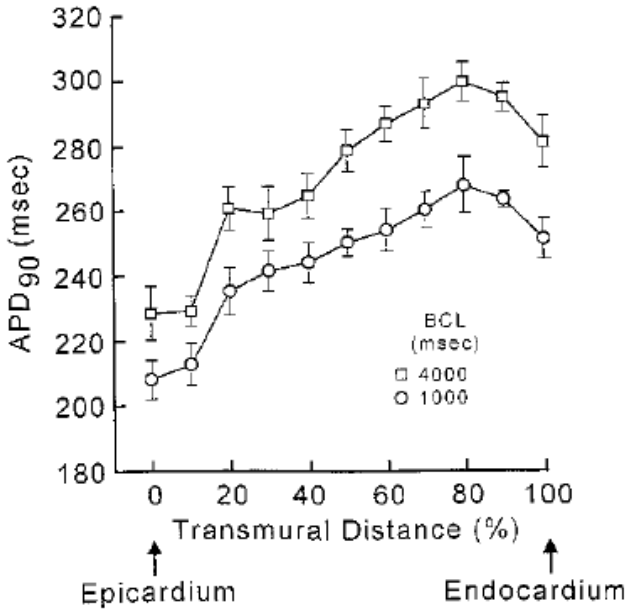




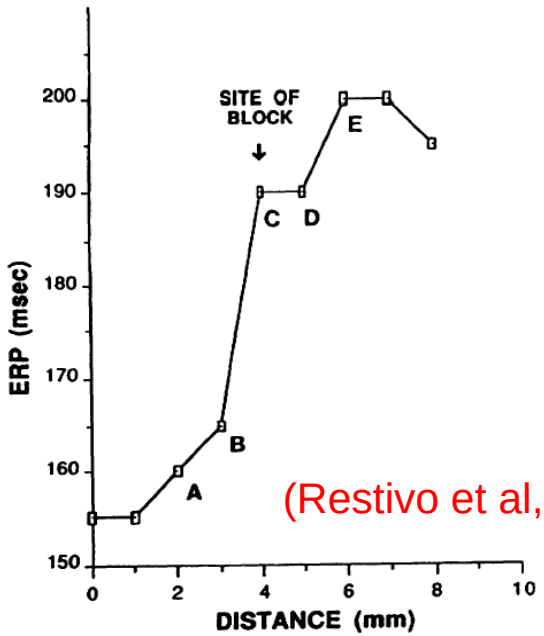
Examples of heterogeneities in the heart



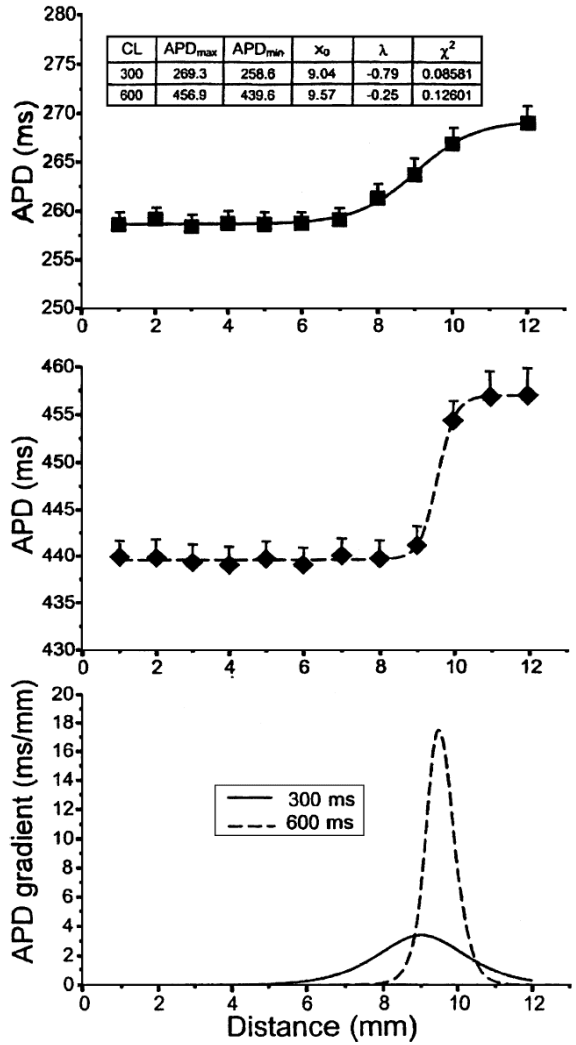
(Akar et al, Circulation 2002)



(Yan et al, Circulation 1998)



(Restivo et al, Circ Res 1990)



(Restivo et al, Circ Res 1990)

A critical repolarization gradient is needed for induction of arrhythmias by low-intensity stimuli

LQT (Akar et al, Circulation 2002)

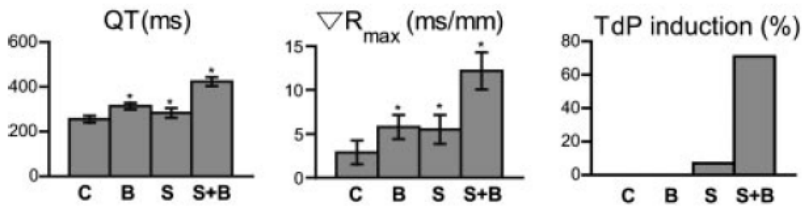
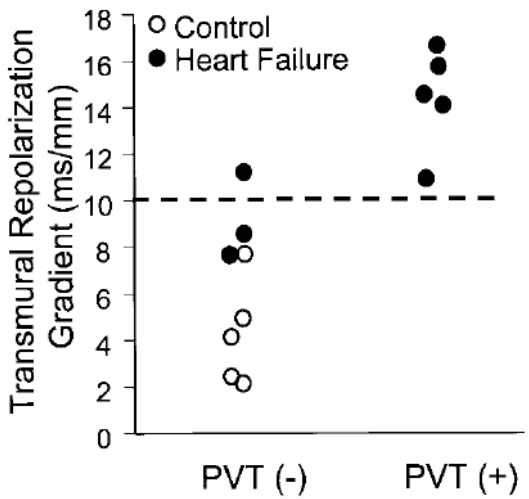
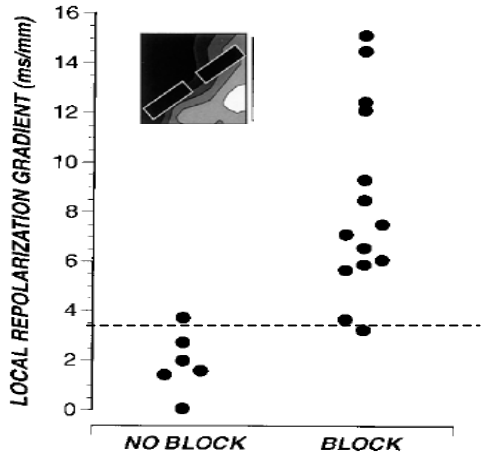


Figure 3. QT interval, maximum transmural repolarization gradient ∇R_{max}, and TdP induction rate for each condition. C indicates control; B, bradycardia; S, d-sotalol; and S+B, d-sotalol+bradycardia. Each condition significantly (*$P<0.01$) prolonged QT interval and ∇R_{max}. TdP induction rate was markedly increased by the synergistic effect of S+B.

HF (Akar et al, Circ Res 2003)



Obstacle (Laurita et al, Circulation 2000)



In contrast, in the absence of a barrier over the same range of S1S2 coupling intervals tested (ie, control hearts), unidirectional block of the S3 beat was observed only once for 12 coupling intervals tested despite the presence of repolarization gradients (3.8±1.3 m/sec) >3.2 ms/mm.

Ischemia (Restivo et al, Circ Res 1990)

Arrhythmias was induced for ERP gradient between 10 ms/mm and 100ms/mm.

Theoretical and numerical studies on vulnerability

There are several studies (mostly by Starmer et al) on vulnerability to unidirectional conduction block in 1D homogeneous tissue with one single PVC, and a finite size electrode.

Fox et al, Circ Res 2002, NJP 2003, Otani et al 2006

Henry & Rappel, PRE 2005

Comtois et al, PRE 2005

Sampson et al, AJP 2002

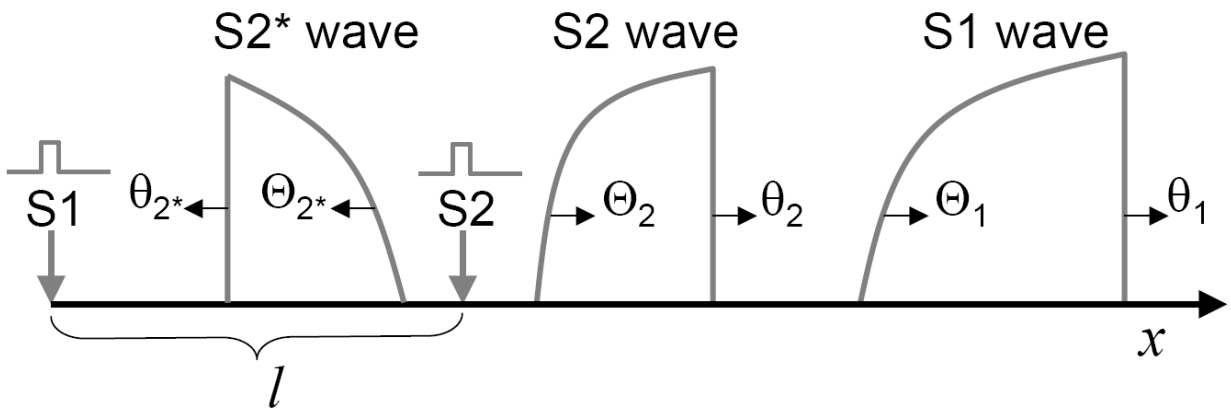
Clayton et al, Biomed Eng Online 2005a, 2005b

