SK Channels Effects in Failing Human Ventricular Myocytes Under β-Adrenergic Stimulation

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Aims: SK channels are small conductance calcium-activated potassium channels that are upregulated in ventricular myocytes under heart failure (HF). In a previous in silico study, SK channel block was found to increase transmural dispersion of repolarization, suggesting an antiarrhythmic role for these channels. However, previous research did not consider the β-adrenergic remodeling and the loss of T-tubular cellular domains characteristic of HF. The current study investigates how SK channel block affects repolarization dispersion and inotropy under β-adrenergic stimulation (β-AS) in the failing ventricle.

Methods: We updated a human ventricular HF electrophysiological model that includes SK channel activity by incorporating the loss of T-tubular domains and a β-adrenergic HF-remodeled signaling module. Simulations were conducted for endocardial, mid-myocardial and epicardial cells at 1 Hz pacing. Action potential duration (APD), CaT peak (CaTmax), CaT duration from maximum upstroke to 80% recovery ($CaTD_{80}$), and the difference $CaTD_{80}$ - APD_{80} were calculated for combinations of β-AS (none vs. full isoproterenol-equivalent β-AS) and SK channel activity (active vs. full block).

Table 1. Biomarkers for SK activity and β-AS combinations

	Without β-AS		With β-AS	
Biomarker	**SK act.**	**SK block**	**SK act.**	**SK block**
ΔAPD_{90}(endo−epi) (ms)	49.5	63.5	38.0	48.0
CaT_{max} epi (μM)	0.34	0.36	0.63	0.67
CaT_{max} mid (μM)	0.59	0.61	1.50	1.52
CaT_{max} endo (μM)	0.27	0.26	0.35	0.34
$CaTD_{80}-APD_{80}$ epi (ms)	209.9	174.9	73.1	44.4
$CaTD_{80}-APD_{80}$ mid (ms)	141.4	83.7	24.0	11.1
$CaTD_{80}-APD_{80}$ endo (ms)	362.5	333.4	283.5	261.6

Results: Without β-AS, SK block prolonged APD_{90} by 20.5%, 18.8%, and 21.9% in epicardial, mid-myocardial, and endocardial cells, respectively. Under β-AS, the prolongation was 14.6% (epicardial) and 16.5% (endocardial), while mid-myocardial cells developed early afterdepolarizations (EADs). SK block increased ΔAPD_{90}(endo−epi) and decreased $CaTD_{80}$ - APD_{80} in all cell types, both with and without β-AS.

Conclusion: SK channels block may affect arrhythmicity under both basal and β-AS in HF. On one hand, SK block increased transmural repolarization heterogeneity and, under β-AS, provoked EADs in mid-myocardial cells. Conversely, SK block decreased the $CaTD_{80}$ - APD_{80} interval across all cell types, which may be protective against delayed afterdepolarizations (DADs).