The APD Restitution Hypothesis Revised: Slope > 1 Does Not Always Determine Alternans and Spiral Wave Breakup

F.H. Fenton[1,2], E.M. Cherry[2,3], H.M. Hastings[2,3], S.J. Evans[1,2]

[1]The Heart Institute, Beth Israel Medical Center, NY; [2]Center for Arrhythmia Research at Hofstra University, NY; [3]Department of Physics, Hofstra University, Hempstead, NY

Abstract

Background. Alternans has been found in many cases to be a precursor of fibrillation. A number of studies have shown the induction of alternans when the slope of the action potential duration (APD) restitution curve is greater than one[1]. However, some experimental and theoretical studies have also found that alternans did not occur during fast pacing despite APD restitution curve slopes greater than one[2]. Methods. We use an ionic cell model that allows direct variation of features not easily altered experimentally, namely, the APD and CV restitutions curves as well as the action potential shape, to isolate the effects of each. Results. We show that electrotonic and memory effects can suppress alternans even in the presence of steep APD restitution. Although alternans may be exhibited in isolated cells, intercellular currents related to the shape of the action potential[3] and conduction velocity restitution affect how alternans develops in tissue and in some cases may prevent its induction entirely. In addition, adaptation to changes in cycle length, or short-term memory, constitutes a second mechanism by which alternans can be suppressed, both in tissue and in isolated cells. We present results demonstrating for the first time that despite steep APD restitution, electrotonic and memory effects can prevent conduction blocks and stabilize reentrant waves in 2D and 3D. Conclusions. In agreement with results from previous studies[4,5], we find that the shape of the action potential can be important in the development of arrhythmias and that the slope of the APD restitution curve alone does not always well predict the onset of alternans. Therefore, incorporating electrotonic and memory effects is necessary to provide a more useful alternans criterion.

Methods

The model consist of 3 currents and 3 variables:

Currents:

$$I_{fi}(V,v) = -v^*p(V-V_c)(1-V)/\tau_d$$

$$I_{so}(V) = V(1-r)(1-v^*k_2)/\tau_o + r/\tau_r$$

$$I_{si}(V,w) = -w(\ 1+\tanh(k_1(V-V_c^{si}))/(2\tau_{si})$$

Gate Variables:

$$\partial_t v(\mathbf{x},t) = (1-p)(1-v)/\tau_v^-(V) - pv/\tau_v^+$$

$$\partial_t w(\mathbf{x},t) = (1-p)(1-w)/\tau_w^- - pw/\tau_w^+$$

Voltage:

$$\partial_t V(\mathbf{x},t) = \nabla \cdot (D\nabla V) - (I_{fi}+I_{so}+I_{si}) / C_m$$

For Model 3 an extra gate and current are used to increase the memory effect :

Current:

$$I_{so}(V) = V(1-r)(1-v^*kk)/\tau_o + r^*V^*y/\tau_r$$

Gate Variable:

$$\partial_t y(\mathbf{x},t) = p^*(1-y)/\tau_y^+ - (1-p)(y-0.1)/\tau_y^-,$$

where $\tau_v^-(V) = (1-q)\ \tau_{v1}^- + q\tau_{v2}^-$; p=0 if V < Vc, 1 if V Vc ;
q=0 if V < Vv,1 if V Vv ; r=0 if V < Vr, 1 if V Vr

The model parameters are varied (see table) to produce 3 different models. Model 1 and Model 2 have no memory and possess the same APD restitution but different AP shape. Model 3 has memory. All models have slope >1 and their conduction velocities (CV) can be varied to study conduction effects by changing τ_v.

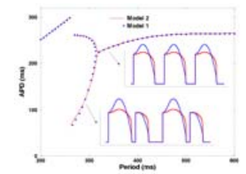
Parameter	τ_v^+	τ_{v1}^-	τ_{v2}^-	τ_w^+	τ_w^-	τ_d	τ_0	τ_r	τ_{si}
Model 1	10	350	80	562	48.5	0.15	1.5	12.5	10
Model 2	10	100	20	800	45	0.15	1.5	31	26.5
Model 3	3.33	55.2	300	600	40	0.075	8.3	38	127

Parameter	τ_y^+	τ_y^-	k_1	k_2	V_c^{si}	V_c	V_r	V_v	V_{fi}
Model 1	—	—	15	0	0.2	0.25	0.16	0.001	0.15
Model 2	—	—	10	1	0.7	0.25	0.6	0.05	0.11
Model 3	1000	191	60	0	0.7	0.25	0.25	0.05	0.25

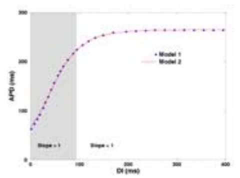
ELECTROTONIC EFFECTS

The Models

Model 1 and Model 2 have the same APD restitution with slope >1 but different AP shape. Compare Model 1 with slower repolarization (triangular AP) and Model 2 with faster repolarization (square AP). Action potential shape can affect tissue dynamics.