Qu et al, Circulation 2000, AJP 2003, AJP 2005

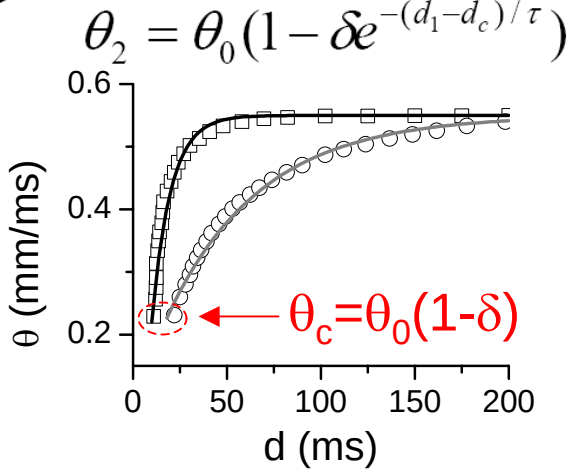
Qu et al, Biophys J 2006a, 2006b
Tran et al, unpublished data

1. Heterogeneous tissue with a single extrasystole

Critical repolarization gradient for conduction block



$$\Theta_1(x) = \frac{\theta_1(x)}{1+\theta_1(x)\cdot a_{1x}(x)} \quad < \theta_c$$



For the S2 wave:

$$a_{1x} > \frac{1}{\theta_c} - \frac{1}{\theta_1} = \frac{\theta_1 - \theta_c}{\theta_1\theta_c}$$

θ_1=0.5 mm/ms
θ_c=0.2 mm/ms
a_{1x}>3 ms/mm

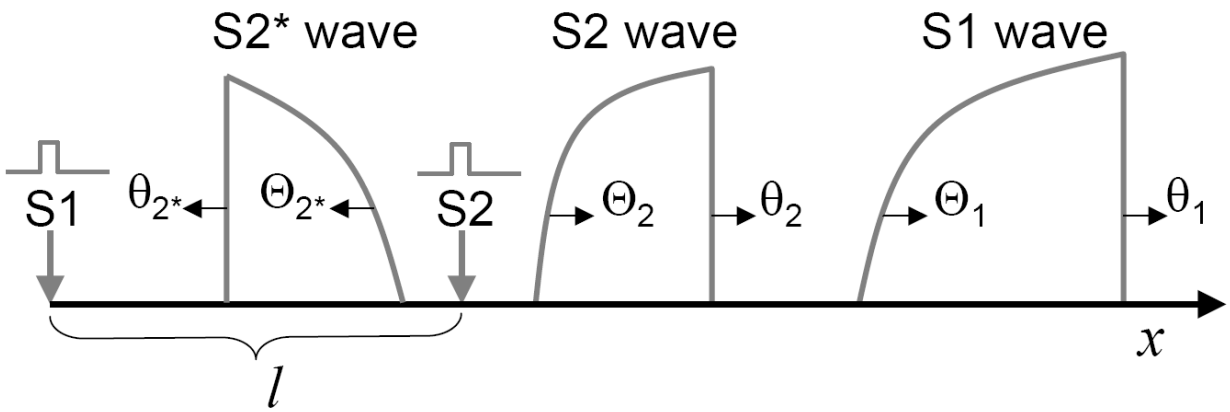
For the S2* wave:

$$a_{1x} < -(\frac{1}{\theta_c} + \frac{1}{\theta_1}) = -\frac{\theta_1 + \theta_c}{\theta_1\theta_c}$$

a_{1x}<-7 ms/mm

(Qu et al, Biophys J 2006a)

A kinematic equation of conduction in 1D cable

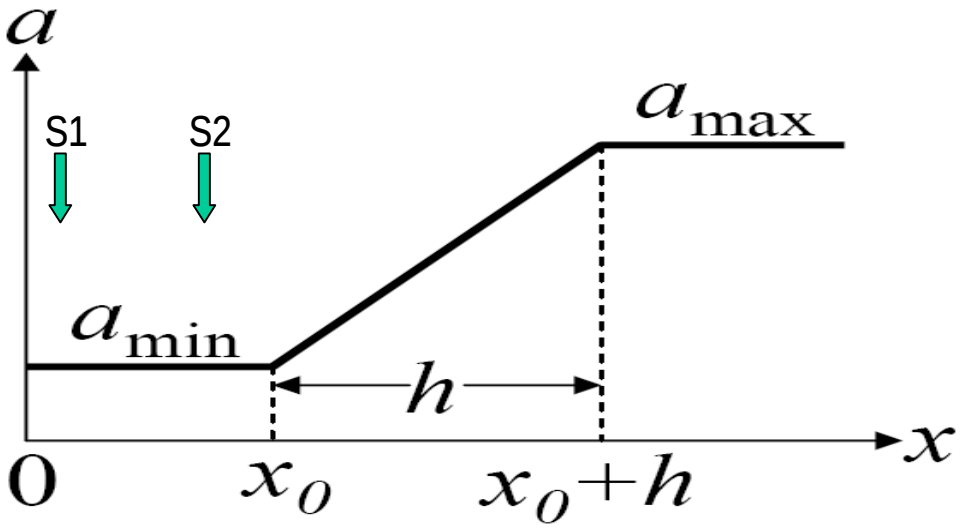


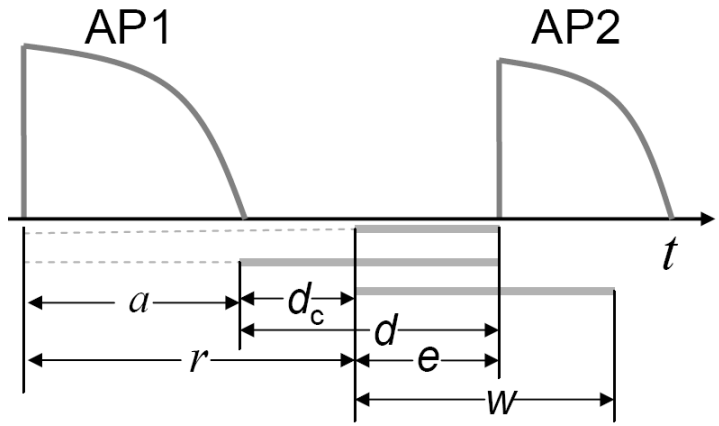
$$\frac{d[d_1(x)]}{dx} = \frac{1}{\theta_2(x)} - \frac{1}{\Theta_1(x)}$$

$$\theta_2 = \theta_0(1 - \delta e^{-(d_1 - d_c)/\tau})$$

(Qu et al, Biophys J 2006a)

Vulnerable window of conduction block in 1D cable: Analytical results (1)

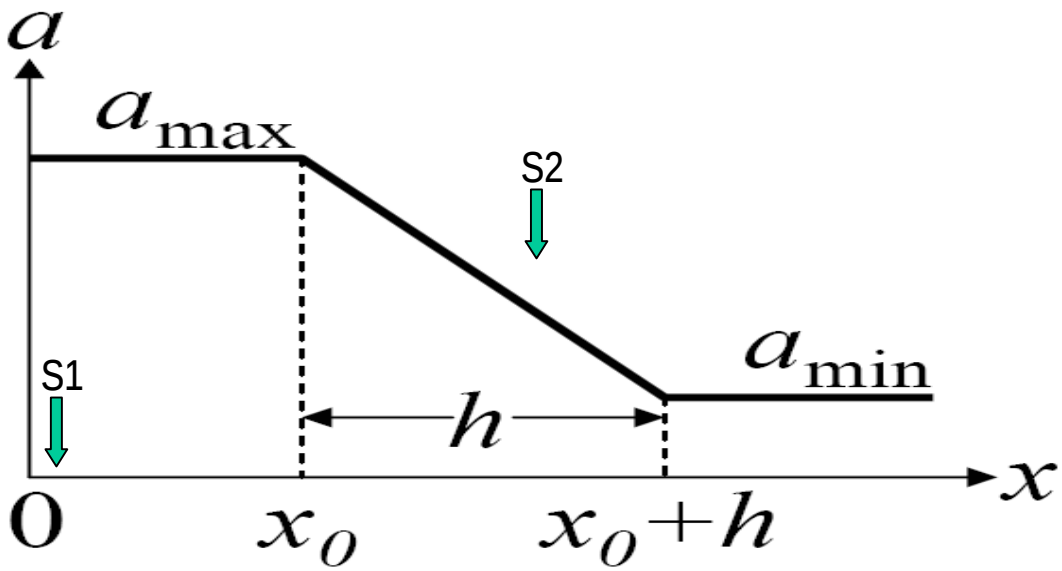




$$w(l)=\begin{cases}\Delta a-\dfrac{\tau}{1+\sigma\theta_0}\ln\dfrac{\sigma\theta_0^2}{\theta_c+\sigma\theta_c\theta_0-\theta_0}, & if\ l<x_0\\ \sigma(x_0+h-l)-\dfrac{\tau}{1+\sigma\theta_0}\ln\dfrac{\sigma\theta_0^2}{\theta_c+\sigma\theta_c\theta_0-\theta_0}, & if\ l\geq x_0\end{cases}$$

(Qu et al, Biophys J 2006a)

Vulnerable window of conduction block in 1D cable: Analytical results (2)

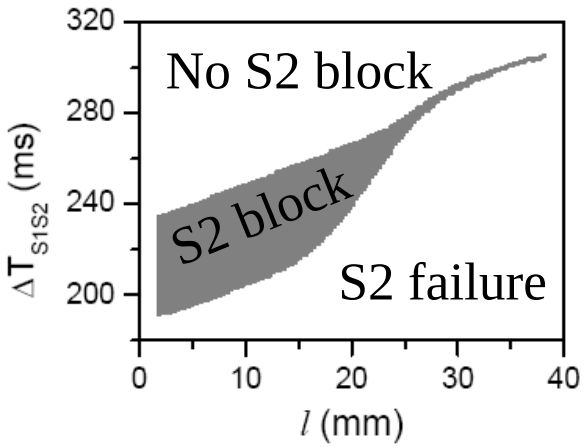


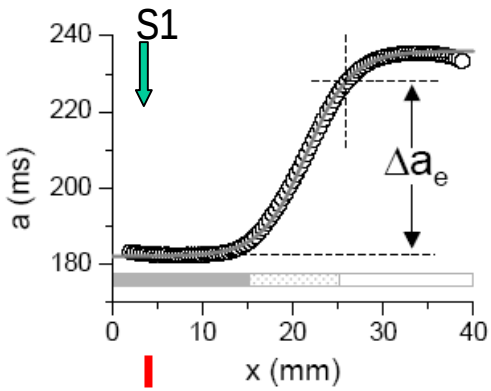
$$w(l)=\begin{cases}\dfrac{\sigma\theta_0-2}{\theta_0}(l-x_0)-\dfrac{\tau}{\sigma\theta_0-1}\ln\dfrac{2\theta_0-\sigma\theta_0^2}{\theta_c-\sigma\theta_c\theta_0+\theta_0}, & if\ l\le x_0+h\\ \Delta a-\dfrac{2}{\theta_0}(l-x_0)-\dfrac{\tau}{\sigma\theta_0-1}\ln\dfrac{2\theta_0-\sigma\theta_0^2}{\theta_c-\sigma\theta_c\theta_0+\theta_0}, & if\ l>x_0+h\end{cases}$$

