Impact of SK Channel Conductance Variations in Endocardial and Epicardial Cells on Arrhythmogenesis in Failing Ventricles: A 1-D Simulation Study

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Abstract

SK channels are small conductance (∼10 pS) calcium-activated potassium channels. Although they have been suggested not to play a relevant role in healthy ventricles, SK channel upregulation has been reported in failing ventricles, with potential implications for arrhythmogenesis. However, the pathophysiological role of small conductance calcium-activated potassium (SK) channels in failing ventricles is poorly understood.

This study examines the impact of SK channel conductance variations in endocardial and epicardial cells on arrhythmogenesis in failing ventricles. Using a 1-D computational model of a ventricular fiber, 25 scenarios were simulated with varying SK channel conductances. The results show that SK channel block generally increases transmural dispersion of repolarization (TDR) and prolongs the QT interval, particularly when epicardial conductance is not markedly higher than endocardial conductance. These findings suggest that SK channel inhibition may contribute to arrhythmia risk in heart failure.

1. Introduction

Heart failure (HF) is marked by a decline in both the electrical and contractile functions of the heart, resulting from structural and functional remodeling. This leads to an inadequate pumping of blood, failing to meet the body's physiological and metabolic needs [1]. HF is frequently accompanied by other metabolic or cardiac pathologies, such as atrial fibrillation (AF), which is the most prevalent arrhythmia in clinical practice [2].

Small conductance calcium-activated potassium (SK) channels (∼10 pS) are an important type of calcium-activated potassium-selective ion channels, although they do not play a relevant role in normal ventricular electrophysiology. In contrast, in failing ventricular myocytes, upregulation of SK channels has been described, indicating a potential pathophysiological role in the context of heart failure [3]. Although SK channels are considered promising therapeutic targets for the treatment of atrial fibrillation, it is not yet clear under what conditions modulation of these channels in the ventricles could exert a proarrhythmic or anti-arrhythmic influence in patients with concomitant HF [4].

In particular, in failing ventricular myocytes, SK channel block has been shown to prolong the action potential duration (APD) [1]. Upregulation of SK channels under pathological conditions could be an adaptive physiological response to shorten APD under conditions of reduced repolarization reserve [5]. However, there is conflicting evidence on their pro- or anti-arrhythmic effects [6], which highlights the need for further research.

In a previous work, we developed and validated a mathematical model of human ventricular electrophysiology under HF, incorporating the activity of SK channels [7]. The conductance values of the SK channels in mid-myocardial, endocardial, and epicardial cells were adjusted on the basis of experimental data, with endocardial and epicardial cells showing a possible range of plausible values. The central value of the identified ranges was used in a model that allowed us to confirm the impact of SK channel activity on HF electrophysiology.

Based on our previous findings, the current study investigates how small variations in the conductance of SK channels of endocardial and epicardial cells influence proarrhythmic markers. Two one-dimensional (1-D) models of ventricular fibers are used to evaluate the effects of conductance variations on transmural dispersion of repolarization (TDR) and QT prolongation, which can correlate with arrhythmia risk in patients with HF [8]. Through these simulations, we seek to better understand how modulation of SK channel activity can influence the electrophysiological properties of the failing human ventricle and its susceptibility to arrhythmia.

2. Methods

2.1. Transmural fiber model

The O'Hara et al. ventricular model (ORd) [9] was used to simulate the electrical activity of epicardial, endocardial and mid-myocardial cells under normal conditions. HF conditions were simulated with the ORdmm-SK model [7], a modified version of the ORd model that includes a formulation for the I_{SK} current and HF-related electrical remodeling in different cell types. Based on these myocyte models, 1-D models of ventricular tissue were constructed to investigate the effects of SK channel modulation on two markers of ventricular arrhythmic risk, TDR and QT prolongation, with the latter calculated from a pseudo-ECG.

In particular, to simulate the electrical activity of a transmural wedge, two different fiber models were created. The first, based on the model described in [7], included three layers: 0.60 cm of endocardial cells, 0.45 cm of mid-myocardial cells, and 0.65 cm of epicardial cells. Since the distribution and behavior of mid-myocardial cells with a longer APD is controversial [10], a second fiber was created without a mid-myocardial layer, consisting of 0.83 cm and 0.87 cm of endocardial and epicardial cells.

The repolarization time (RT) and TDR were calculated as in [8]. In short, APD_{90} was computed for all simulated positions located 0.15 cm to 1.55 cm from the endocardial end of the strand, to avoid border effects. Then, RT was calculated for each cell as the sum of APD_{90} plus the time required by the wavefront to reach that cell. TDR was calculated as the difference between the maximum and minimum RT along the fiber. Finally, pseudo-ECGs were computed as the extracellular potential (Φ) recorded by an electrode placed 1.7 cm away from the epicardial end of the fiber, and QT intervals were delineated using a single-lead technique [11].

2.2. Conductance variations in endocardial and epicardial cells

For the endocardial and epicardial ORdmm-SK model, a range of suitable G_{SK} values spanning from 4.288 μS/μF to 8.654 μS/μF was identified in previous work [7]. The final value for the SK conductance in that work was selected as the midpoint of that range, specifically 6.471 μS/μF, which was taken as the reference value for the current study.

