Fibrillation Without Alternans in Porcine Ventricles: Experiments, Theory, and Numerical Simulations

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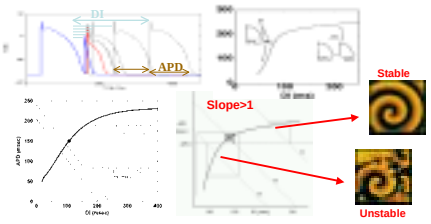
Abstract

Introduction. Experiments in porcine ventricles have shown that while fibrillation is readily induced by a premature stimulus, alternans does not appear to play a role in its induction despite APD restitution slope greater than one. However, the reasons for this behavior are not well understood. **Methods.** Using data obtained directly from experiments, we developed an ionic cell model of the porcine ventricular action potential. The model accurately reproduces the action potential shape, threshold for excitation, and maximum upstroke velocity, as well as the steady-state action potential duration restitution (APDR) curve and the conduction velocity (CV) restitution curve measured experimentally. No regional variations in ionic currents were incorporated because experiments have shown little change in action potential morphology throughout young porcine ventricles. The cell model was combined with an anatomically realistic porcine ventricular model that includes fiber orientation data. **Results.** As in experiments, the simulations in tissue do not develop electrical alternans at fast pacing rates despite APD restitution slope greater than one over a range of cycle lengths. Therefore, induction of fibrillation was not possible in this model of the porcine ventricles by any fast pacing protocol. However, as in experiments, it was possible to initiate fibrillation by applying a premature stimulus during the T-wave. **Conclusions.** In the model, the relatively large electrotonic effects during repolarization due to the specific shape of the porcine action potential produced a stabilizing effect that suppressed alternans in tissue. Our model provides a possible explanation for the lack of alternans found experimentally in porcine ventricles subject to fast pacing.

APD Restitution and Alternans

One mechanism believed to be responsible for electrical alternans and conduction block is steep APD restitution.[1,2]



Is there a problem with the theory?

However, there are experiments that show:

- No alternans despite dynamic APDR slope >1
  - Gauthier et al., PRL 2995-2998, 1999 (in frog)
  - Banville et al., JCE 455-463, 2004 (in pig)
- VF activity with dynamic APDR slope <1
  - Hao et al., AJP H390-H394, 2004 (in pig)
- Termination of VF by tissue reduction (no drugs)
  - Janse et al., JCE 512-521, 1995 (in pig)
  - Kim et al., JCI 2486-2500, 1997 (in pig) (even though the size of the remaining tissue could sustain a few wavelets)

APDR is an important determinant for cardiac dynamics; however, ***APDR alone is not always a good predictor for instabilities.***

Other characteristics of cardiac tissue are important destabilizing factors for reentry:

- Minimum DI.
- AP morphology (electrotonic effects).
- CV restitution.
- Fiber orientation (rotational anisotropy).

Also: calcium dynamics, electromechanical feedback, ion channel distribution, and disease.

Objective

Demonstrate that computer simulations can reproduce experimental results and thus can be used to understand cardiac dynamics.

Show that the APDR hypothesis does not seem to apply in this case.

Explain how other mechanisms potentially may explain the observed wave breaks and complex dynamics.

Ionic Model

A potentially important characteristic of the porcine ventricular AP is a relatively fast phase 3 (repolarization). This can produce strong electrotonic effects (ξ c'/c2) that can prevent alternans.[3,4,5]

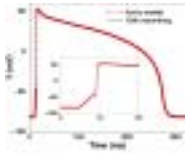
Experiments:

Lee et al., AJP 2001 Kim et al., Circ 1999 Omichi et al., AJP 2002

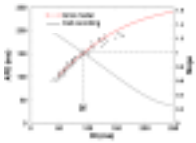
Stankovicova et al., Card Res 2000 Hao et al., AJP 2004

The ionic model is fitted to reproduce the AP dynamics of Banville et al.

Porcine Action Potential

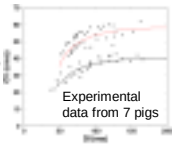


Porcine AP Restitution



Slope > 1 for DI < 91 ms

Porcine CV Restitution



Points are from experiments; curves are from the ionic model.

Experimental:

APD_{max} = 255 ± 40 ms (Rodriguez et al., Card. Res., 1996)

$(dv/dt)_{max}$ = 130 ± V/s (Rodriguez et al.)