(Qu et al, Biophys J 2006a)

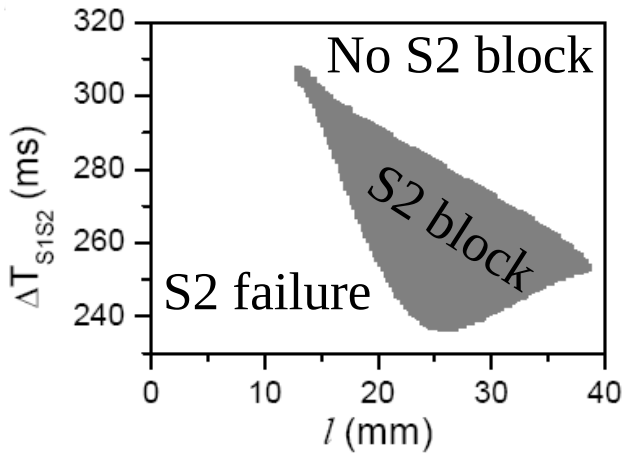
Vulnerable window of conduction block in 1D cable: Numerical simulations

LR1 Model

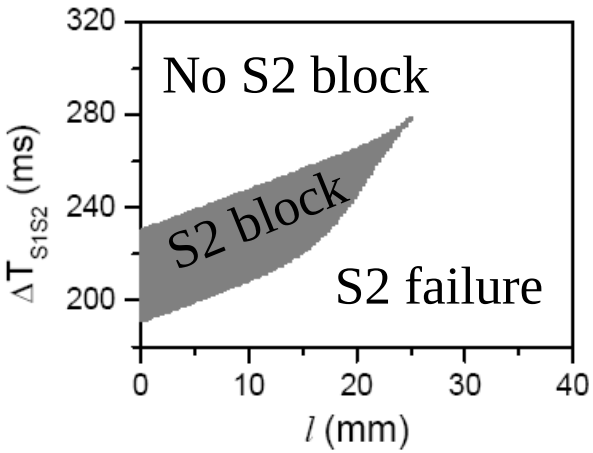


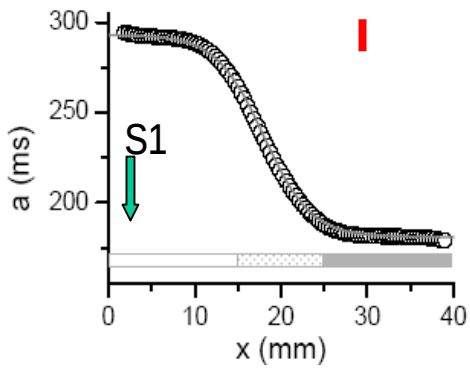


LR1 Model

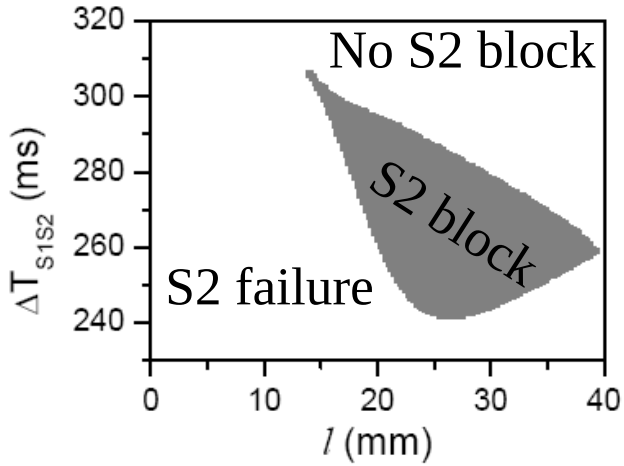


Kinematic Equation



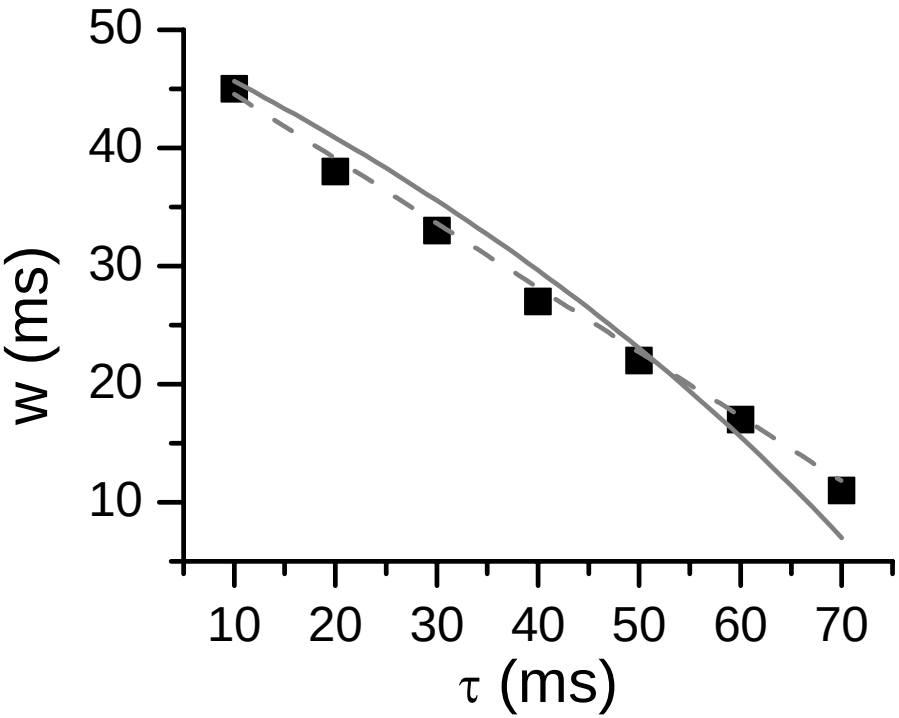


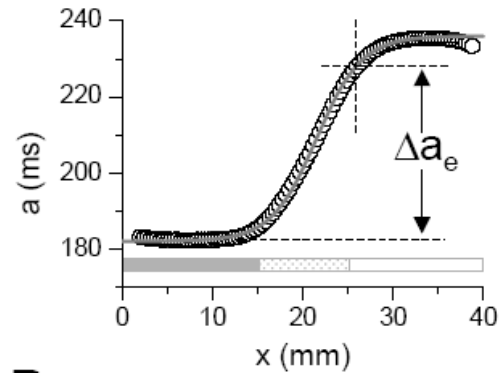
Kinematic Equation

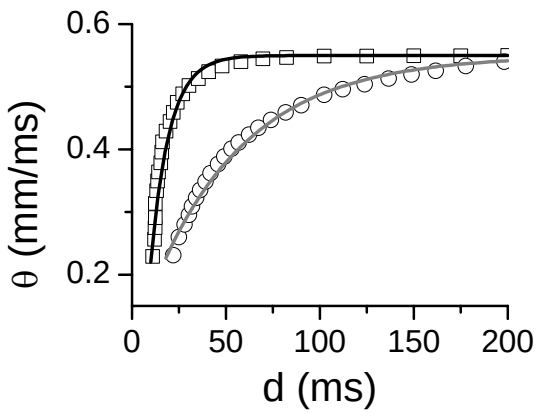


(Qu et al, Biophys J 2006a)

Vulnerable window of conduction block in 1D cable: Effects of CV restitution

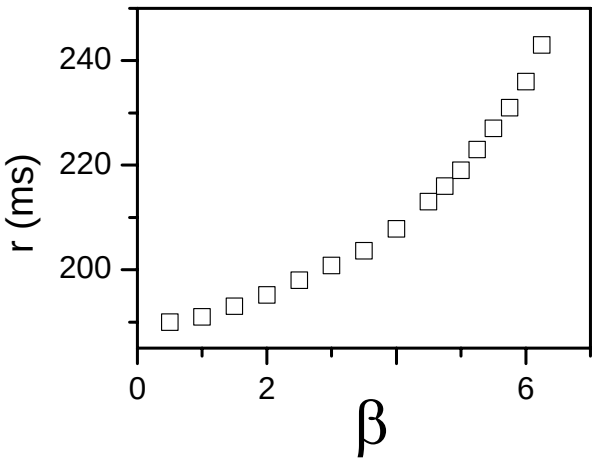


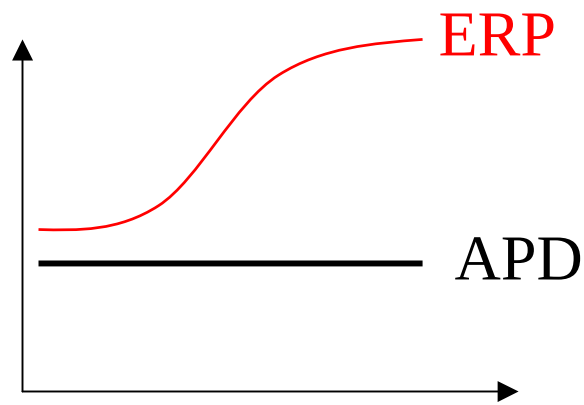


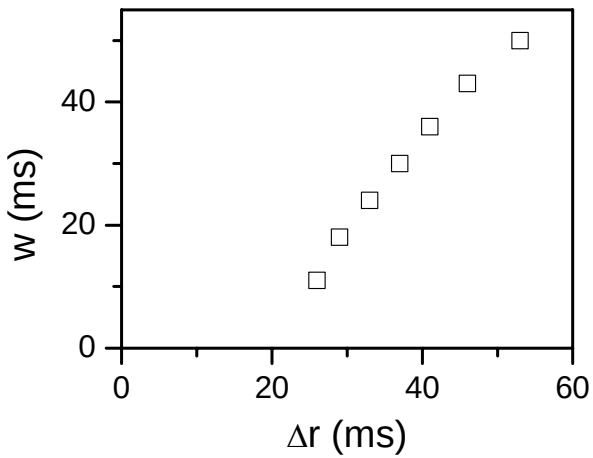


(Qu et al, Biophys J 2006a)

