A Simulation Study of Atrial Fibrillation Initiation: Differences in Resting Membrane Potential Can Produce Spontaneous Activations at the Pulmonary Vein-Left Atrial Junction

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Abstract

Introduction. Much attention has been given to the role of pulmonary vein (PV) focal activity during atrial fibrillation (AF). However, it still is not clear if PV preparations are auto-oscillatory and can produce ectopic beats when paced at physiological rates. An alternative hypothesis proposes that the resting membrane potentials (RMPs) of left atrial (LA) and PV cardiomyocytes may differ sufficiently to produce, by electrotonic effects, repeated spontaneous activations that propagate through the atria and potentially generate AF. **Methods and Results.** Using action potential (AP) recordings obtained experimentally, we developed ionic models of canine PV and LA cardiomyocyte APs that reproduce rate of rise, morphology, RMP (-74 mV in LA versus -65mV in PV), and rate adaptation. To study how different RMPs affected propagation, we created adjoining regions of PV and LA tissue of varying sizes. Electrotonic currents between adjacent regions originated when cells were at rest, due to differences in RMP, with coupling strength governing the spatial voltage profile between the two RMPs. We found that spontaneous activations arose in highly specific circumstances that can be understood by analyzing the interactions among spatial voltage profile, recovery from Na+ channel inactivation, and excitation threshold (ET). In particular, not only differences in RMP, but also differences in ET (such as those caused by stretch, memory, aging, and other mechanisms), were necessary for spontaneous activity to arise and propagate into the LA. **Conclusions.** PV focal activity leading to AF in some cases may arise not from auto-oscillatory behavior, but rather from experimentally observed RMP differences that result in continuous re-excitation via electrotonic current passage between adjacent regions.

Methods

The model consists of the following equations:

Currents: $I_{ti}(V,v) = -v^*p(V-V_c)(V_m-V)/\tau_{ti}$

$I_{so}(V) = (V-V_o)(1-r)/\tau_o + r^*0.009$

$+rb^*(1+\tanh(k_2(V-V_c^{so})))/2$

$I_{si}(V,w) = -w^*d/\tau_{si}$

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

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

$\partial_t d(\mathbf{x},t) = (1-p)^*dxd(V,d)/\tau_d^- + p^*dxd(V,d)/\tau_d^+$

$dxd = (0.5^*(1+\tanh(k_t(V-V_c^{si}))-d)$

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

where $\tau_v^-(V) = (1-q)\,\tau_{v1}^- + q\tau_{v2}^-$; For L.A. $\tau_v(V) = \tau_{so}$ and for P.V.

$\tau_o(V) = \tau_{oo}[s1+(1-s1)^*((-17.14^*s2^*V+7)+2.2^*(1-s2))]$

p=0 if V < V_c, 1 if V≥ V_c ; s1=1 if V > 0.35, 0 if V <0.35;

q=0 if V < V_v, 1 if V≥ V_v ; r=0 if V < V_v, 1 if V≥ V_v ;

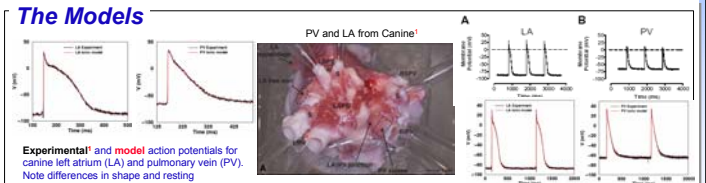
s2=1 if V > 0.28, 0 if V < 0.28; C_m=1, D=0.001cm²/s

The model parameters are varied (see table) to produce the action potentials for pulmonary vein (PV) and left atrium (LA).

Parameter	τ_v^+	τ_{v1}^-	τ_{v2}^-	τ_w^+	τ_w^-	τ_{si}	τ_{oo}	rb	τ_{si}
Left Atrium	3.33	50	50	160	75	0.065	39	0.106	31.83
Pulmonary Vein	3.33	50	30	160	75	0.187	55	0.016	47.53

Parameter	τ_d^+	τ_d^-	k_t	k_2	V_c^{si}	V_c	V_v	V_v	V_c^{so}	V_o
Left Atrium	50	0.833	3	50	0.8	0.08	0.3	0.155	0.84	0
Pulmonary Vein	50	0.833	3	14.28	0.8	0.25	0.6	0.21	0.9	0.15

The Models



Experimental[1] and **model** action potentials for canine left atrium (LA) and pulmonary vein (PV). Note differences in shape and resting membrane potential.

