Proarrhythmic effects of Flecainide and Dofetilide on electrophysiological properties of atrial myocytes: a computational approach

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AFib TrainNet — Marie Curie Actions

MOTIVATION

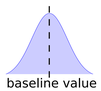
Flecainide and Dofetilide are commonly used drugs for cardioversion of atrial fibrillation and rhythm control, but pose proarrhythmic risks in patients with underlying structural heart disease. Therefore, quantification of their effects on electrophysiological properties of atrial myocytes can provide further insight into their potential arrhythmic risk.

POPULATION OF MODELS (PoM) APPROACH

Incorporating variability in single cell model

Normal distributions with variabl
variances of parameters

~ -40% – +40%



2 populations of 1000 models:

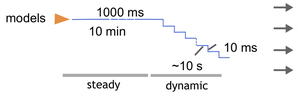
Normal sinus rhythm (nSR)

Chronic AF (cAF)

Parameters varied

Ionic conductances	G_{CaL}, G_{Na}, G_{K1}, G_{Kr}, G_{Ks}, G_{Kur}, G_{to}, G_{NaL}, G_{NaK}, G_{NCX}, G_{CaP}
RyR conductance and time constants	RyRmax, RyRmaxss, RyRtauad, Ryrtauact, RyRtauact, RyRtauactss, RyRtauinact
SERCA2a density	cpumpsbase

Pacing protocol



Biomarkers

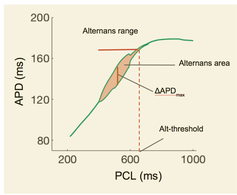
Action Potential

AP duration (APD90)
AP amplitude (APA)
Resting potential (RMP)
Upstroke velocity (dVdt)

EAD occurrence
EAD duration

APD Restitution [1]

Alternans threshold
Alternans range
Alternans area
Maximum long-short APD
Aternans occurrence



Calibrations of PoMs with experimental values [2]

nSR

APD90: 190 – 440 ms
APA: 75 – 120 mV
RMP: -85 – -65 mV
Upstroke velocity: 40 – 420 V/s

cAF

APD90: 140 – 330 ms
APA: 80 – 130 mV
RMP: -85 – -65 mV
Upstroke velocity: 40 – 420 V/s

Application of Dofetilide and Flecainide to the PoMs

Calibrated control nSR and cAF PoMs → Variability of parameters in calibrated PoMs → Resampling of parameters (n=1000) → Dose dependent block of ion channels → % Failed repolarization, % Alternans occurrence, % EADs occurrence

SENSITIVITY ANALYSIS

Multivariate linear regression

Input parameters (m x p) · Regression coefficients (p x n) = Output biomarkers (m x n)

$$\mathbf{X} \cdot \mathbf{B} = \mathbf{Y}$$

Logistic regression

$$\text{Probability } \mathbf{P(y|x)} = \frac{e^{(\mathbf{b_0} + \mathbf{B}\cdot\mathbf{X})}}{1 + e^{(\mathbf{b_0} + \mathbf{B}\cdot\mathbf{X})}}$$

Statistical analysis:

F-test with 90% confidence interval

BLOCKADE PROFILE OF DRUGS

Table I. Values of Cmax, IC50 and nh used to calculate dose dependent percentage block of ion channels [3].

		ICaL	IKr	IK1	Ito	IKs	INaL	INa
Defetilide	IC_{50}	∞	1.0	∞	∞	∞	∞	∞
$C_{max} = 2.1$	nh	1	0.6	1	1	1	1	1
Flecanide	IC_{50}	25599	692	∞	9266	∞	18870	6677
$C_{max} = 752.9$	nh	1.4	0.8	1	0.7	1	0.6	1.9

$$\%\,\text{block} = \frac{(C_{max} * dose)^{nh}}{IC_{50}{}^{nh} + (Cmax * dose)^{nh}}$$

dose = 0.1, 0.3, 0.6, 1.6 , 4.0, 10.0

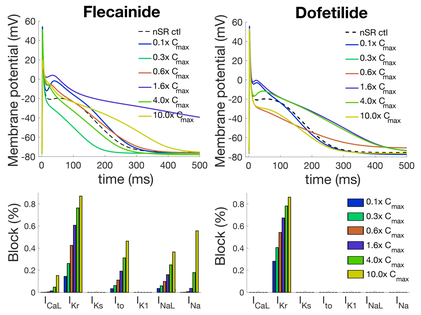


Fig 1. Ion channel block profile of Flecainide and Dofetilide [3].