Vulnerable window of conduction block in 1D cable: Effects of dispersion of refractoriness



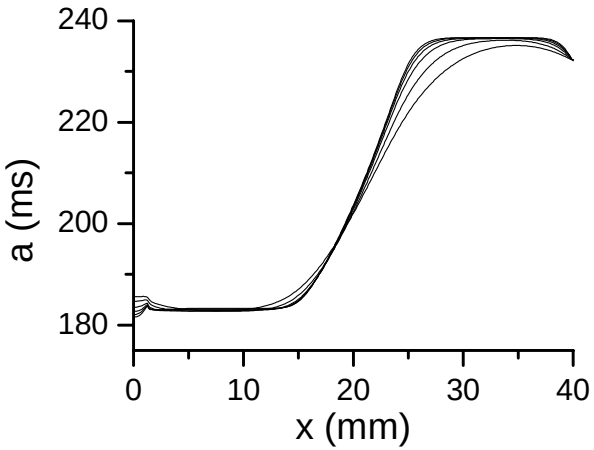


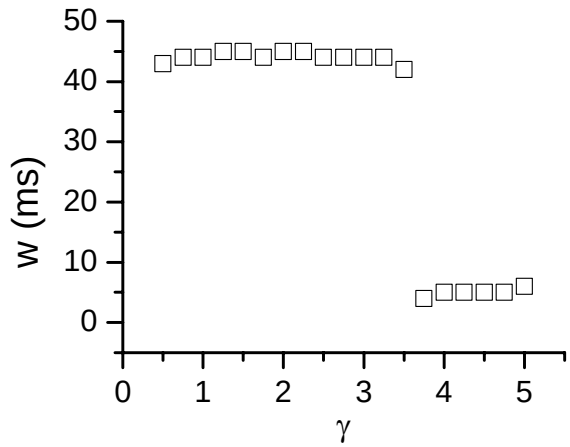


The ERP gradient was generated by linearly changing $\bar{G}_{Namax} = 16$ to $\bar{G}_{Namin} = 16(1-(\beta/10))$ mS/cm^2, and $\tau_{jmin} = \tau_j$ to $\tau_{jmax} = \beta\tau_j$ in a region $h = 10$ mm,

(Qu et al, Biophys J 2006a)

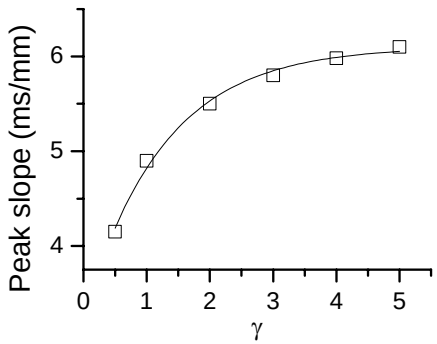
Vulnerable window of conduction block in 1D cable: Effects of cell coupling

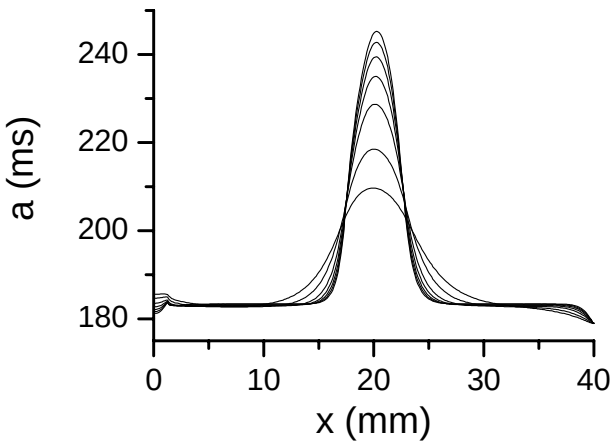


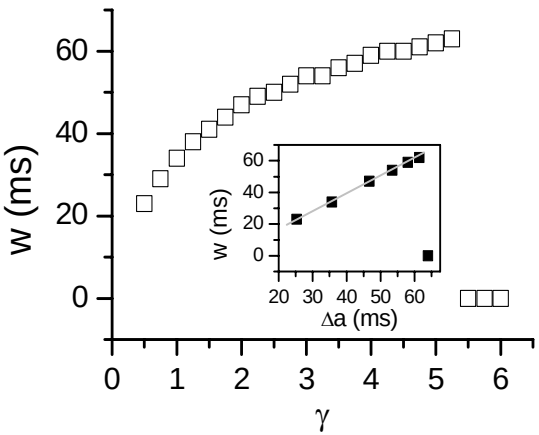


$$a_{1x} > \frac{1}{\theta_c} - \frac{1}{\theta_1} = \frac{\theta_1 - \theta_c}{\theta_1 \theta_c}$$

$$\theta \propto \sqrt{D} \rightarrow \theta' = \theta / \sqrt{\gamma}$$

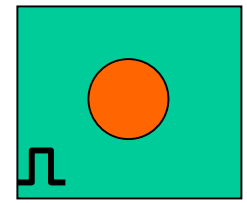




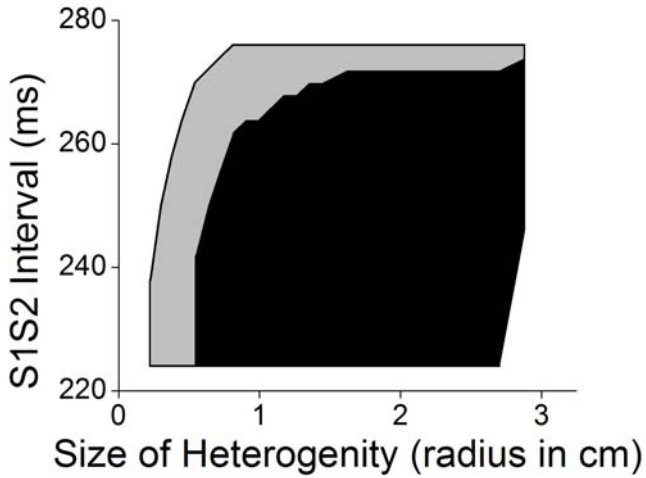


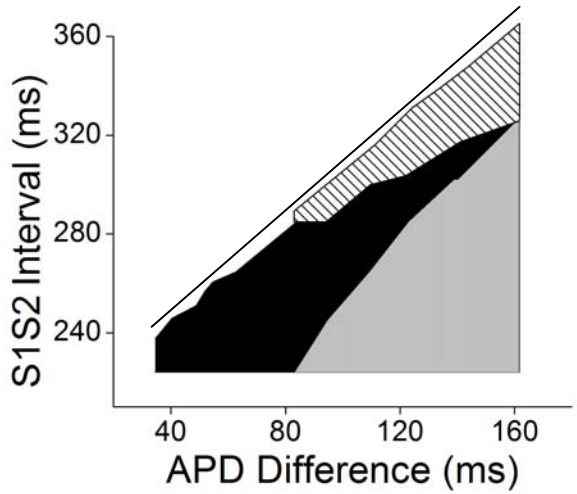
(Qu et al, Biophys J 2006a)

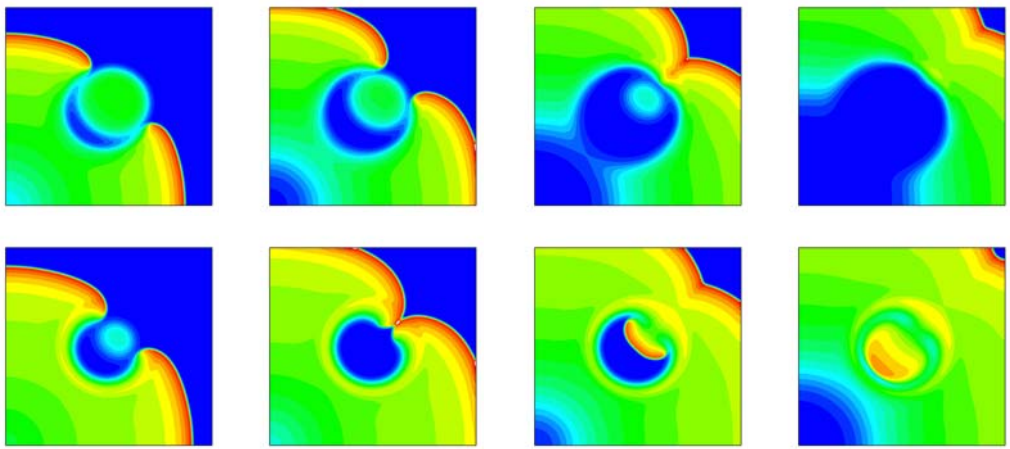
Vulnerable window of reentry in 2D tissue: Refractory barrier and spatial dimension