Ionic model:

APD_{max} = 264 ms (fitted to experimental microelectrode)

$(dv/dt)_{max}$ = 130 V/s (fitted to Rodriguez)

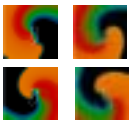
The ionic model reproduces:

- **Shape of AP.**
- **Threshold of excitation.**
- **Maximum upstroke velocity $(dv/dt)_{max}$.**
- **APD restitution.**
- **CV restitution.**
- **No alternans when paced in tissue at high frequencies.**

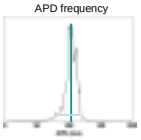
Dynamics in Two Dimensions

2D simulations

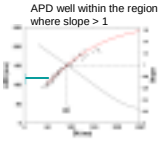
Stable reentry despite period in the slope >1 region (there is no alternans)



APD frequency



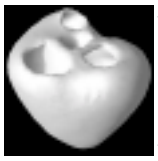
APD well within the region where slope > 1



As in the experiments of Banville et al[6], no alternans was observed in the ionic model. In the model this is due to the strong electrotonic effects (ξ c'/c^2) (when using the experimentally measured CV restitution).

Can the model produce VF in porcine ventricles? If so, how?

Porcine Ventricular Structure



Porcine ventricular structure obtained by dissection at 250 microns. From Stevens, LeGrice, and Hunter, J. Biomech 2003.[7]

Ventricular values:

Volume: ~ 87 cm3
Average RV thickness: ~0.2 cm
Average LV thickness: ~0.8 cm
Average Septum thickness: ~1.2 cm
Epicardial surface area: ~280 cm^2
Apex to base: 7.2 cm

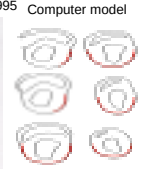
Slice 5.5 cm from apex | Slice 4.5 cm from apex | Slice 0.7 cm from apex

Minimum Mass for VF

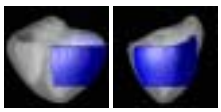
Freezing of Endocardium Converts VF to VT

Thinning experiments:
Janse et al. JCE 1995

Computer model

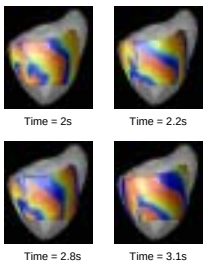


Views of surviving epicardium in 3D

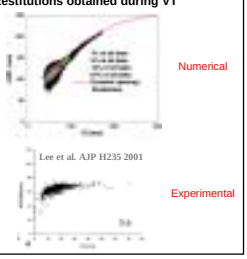


A small, thin live layer of epicardium after freezing the endocardium sustains VT but not VF.

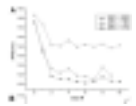
VT_{period}=186±12 ms, Banville et al.
VT_{period} =176.2 ms, Simulation



Restitutions obtained during VT

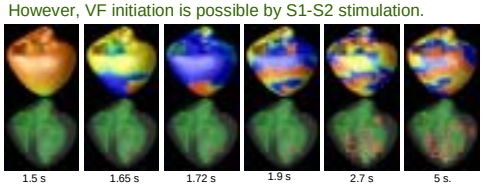


Dynamics in Three Dimensions



Constant pacing at various short CLs does not induce VF. In addition, no alternans is observed at any CL. (experimentally and numerically)

However, VF initiation is possible by S1-S2 stimulation.

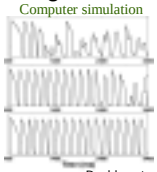


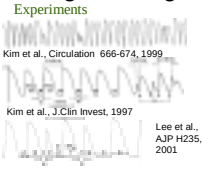
1.5 s | 1.65 s | 1.72 s | 1.9 s | 2.7 s | 5 s.

1 sec of simulation time takes 5 hours on a 96-processor Beowulf (3GHz Xeon).

Signal Recording During VF in Pig

Computer simulation | Experiments



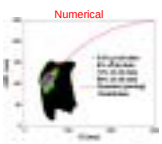


Double potentials occur close to the spiral core.

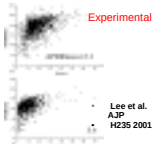
Experiments: T=157±10 ms
Simulations: T=161.7 ms

Restitutions obtained during VF

Numerical



Experimental



Summary and Conclusions

- We developed a new ionic model of the porcine ventricular action potential.
- Electrotonic effects prevent alternans in this model, and, as in experiments, VF could be initiated only by an extra stimulus and not by fast pacing.
- The wave breaks that occurred during VF were not due to steep APDR but instead were caused by head-tail interactions + ventricular structure, complex fiber orientation, and wave tip dynamics.
- During VF some short-lived intramural reentry occurred but most reentries were transmural. In some cases stable transmural reentry was observed for several seconds during VF.
- VF converted to VT when tissue size was reduced.
- Signals and periods obtained numerically in all cases were very close to those obtained in experiments.

Other important points:

- Double potentials produce spurious points in the APD restitution curve.
- APD restitution measured during VT is flat, but flattening restitution does not necessarily eliminate VF.
- VF may convert to VT for other reasons (minimum DI, change in tip dynamics, wavelength, conduction velocity restitution, etc.

References

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