Impact of disease state on arrhythmic event detection using APD modeling

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Introduction

The goal of the CiPA paradigm is to allow the preclinical detection of not simply drug-associated QTc prolongation but also proarrhythmic events. However, it is well known that the incidence of the drug-associated event of interest, torsades, is relatively rare. We explored, using *in silico* action potential modeling, the influence of various underlying cardiac risk factors (heart failure (HF) and ventricular hypertrophy (VH)) on the incidence of proarrhythmic events (e.g. early afterdepolarizations, EAD).

Methods

Simulations under normal conditions:

- Cell geometry, channel conductance, state variables and scaling factors for endocardial myocytes as described in O'Hara-Rudy dynamic model (1)
- External ionic concentrations (mM): $[Na^+]_o$ 140 - $[Ca^{++}]_o$ 1.8 - $[K^+]_o$ 5.4
- Cycle length: 1000 msec. Beat number: 100

Simulations under HF (2):

O'Hara-Rudy dynamic model (1) with ⇗I_{NaL} 200%, ⇗τ_{NaL} 200%, ⇘I_{to} 40%, ⇗I_{ncx} 75%, ⇘I_{K1} 32%, ⇘I_{NaK} 10%, ⇘I_{up}/I_{serca} 50 %, ⇗I_{leak} 500 %, ⇘I_{Nab} 100% and ⇗I_{Cab} 53%

Simulations under VF (3)

O'Hara-Rudy dynamic model (1) with ⇗I_{NaL} 165%, ⇗I_{Nab} 165%, ⇗I_{CaL} 40%, ⇗τI_{CaL} fast inactivation 35%, ⇗τI_{CaL} slow inactivation 20%, ⇗I_{NCX} 30 %, ⇗ cell radius to reproduce ⇗cell volume of 90 %, ⇘Ito 70%, ⇘I_{K1} 30%, ⇘I_{Kr} 45%, ⇘I_{Ks} 45%, ⇘I_{NaK} 30%, ⇘Jup 25%, ⇘Jrel 20%, ⇘KTRPN 50%.

Effect of drugs on AP (4):

- channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of IC_{50s} and the tested concentration

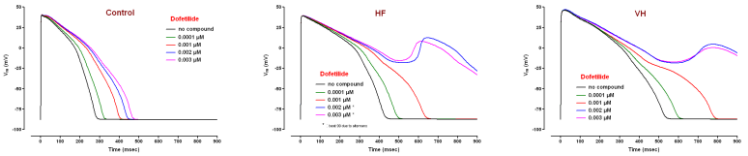
% current inhibition (5):

Ion channel inhibition data from Crumb et al.

Results

Dofetilide :

At a pacing rate of 1Hz, under normal conditions, dofetilide (0.0001-0.003 µM) was associated with a maximal increase in APD_{90} of 70%, without EADs. Free plasma concentrations of ≈ 2nM have been associated with a 70-80 ms increase in QTc and no torsades in healthy volunteers. In contrast, under HF and VH conditions, EADs were observed beginning at 0.002 µM.



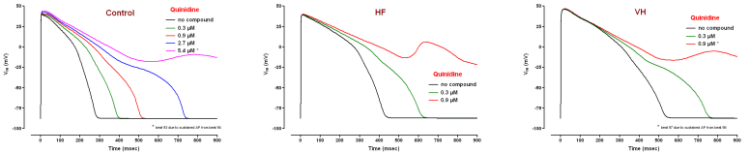
APD90(△%)

Dofetilide (µM)

Conc.	0.0001	0.001	0.002	0.003
Control	13.7	42.6	56.7	67.3
HF	14.5	48.6	EAD	EAD
VH	13.3	49.0	EAD	EAD

Quinidine :

Similarly, quinidine (0.3-5.4 µM) was only associated with EADs at the highest concentration examined under normal conditions but under diseased conditions, EADs were observed at all concentrations above 0.3µ M.



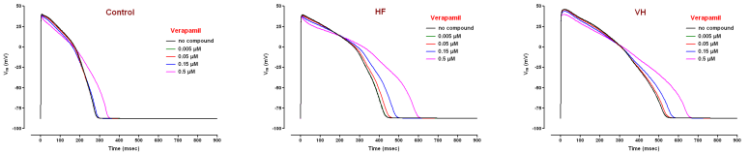
APD90(△%)

Quinidine (µM)

Conc.	0.3	0.9	2.7	5.4
Control	39.1	83.2	165.7	EAD
HF	44.2	EAD		
VH	43.00	EAD		

Verapamil :

APD_{90} prolongation with verapamil (0.005-0.5 µM) was modest, approximately 22-40 % at 0.5µM, and under no conditions were EADs observed.



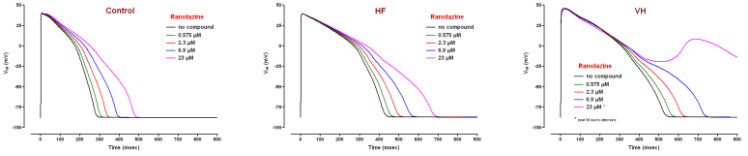
APD90(△%)

Verapamil (µM)

Conc.	0.005	0.05	0.15	0.5
Control	-0.2	-0.3	2.0	21.9
HF	0.4	4.3	13.2	39.6
VH	0.3	2.3	6.9	23.4

Ranolazine :

Ranolazine (0.575-23 µM) was associated with a 59-72% increase in APD_{90} at 23 µM but EADs were only observed in VH conditions and only at the highest concentration tested.



APD90(△%)

Ranolazine (µM)

Conc.	0.575	2.3	6.9	23
Control	7.6	19.3	38.7	71.5
HF	6.3	16.0	30.3	59.0
VH	6.6	17.0	38.8	EAD

Conclusions

These results provide mechanistic support for the impact of pre-existing cardiovascular disease on arrhythmic events and suggest that in order to fully realize the goal of the CiPA paradigm, e.g. arrhythmia detection, disease state modeling may need to be incorporated.

References

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