S1,S2

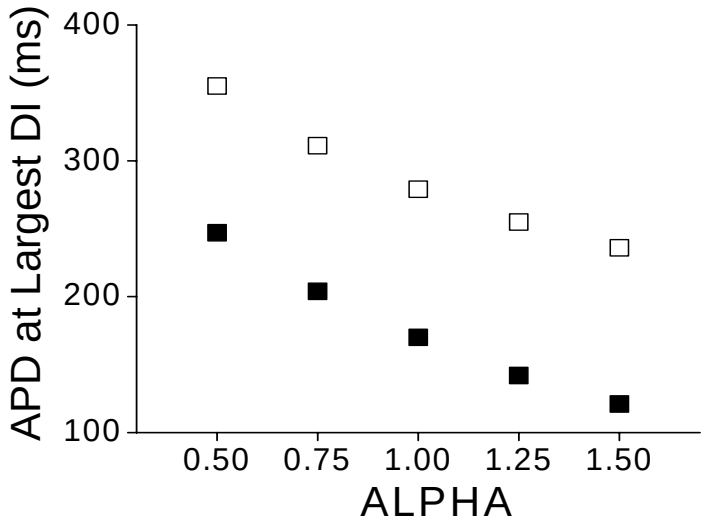


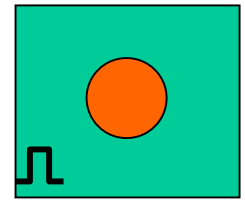


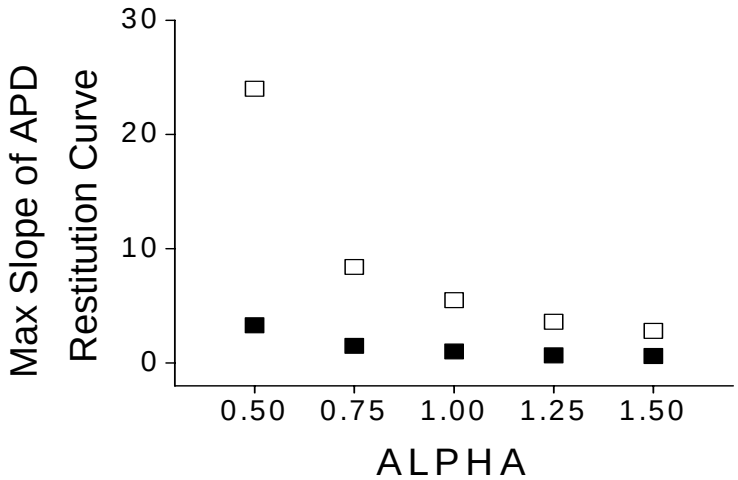


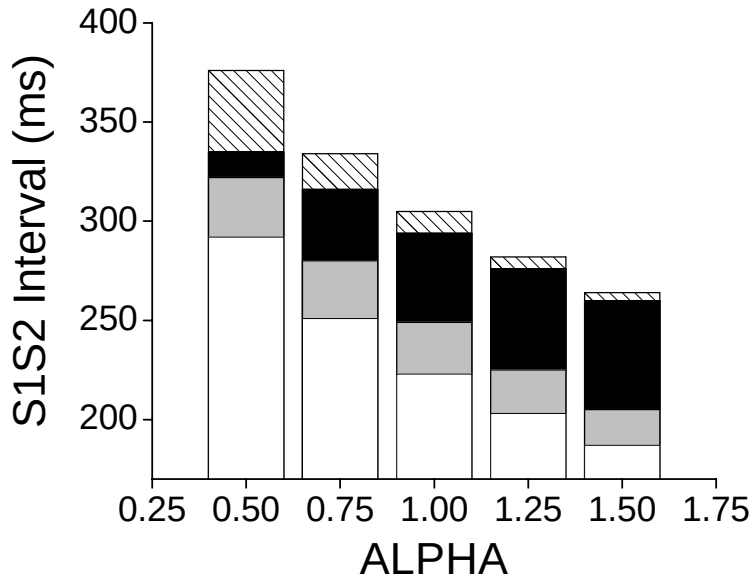
(Tran et al, unpublished data)

Vulnerable window of reentry in 2D tissue: Effects of APD restitution



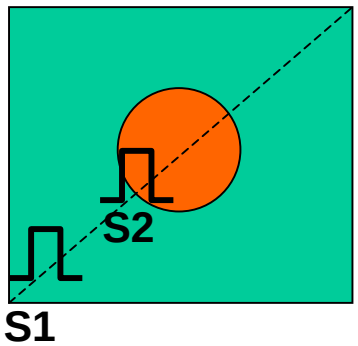


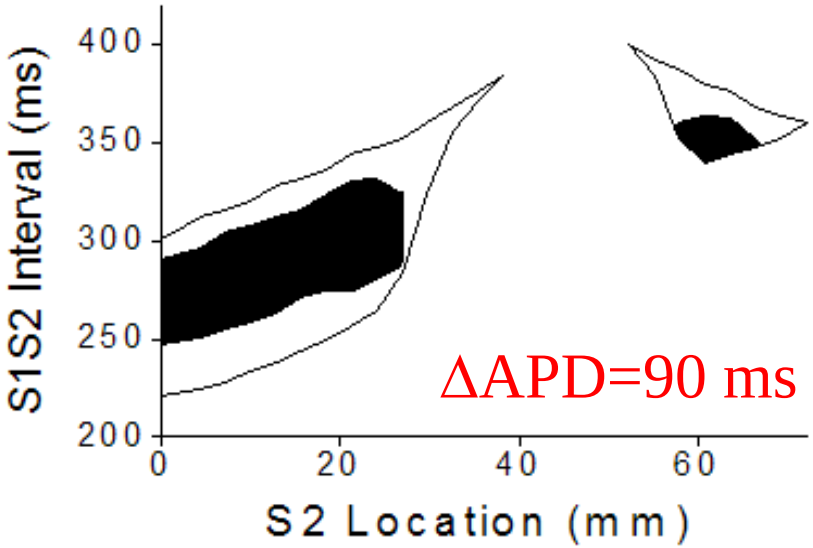


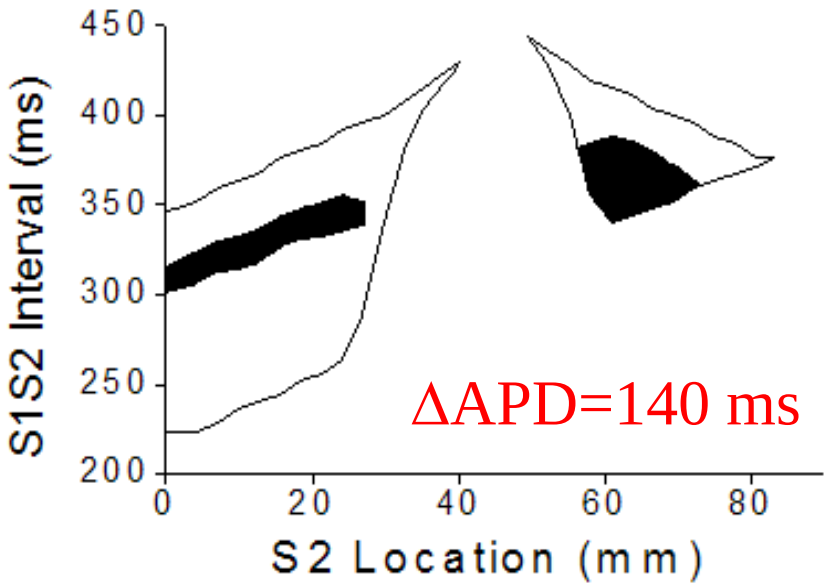


(Tran et al, unpublished data)

Vulnerable window of reentry in 2D tissue: Effects of stimulation location





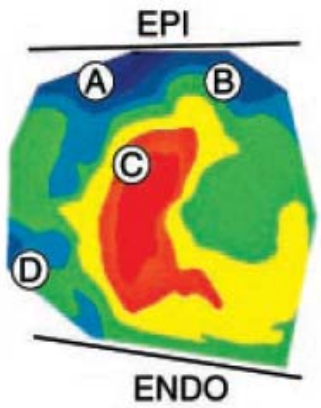


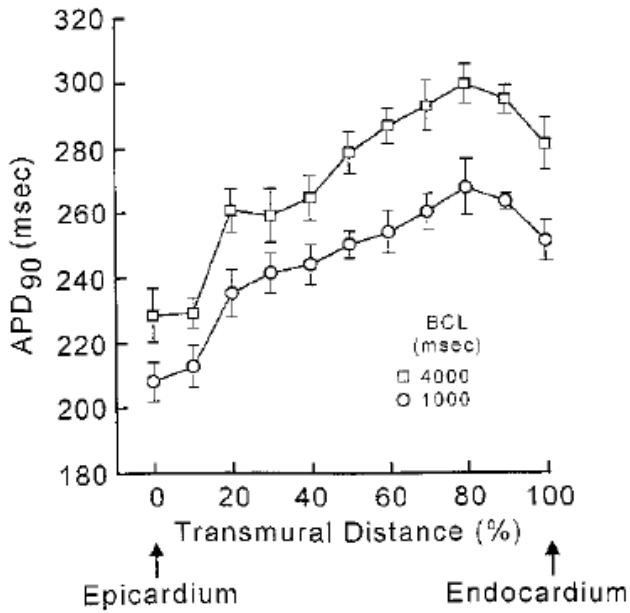
(Tran et al, unpublished data)

Implications from the modeling studies

1. The critical gradient of refractoriness required for conduction block is larger in transverse directions than the longitudinal one; larger for diseased hearts than normal hearts due to cell decoupling.

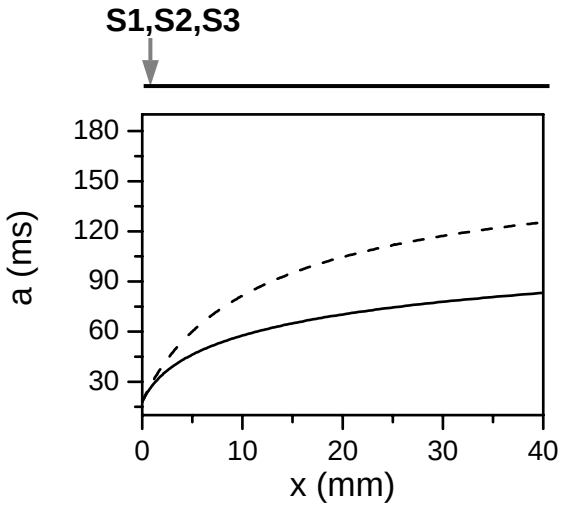
2. Since the sinus beat propagates from endocardial region to epicardial region, a single PVC from endocardial region may be easier to cause reentrant arrhythmias than the one from the epicardial region.



