Computational modeling for antiarrhythmic drugs for atrial fibrillation according to the genotypes

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Funding Acknowledgements: Type of funding sources: Public grant(s) – National budget only. Main funding source(s): This work was supported by a grant [HI19C0114] from the Ministry of Health and Welfare. Additionally, the work was funded by grants [NRF-2019R1C1C100907512], and [NRF-2020R1A2B01001695] from the Basic Science Research Program run by the National Research Foundation of Korea (NRF) under the Ministry of Science, ICT & Future Planning (MSIP).

Background: The efficacy of antiarrhythmic drugs (AAD) can vary in patients with atrial fibrillation (AF) and the PITX2 gene affects the responsiveness of AADs. We explored the virtual AAD (V-AAD) responses between wild-type and PITX2+/- deficient AF conditions by realistic in-silico AF modeling.

Methods: We tested the V-AADs in AF modeling integrated with patients' 3D-computed tomography and 3D-electroanatomical mapping, acquired in 25 patients (68% male, 59.8 ± 9.8 years old, 32.0% paroxysmal type). The ion currents for the PITX2+/- deficiency and each AAD (amiodarone, sotalol, dronedarone, flecainide, and propafenone) were defined based on previous publications.

Results: We compared the wild-type and PITX2+/- deficiency in terms of the action potential duration (APD90), conduction velocity (CV), maximal slope of restitution (Smax), and wave-dynamic parameters, such as the dominant frequency (DF), phase singularities (PS), and AF termination rates according to the V-AADs. The PITX2+/- deficient model exhibited a shorter APD90 ($p < 0.001$), a lower Smax ($p < 0.001$), mean DF ($p = 0.012$), PS number ($p < 0.001$), and a longer AF cycle length (AFCL, $p = 0.011$). Five V-AADs changed the electrophysiology in a dose dependent manner. AAD-induced AFCL lengthening ($p < 0.001$) and reductions in the CV ($p = 0.033$), peak DF ($p < 0.001$) and PS number ($p < 0.001$) were more significant in PITX2+/- deficient than wild-type AF. PITX2+/- deficient AF was easier to terminate with class IC AADs than the wild-type AF ($p = 0.018$).

Conclusions: The computational modeling-guided AAD test was feasible for evaluating the efficacy of multiple AADs in patients with AF. AF wave-dynamics and electrophysiological characteristics are different among the PITX2 deficient and the wild-type genotype models.

	Baseline			Changes after AAD			Class IC			Class III		
	Wild-type	PITX2+/-	p-value	Wild-type	PITX2+/-	p-value	Wild-type	PITX2+/-	p-value	Wild-type	PITX2+/-	p-value
APD90, (ms)	243.7 ± 33.8	184.4 ± 15.5	<0.001	38.2 ± 37.3	43.4 ± 56.2	0.223	275.9 ± 43.5	219.0 ± 39.2	<0.001	284.9 ± 32.8	233.8 ± 71.4	<0.001
CV, (m/s)	0.78 ± 0.32	0.70 ± 0.21	0.347	-0.15 ± 0.18	-0.20 ± 0.26	0.033	0.63 ± 0.32	0.53 ± 0.30	0.027	0.60 ± 0.36	0.43 ± 0.33	<0.001
Mean Smax	0.787 ± 0.28	0.531 ± 0.18	<0.001	0.005 ± 0.26	0.115 ± 0.24	<0.001	0.828 ± 0.31	0.694 ± 0.32	0.003	0.768 ± 0.32	0.608 ± 0.27	<0.001
Mean AFCL, (ms)	146.96 ± 24.61	164.78 ± 22.73	0.011	22.62 ± 24.55	37.92 ± 32.72	<0.001	165.44 ± 36.96	190.85 ± 35.61	<0.001	169.05 ± 25.26	203.35 ± 34.78	<0.001
Peak DF, (Hz)	10.68 ± 2.97	11.82 ± 3.34	0.211	-2.98 ± 4.94	-5.46 ± 4.66	<0.001	10.01 ± 4.39	7.23 ± 4.20	<0.001	6.30 ± 4.32	5.80 ± 4.07	0.301
Mean DF, (Hz)	6.80 ± 0.88	6.22 ± 0.71	0.012	-1.95 ± 2.44	-2.20 ± 1.99	0.206	5.75 ± 1.78	4.53 ± 2.00	<0.001	4.14 ± 2.39	3.69 ± 2.00	0.077
PS Number, (N)	101086 ± 96088	14150 ± 24778	<0.001	-59322 ± 99288	-7409 ± 27856	<0.001	50579 ± 65236	11568 ± 21868	<0.001	32951 ± 55864	3524 ± 8302	<0.001
PS Life Span, (ms)	109.36 ± 113.90	102.24 ± 226.64	0.889	-24.87 ± 72.06	-41.38 ± 126.35	0.073	103.36 ± 180.68	68.05 ± 162.79	0.148	71.91 ± 141.86	55.99 ± 217.97	0.454

Table. Effects of AADs in the Wild-type and PITX2+/- Deficiency group

Abstract Figure. Wild-type vs. PITX2+/- baseline model

Figure. Wild-type vs. *PITX2*$^{+/-}$ baseline model analysis