An In-Silico study of the effects of conductance variation on the regionally based action potential morphology.

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Abstract:

Improved understanding of the effects of variability in electrophysiological activity within the human heart is key to understanding and predicting cardiovascular response to disease and treatments. Previous studies have considered either regional variation in action potentials or inter-subject variability within one region. We hypothesize that the regional differences in morphology derive, not only from variation in dependence on individual conductance, but also on the relationship between multiple conductances. Using the Monte-Carlo sampling method and the Maleckar model, we created an in-silico population, varying each conductance +/-100%. The population was divided into regional groups based on the biomarkers: APD90, APD50, APD20, RMP, and APA. We observe the significance of the variation of 9 different conductances on the AP morphology for each atrial region.

Results showed the significant dependence on various ion channel concentrations differed among atrial regions, Figure 1. GNaK concentration had a significant impact on APD50 for CT/BB, LA and LAA, but not the other atrial regions. CT/BB and LAA were the only regions where gKur lacked a significant impact on the APD20 biomarker. GITo, gKur, gKr, gKs and gK1 all had significant impacts on each atrial region, however the only significant cross-correlation between these ion channels, effecting APD90 was gKur and gk1, ($p = 2.3x10^{-80}$). Similar results were found for APD50 and RMP.

The total population showed a significant relationship with the cross correlation of gINa and gNaCa for APA ($p = 2.3x10^{-88}$) and gINa and gK1 for APD50 ($p = 4.11x10^{-23}$), among others. This shows that not only are there relationships between individual ion channel concentrations and the AP morphology, but also between the combination of various conductances and AP morphology. The regionally based populations are to be applied to a three-dimensional model to determine if intra-regional variability significantly effects wave front propagation and re-entry patterns.

	gINa			gITo			gKur			gKr			gKs			gK1			gCal			gNaK			gNaCa		
APD90	8	6	9	5	4	5	2	3	3	6	7	4	7	8	6	1	1	1	4	5	8	3	2	2	9	9	7
	9	9	9	7	3	4	2	2	2	6	4	5	4	7	8	1	1	1	5	6	7	3	5	3	8	8	6
	6	9		4	5		3	2		7	6		9	7		1	1		5	4		2	3		8	8	
APD50	3	3	2	6	6	8	1	1	1	7	8	9	8	9	6	4	5	4	2	2	3	9	4	7	5	7	5
	3	2	2	7	8	6	1	1	1	9	9	9	5	6	8	8	4	5	2	3	3	4	7	7	6	5	4
	1	3		4	4		6	1		9	9		8	8		2	6		7	2		3	7		5	5	
APD20	1	1	2	2	2	1	4	4	5	8	9	9	7	7	8	6	6	3	3	3	4	5	5	6	9	8	7
	2	2	2	1	1	1	9	5	6	7	8	7	8	9	8	3	3	3	5	4	4	4	6	5	6	7	9
	2	2		1	1		4	4		7	9		9	7		6	6		3	3		5	5		8	8	
APA	1	1	1	4	5	4	6	4	5	8	6	6	7	7	9	2	2	3	5	9	7	3	3	2	9	8	8
	1	1	1	5	5	5	3	4	3	7	9	9	8	8	8	4	3	4	9	6	6	2	2	2	6	7	7
	1	1		4	4		6	6		9	9		8	8		2	2		7	5		3	3		5	7	
RMP	5	2	4	7	5	6	3	6	9	9	7	7	8	4	8	1	1	1	4	9	3	2	3	2	6	8	5
	7	4	4	8	9	9	6	3	3	9	5	6	5	7	7	1	1	1	3	8	8	2	2	2	4	6	5
	7	5		6	7		4	4		9	8		3	6		1	1		8	3		2	2		5	9	

Key

RA	LA	RAA
CT/BB	PM	LAA
AVR	Total Population	

Significant regionally
Insignificant regionally
Significant for total population
Insignificant for total population

1= most significant (largest coefficient)
9= least significant (smallest coefficient)

Figure 1: Regionally based significance of each ion channel conductance with respect to the biomarkers APD90, APD50, APD20, APA and RMP. The significance of each ion channel conductance is also shown with respect to the total population