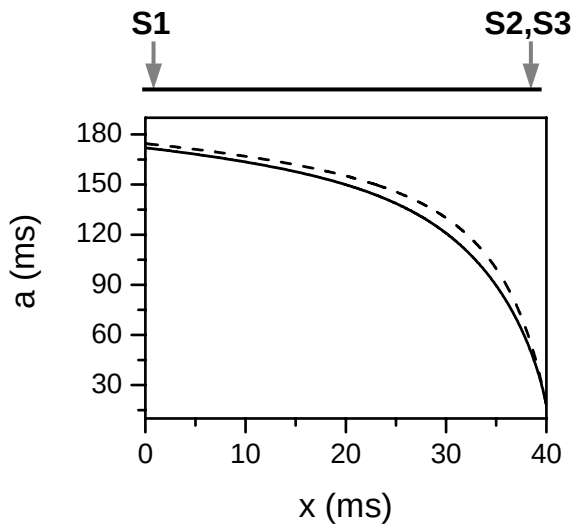


2. Homogeneous tissue with multiple extrasystoles

APD dispersion induced by a PVC and critical slope of APD restitution for conduction block



$$f_d^{'} > \frac{\theta_2 - (1-\delta)\theta_0}{(1-\delta)(\theta_0 - \theta_2)}$$



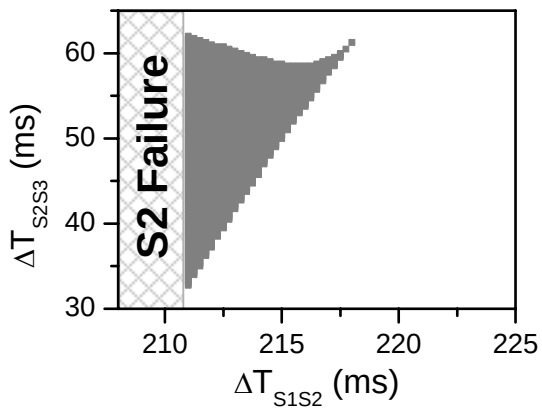
$$f_d^{'} > \frac{\theta_2 - (1-\delta)\theta_0}{(1-\delta)(\theta_0 + \theta_2)}$$

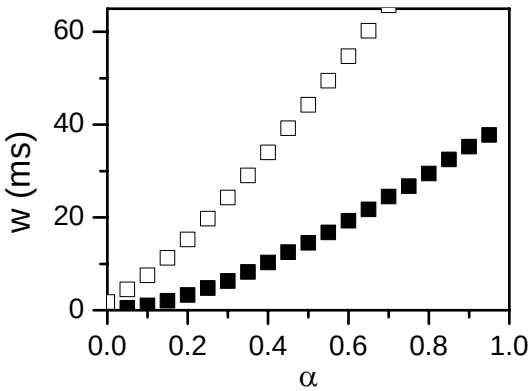
(Qu et al, Biophys J 2006b)

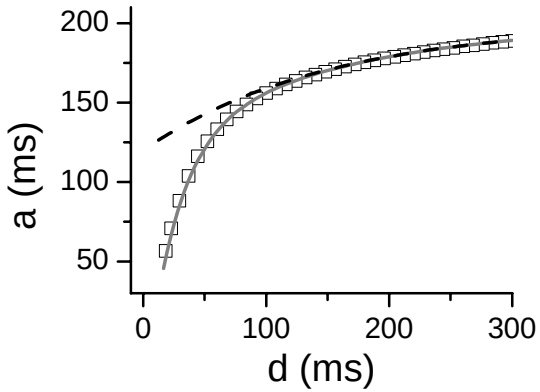
Vulnerable window of conduction block with two PVCs: Simulation of the Kinematic equation

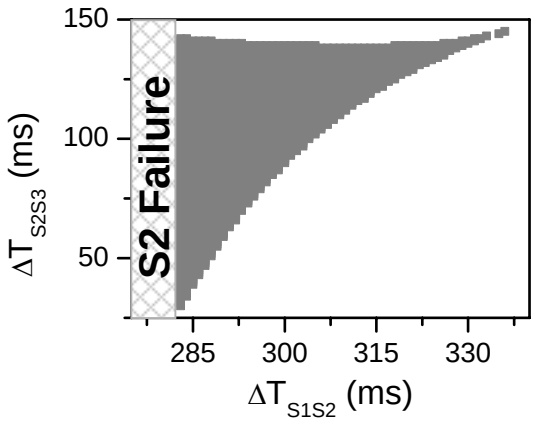
$$\frac{d[d_2(x)]}{dx} = \frac{1}{\theta_3(x)} - \frac{1}{\Theta_2(x)}$$

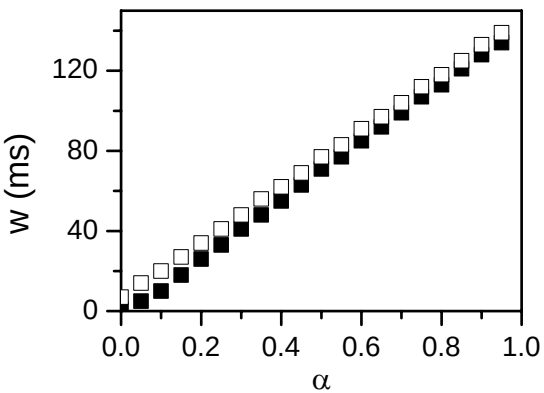
$$a_2 = a_0(1 - \alpha e^{-d_1/25} - \beta e^{-d_1/150})$$











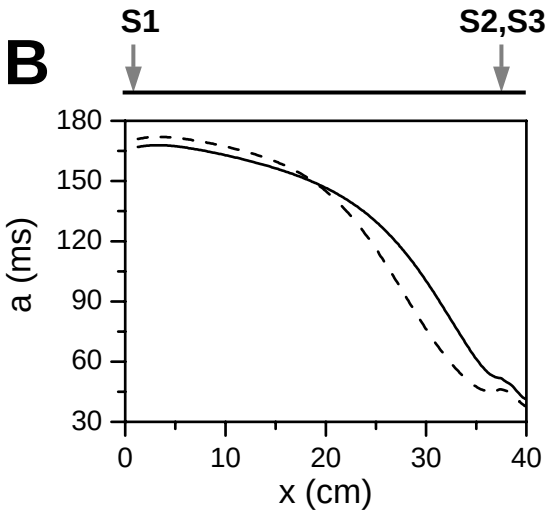
(Qu et al, Biophys J 2006b)

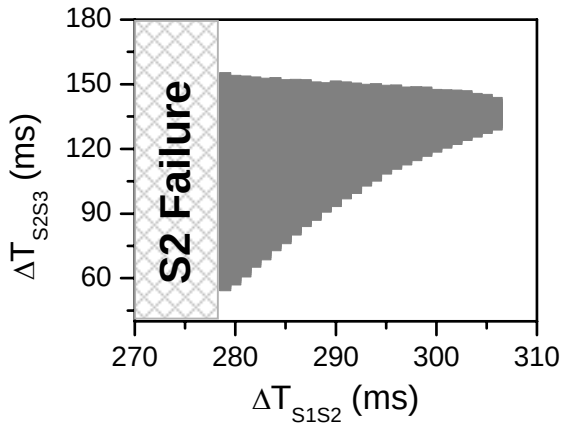
Vulnerable window of conduction block with two PVCs: Simulation of the LR1 model in a 1D cable

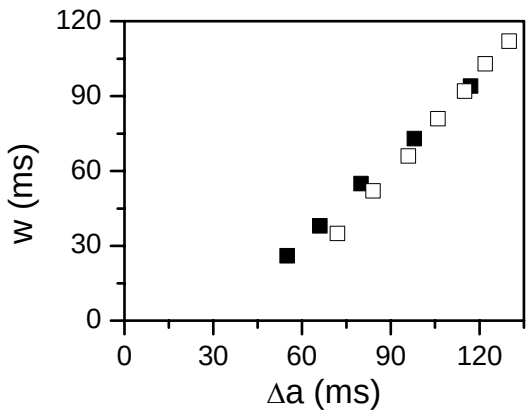
A

No vulnerable window for conduction block is detectable.