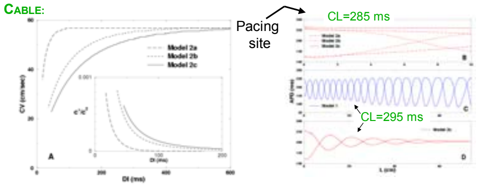


Model 1 (triangular) and Model 2 (square) have the same alternans amplitude (above) and APD restitution (below) in an isolated cell.



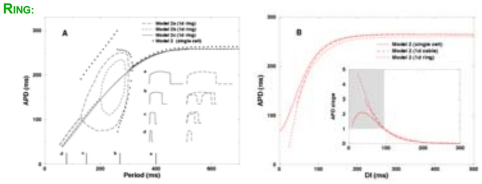
Dynamics in 1D

CABLE:



A: Three CV restitution curves for Model 2. Inset shows c'/c2 (ratio of CV restitution slope to square of CV). B: APD on two successive beats at steady state along a 1D cable. Model 2a: concordant alternans. Model 2b: discordant alternans. Model 2c: discordant alternans led to block and 2:1. C: For Model 1, alternans amplitude grows with distance from pacing site. D: For Model 2c, alternans amplitude decreases with distance from pacing site.

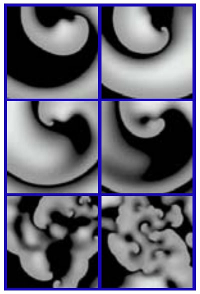
RING:



A: Rate adaptation in rings and isolated cell. Shallow CV restitution suppresses alternans in model 2 despite slope >1. Inset: spatial profiles at periods=400, 200, 148, 76 ms. B: APD restitution curves from isolated cell, 1D cable, 1D ring and their slopes, with maximum slope obtained in ring (slope =4.6) and no alternans is present.

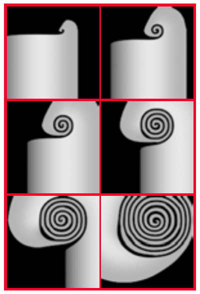
2D

Model 1 (triangular):
Alternans and breakup



12.5 x 12.5 cm

Model 2 (square):
No Alternans and stable



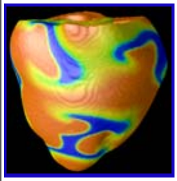
17.5 x 17.5 cm

3D

Simulations in rabbit ventricles[6]
including anisotropic fiber rotation

Model 1 (triangular)

Alternans and
spiral wave breakup

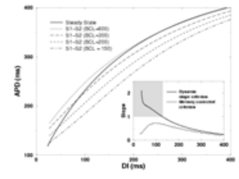


Model 2 (square)

No alternans,
stable spiral wave

MEMORY EFFECTS

The Model

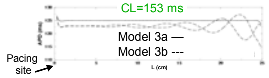


Dynamic (solid) and S1-S2 (dashed) restitution curves for the memory model.

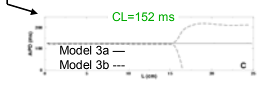
No alternans in the dynamic restitution despite slope > 1. Inset shows corrected criterion when memory is included: $|1-S_{S1\text{-}S2}(1+(1/S_{dyn}))|<1$.[5]

1D

Two different CV restitution curves.



APDs for two successive beats at steady state.
Model 3a: stable
Model 3b: alternans, amplitude increases with distance from pacing site.



APDs for beats 20 and 21.
Model 3a: stable 1:1 conduction
Model 3b: alternans with conduction block and 2:1 conduction far from the pacing site.

2D

Model 3a

Model 3b

In both models, alternans is suppressed.

Conclusions

Even when the slope of the APD restitution curve is greater than one over a large range of pacing cycle lengths, electrotonic and memory effects under some conditions can prevent or induce alternans. Therefore, the onset of alternans and the dynamics of reentrant waves in cardiac tissue cannot be well predicted by only the APD and CV restitution curves. Memory and electrotonic effects are important and need to be considered.

Important points:

- Action potential shape can be an important determinant of dynamics in tissue.
- Alternans in isolated cells does not guarantee alternans in tissue.
- Suppression of alternans in isolated cells does not guarantee suppression of alternans in tissue.
- Conduction velocity restitution can promote or suppress alternans in tissue.

References

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