Upstroke velocity: PV= 98+ 9 V/s in experiment, 98 V/s in ionic model

LA = 259+16 V/s in experiment, 260 V/s in ionic model

Dynamics in One Dimension

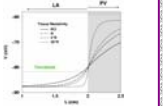
When the LA activation threshold is lower than the PV resting membrane potential, the difference in RMP can produce a current[6] that produces spontaneous activations depending on:

- Tissue resistivity.
- Difference in RMPs.
- I_{Na} reactivation.
- Difference in activation thresholds, which may decrease with age, etc.[2,3,4,7]

I_{Na} Inactivation and Reactivation

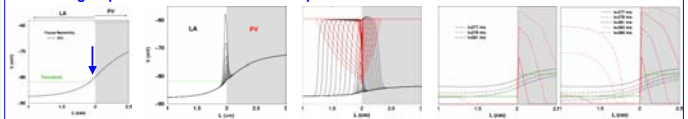
Reactivation of I_{Na} is the key to whether a true activation can develop. An action potential can occur **only** when the channels have reactivated.

Tissue Resistivity



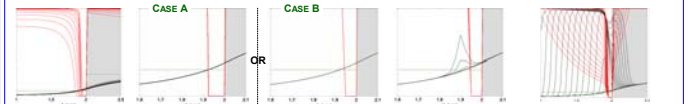
Changing the tissue resistivity changes the voltage profile across the PV-LA interface. For low resistivity, LA tissue may be pulled above threshold by the electrotonic current.

How a single spontaneous activation can be produced



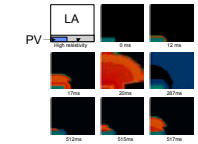
1. Electrotonic effects bring the voltage above threshold for some LA cells near the PV.
2. The cells above threshold produce an activation that propagates into both LA and PV.
3. As the activation propagates, sodium channels inactivate.
4. During late repolarization, sodium channels reactivate as the voltage falls below threshold.

How repetitive spontaneous activations can be produced



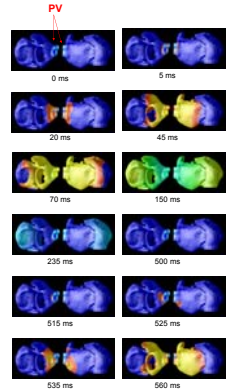
1. After an initial activation, sodium channels remain inactivated in regions where the voltage never went below threshold.
2A. All LA cells with voltage above threshold have inactivated sodium channels. No more activations are possible.
2B. Some LA cells with voltage above threshold have inactivated sodium channels, but some have reactivated.
3B. The LA cells above threshold with reactivated sodium channels can produce an activation that propagates only to the LA.
4B. As the LA cells fully depolarize, electrotonic effects bring the voltage of cells whose sodium channels are still inactivated above threshold without I_{Na}, and propagation proceeds to the PV.

Two Dimensions



Formation and propagation of an activation from the PV region. An area of high resistivity between LA and PV modulates the electrotonic effects to allow spontaneous activity. Black is polarized tissue, red is depolarized.

Three Dimensions



Formation and propagation of successive activations from the left pulmonary veins in a model of the human atria[4]. Two activations are shown in the series, with each image displaying two views of the left and right atria. Note that the activations begin in different regions. An area of high resistivity between LA and PV modulates the electrotonic effects to allow spontaneous activity. Blue is polarized tissue, red is depolarized.

Conclusions

Pulmonary vein focal activity leading to atrial fibrillation in some cases may arise not from auto-oscillatory behavior, but rather from experimentally observed differences in resting membrane potential that result in continuous re-excitation via electrotonic current passage between adjacent left atrium and pulmonary vein regions.

Spontaneous activations can occur when the different resting membrane potentials between LA and PV and cellular coupling produce a voltage profile that meets the following conditions:

- Activation threshold for LA tissue must be lower than the PV resting membrane potential.
- Voltage for part of the LA side of the LA-PV interface must recover enough for I_{Na} to reactivate.
- Electrotonic current from different resting membrane potentials then must be large enough to bring the LA side of the LA-PV interface above threshold.

References

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