B

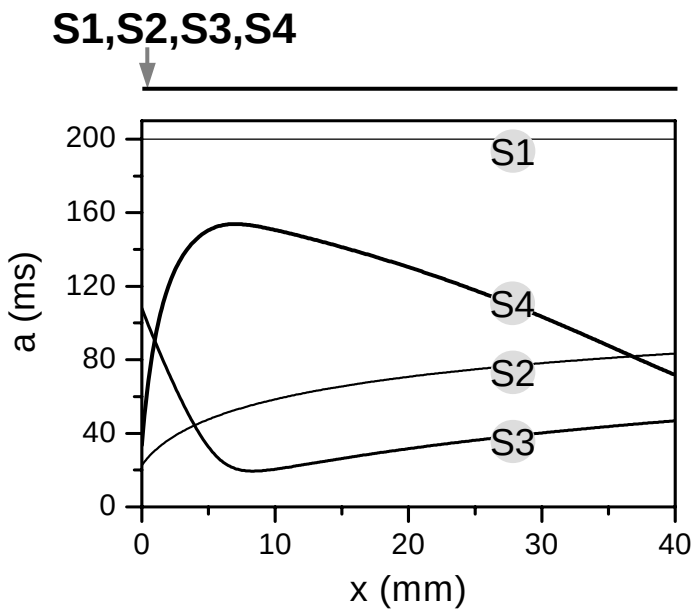


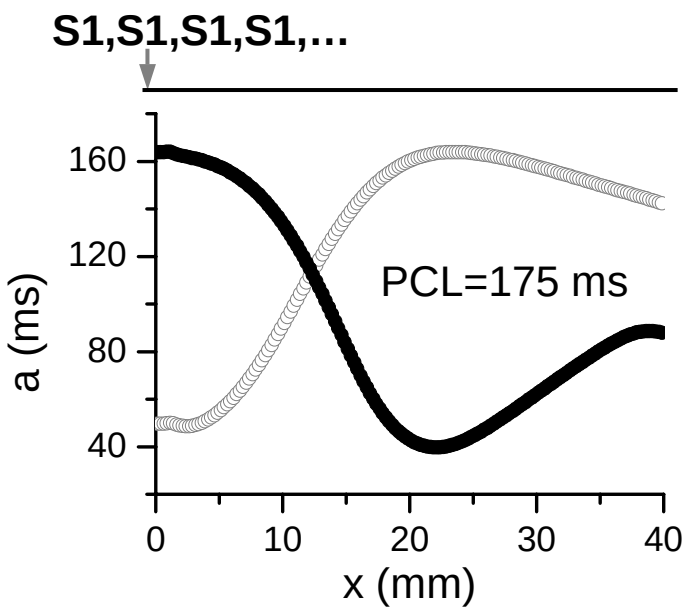


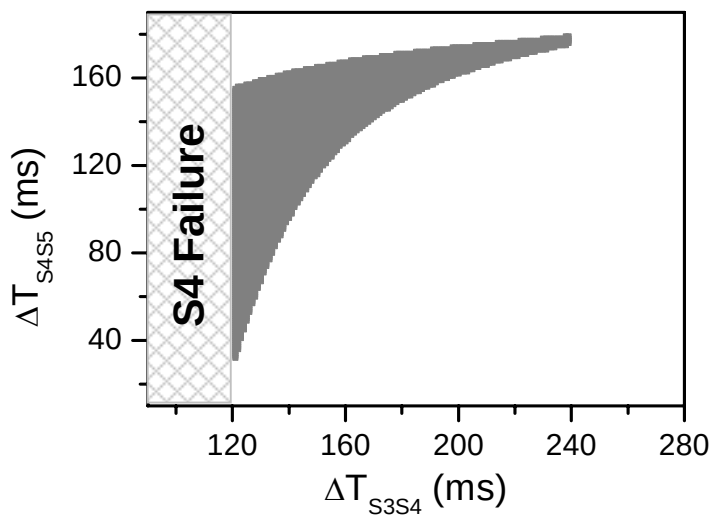


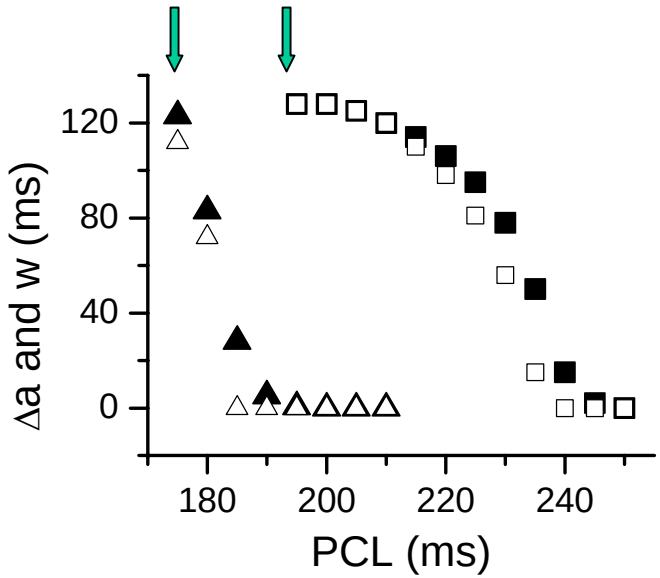
(Qu et al, Biophys J 2006b)

Vulnerable window of conduction block with Multi-PVCs

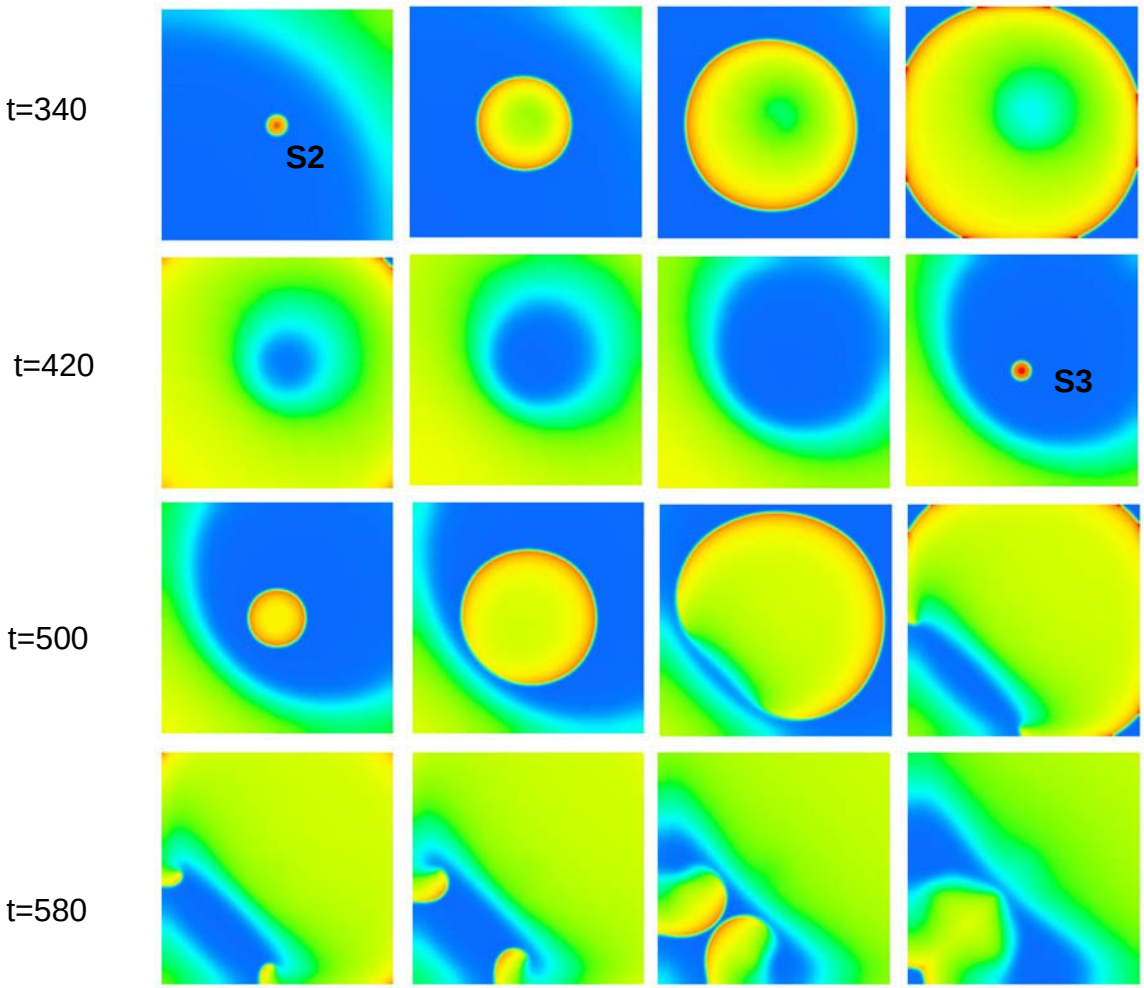


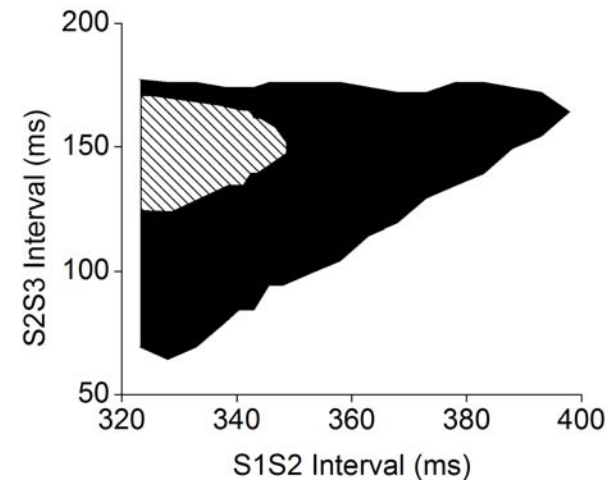


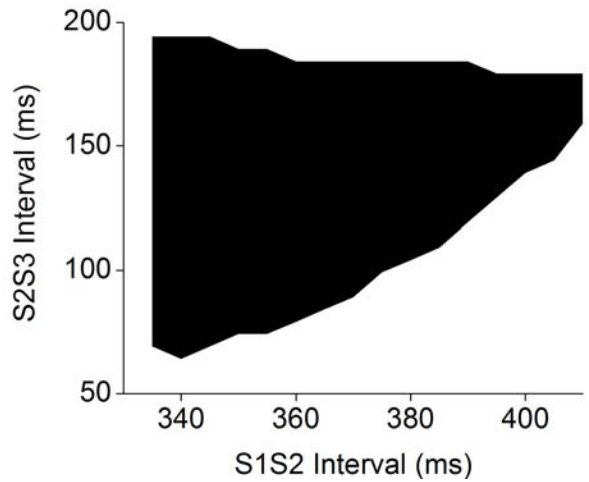




Vulnerable window of reentry in 2D tissue with two PVCs: Effects of CV restitution





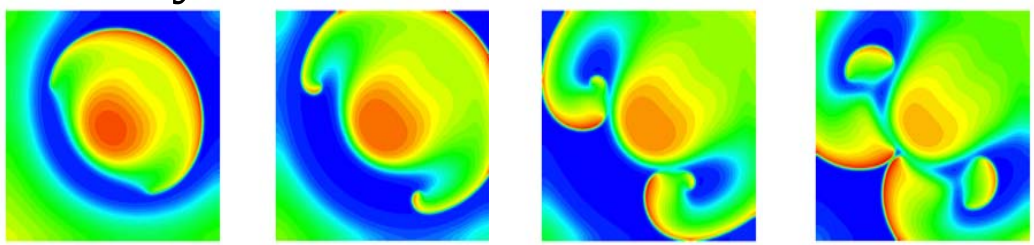


(Tran et al, unpublished data)

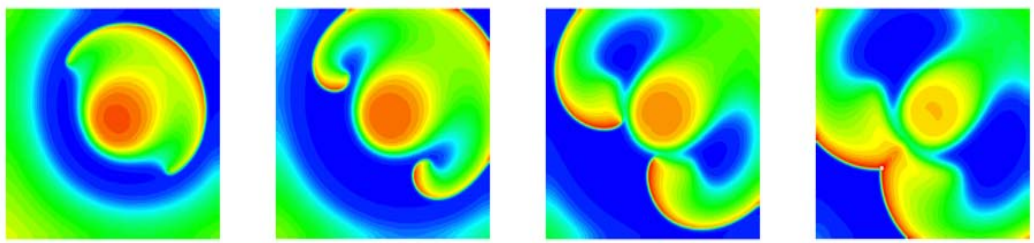
Vulnerable window of reentry in 2D tissue with two PVCs: Effects of APD restitution

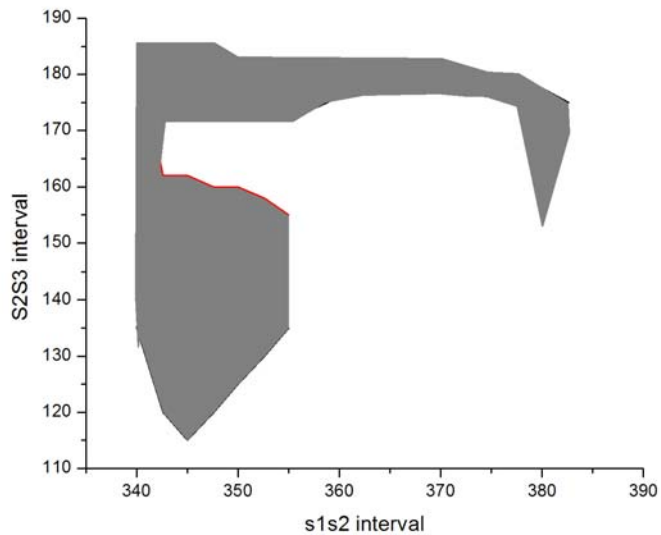
If the APD restitution curve is shallow, no reentry can be induced by this S1S2S3 protocol. Reentry can be induced only when APD restitution curve is steep enough. However, if the APD restitution curve is very steep, the vulnerable window may become even smaller.