CONTROL nSR AND cAF PoMs

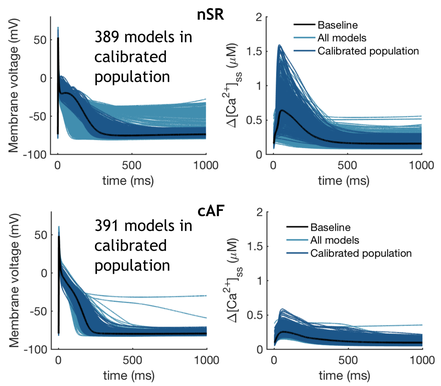


Fig 2. Control nSR (upper) and cAF (lower) PoMs.

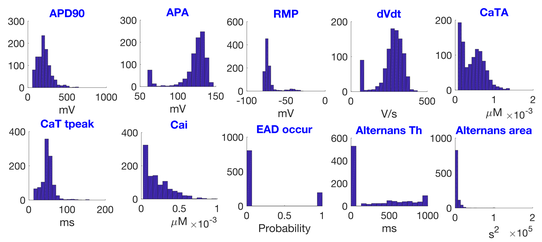


Fig 3. Distributions of biomarkers of the control nSR PoM.

EFFECTS OF DOFETILIDE AND FLECAINIDE ON ELECTROPHYSIOLOGICAL PROPERTIES

Table IIa and IIb. Incidence of abnormal AP shape (defined as models whose biomarkers do not all lie within the values used for calibration of the nSR and cAF PoMs - see Methods section), EADs, repolarization failure, and APD alternans in the nSR (IIa) and cAF (IIb) PoMs.

Incidence (%)	Abnormal AP	Failed repol.	EADs	APD alternans
nSR Control	59.2	10.2	19.5	99.8
Dof 0.1x C_{max}	38.8	5.3	5.9	61.2
Dof 0.3x C_{max}	35.4	4.2	4.0	60.1
Dof 0.6x C_{max}	29.1	6.3	4.4	65.6
Dof 1.6x C_{max}	27.5	6.7	2.2	64.8
Dof 4.0x C_{max}	27.7	7.0	3.4	64.2
Dof 10.0x C_{max}	29.6	7.8	3.2	66
Flec 0.1x C_{max}	41.1	4.5	9.7	63.7
Flec 0.3x C_{max}	38.4	6.0	7.3	59.9
Flec 0.6x C_{max}	28.4	5.6	4.6	61.7
Flec 1.6x C_{max}	26.3	8.3	4.6	62.8
Flec 4.0x C_{max}	29.7	13.3	8.7	62.0
Flec 10.0x C_{max}	73.6	48.3	41.0	44.1

Incidence (%)	Abnormal AP	Failed repol.	EADs	APD alternans
cAF Control	58.2	0.2	0.1	28.4
Dof 0.1x C_{max}	60.9	0.2	0.3	28.1
Dof 0.3x C_{max}	57.5	0.0	0.1	27.7
Dof 0.6x C_{max}	53.8	0.2	0.2	28.5
Dof 1.6x C_{max}	52.1	0.2	0.4	42.0
Dof 4.0x C_{max}	55.1	0.6	0.5	43.0
Dof 10.0x C_{max}	52.2	0.2	0.3	100.0
Flec 0.1x C_{max}	68.0	0.0	0.3	26.4
Flec 0.3x C_{max}	63.7	0.1	0.4	26.2
Flec 0.6x C_{max}	56.7	0.1	0.2	30.1
Flec 1.6x C_{max}	51.1	0.0	0.4	32.4
Flec 4.0x C_{max}	36.1	0.2	0.2	42.2
Flec 10.0x C_{max}	28.4	2.9	1.4	50.1

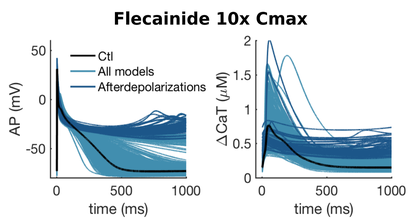


Fig 4. (Left) AP (left) and calcium transient (right) traces of Flecainide 10x Cmax population. This population showed 11% incidence of EADs at 1Hz pacing (one beat).