Reentry



Block





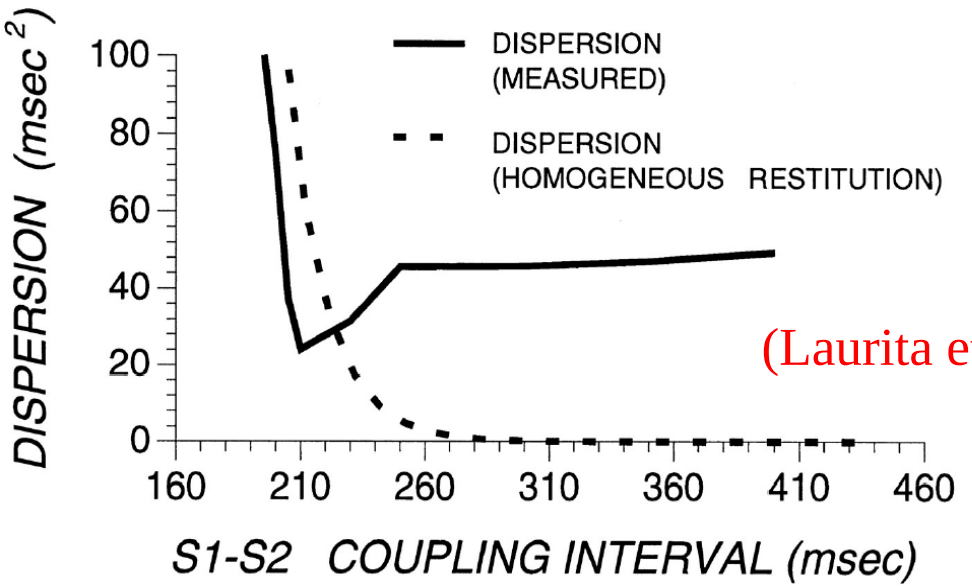
(Tran et al, unpublished data)

Implications from the modeling studies

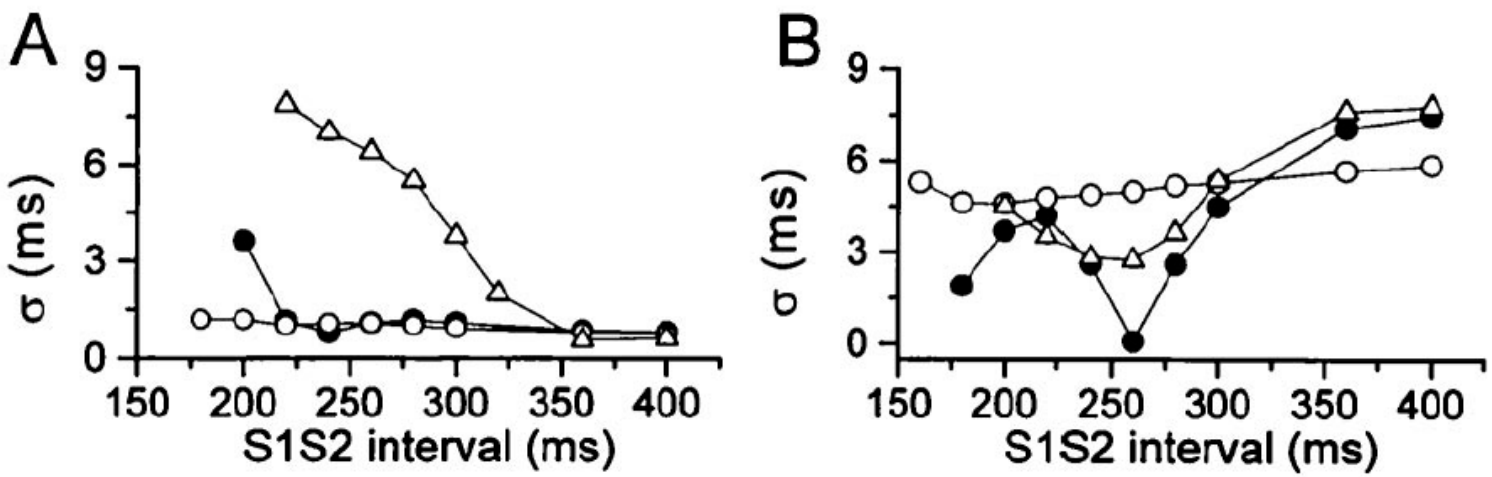
Pre-existing (intrinsic) tissue heterogeneity in refractoriness is not required for initiation of reentrant arrhythmias, as long as the tissue has proper APD and CV restitution characteristics and properly timed multiple PVCs.

3. Heterogeneous tissue with multiple extrasystoles

Modulation of dispersion of refractoriness by a PVC

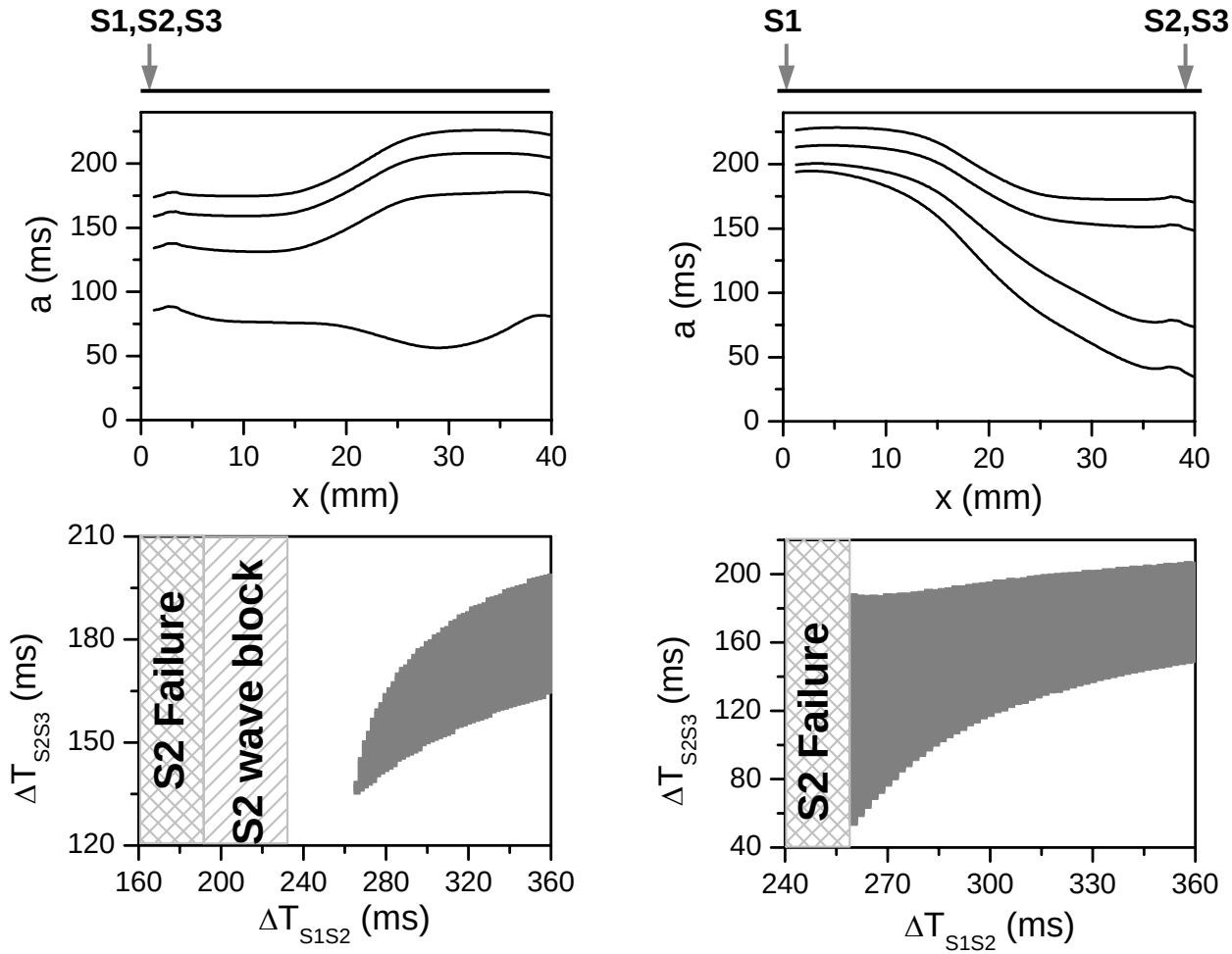


(Laurita et al, Circulation 1996)



(Qu et al, Circulation 2000)

Vulnerable window of conduction block with two PVCs: Effects of stimulation location



(Qu et al, Biophys J 2006b)

Implications from the modeling studies

Two consecutive PVCs (doublets) originated from the epicardial region are more arrhythmogenic than the ones from the endocardial region.

Conclusions

1. A critical refractory gradient is needed for conduction block, which is determined by CV restitution properties; once the critical gradient is reached, the vulnerable window is proportional to the height of the refractory barrier.

2. In addition to the pre-existing gradient of refractoriness, APD and CV restitution curves are two key parameters for regulating the vulnerable window of conduction block and reentry.

3. What about intracellular calcium cycling?

4. Where the PVCs occur in heart cannot be controlled, however, the effects of stimulation sequence and locations on vulnerability to reentry should be implicative for induction of reentry in experiments, especially clinical EP studies.

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