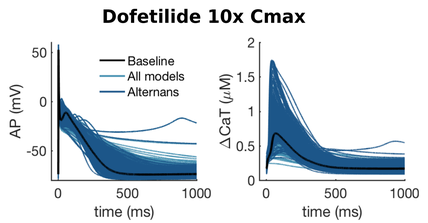


Fig 5. AP (left) and calcium transient (right) traces of Dofetilide 10x Cmax population. This population showed 76% incidence of APD alternans under dynamic pacing.

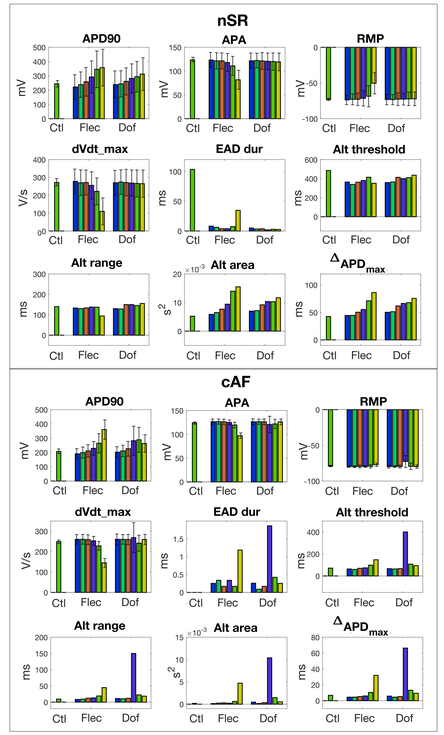


Fig 6. Mean values of biomarkers in control in nSR (top) and cAF (bottom), of Flecainade and Dofetilide populations with 6 different doses. Error bar represent standard deviation of distributions (only for quasi-normal distributions).

SENSITIVITY ANALYSIS

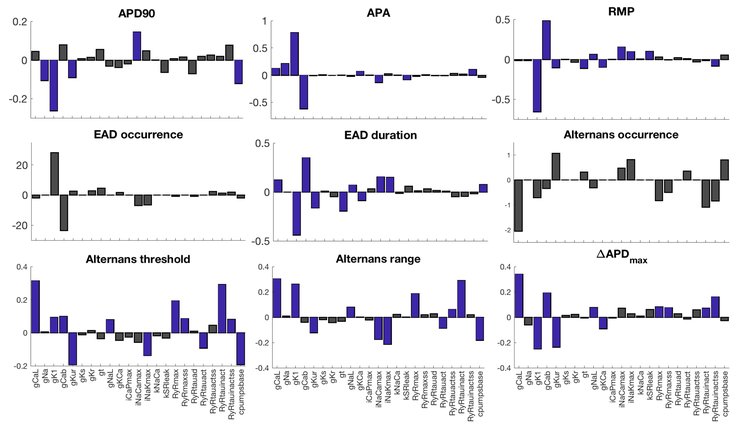


Fig 7. Sensitivity analysis of biomarkers of the Flecainide 10x Cmax population. Bars correspond to the regression correlection coefficients (B), and indicate the role of each model parameter in observed variability in the biomarkers. Blue bars indicate correlation coefficients with statistic significance (F-test, p-value<0.1), and gray bars show coefficients with no statistical significance.

CONCLUSIONS

- This work showcases an application of the populations of models and sensitivity analysis approach for in silico drug screening for atrial fibrillation.
- The results show altered electrophysiological behavior (particularly afterdepolarizations) when higher doses of Flecainide and Dofetilide are applied to a population ofmodels of the normal atrial cell.
- Sensitivity analysis suggests that the alternans-promoting behaviours of Flecainide and Dofetilide are driven by different mechanisms, and that APD alternans is driven by a complex interaction of cellular alterations. .

FUTURE WORK

Perform a more mechanistic exploration of the effect of selected CiPA drugs on atrial electrophysiology at different stages of atrial remodeling. Compare simulation results with available experimental data.

REFERENCES

[1] Vagos et al, Chaos (2017); [2] Sanchez et al, PLoS One (2014); [3] W. Crumb Jr et al, J Pharmacol Toxicol Methods (2016); [4] E. Passini et al, Front. Physio. (2017)

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