Five values were selected for this study within the identified range of SK conductance values. These values included the minimum (G_{min} = 4.288 μS/μF), maximum (G_{max} = 8.654 μS/μF) and central value of the range (G_{ref} = 6.471 μS/μF). Furthermore, the central values of two subranges, (G_{min},G_{ref}) and (G_{ref},G_{max}), were also considered for the simulations.

A total of 25 different simulations were performed in which the five conductance values presented for endocardial and epicardial cells were combined. A 100% block of the SK channels was also simulated for each of these combinations to measure the variation in TDR (ΔTDR) and the prolongation of the QT interval under full SK channel blockade.

2.3. Numerical simulations

Simulations were implemented in FORTRAN and run using ELVIRA software [12]. A semi-implicit operator-splitting scheme was used for numerical integration with a time step of 0.002 ms and a spatial discretization of 0.01 cm. The models were stimulated with monophasic current pulses of an amplitude corresponding to twice the diastolic threshold (248 $\mu A/\mu F$) and 1-ms duration. The models were paced for 600 cycles to ensure steady state was reached. Subsequently, 20 cycles were simulated in all cases.

3. Results

3.1. Fiber with mid-myocardial cells

Table 1 shows the variations in TDR after SK channel block for each of the simulated combinations of conductance values for endocardial and epicardial cells in the fiber with mid-myocardial cells. The white color represents the variation in TDR when the conductance of the epicardial and endocardial cells is the reference value ((x) in Table 1). The dark grays correspond to the combinations for which the variation in TDR are maximum and minimum, highlighting the deviation range with respect to the reference value ((+) and (-), respectively, in Table 1).

The repolarization times and pseudo-ECG waveforms for the combinations that resulted in the maximum and minimum ΔTDR values, as well as for the reference values, are graphically represented in Figure 1. These values were compared with the ORd model and with the HF model under SK channel blockade.

3.2. Fiber without mid-myocardial cells

Similarly, Table 2 shows the variations in TDR after SK channel blockade for each of the simulated combinations of conductance values for endocardial and epicardial cells in the fiber without mid-myocardial cells. In this case, the same gradient scale and reference markers described in the previous subsection were analyzed.

The corresponding repolarization times and pseudo-ECG waveforms are shown in Figure 2. These values are also compared with the ORd model and with the HF model under SK channel blockade.

G_{endo} \ G_{epi}	4.288 (G_{min})	5.378	6.471 (G_{ref})	7.562	8.654 (G_{max})
4.288 (G_{min})	20.7	13.4	6	-1.2	-7.9 (-)
5.378	23.9 (+)	16.7	9.5	2.4	-4.5
6.471 (G_{ref})	21.8	19.8	12.6 (x)	5.6	-1.2
7.562	13.2	15.6	15.5	8.6	1.9
8.654 (G_{max})	4.5	7	9.4	11.3	4.7

Table 1. ΔTDR after SK channel block for each combination of SK conductance values in the first fiber.

G_{endo} \ G_{epi}	4.288 (G_{min})	5.378	6.471 (G_{ref})	7.562	8.654 (G_{max})
4.288 (G_{min})	8	0.2	-7.7	-15.5	-23.4 (-)
5.378	17.3	10	2.5	-5	-12.6
6.471 (G_{ref})	25.6	19	12 (x)	4.8	-2.4
7.562	23.5	26.9	20.6	13.9	7.1
8.654 (G_{max})	12.3	21.9	27.1 (+)	22.1	15.8

Table 2. ΔTDR values after SK channel blockade for each combination of SK conductance values in the second fiber.

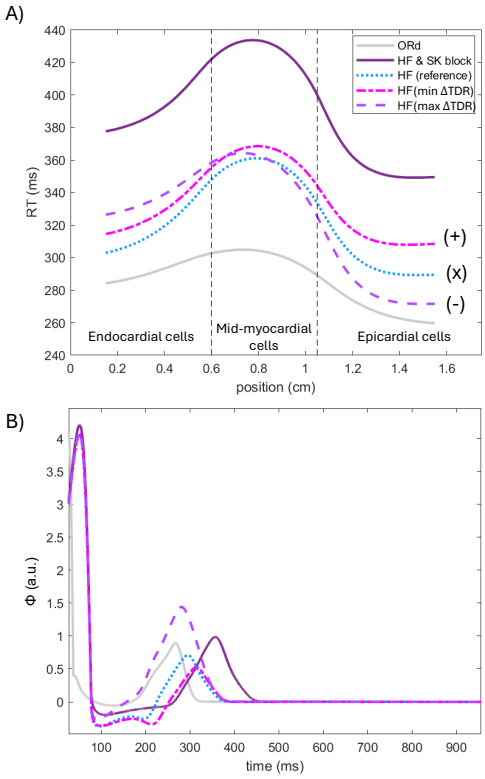

Figure 1. Repolarization time (A) and pseudo-ECG (B) in normal conditions, failing conditions with I_{SK} block and failing conditions for the reference, maximum and minimal values of ΔTDR ((x), (+) and (-), respectively) in the first fiber.

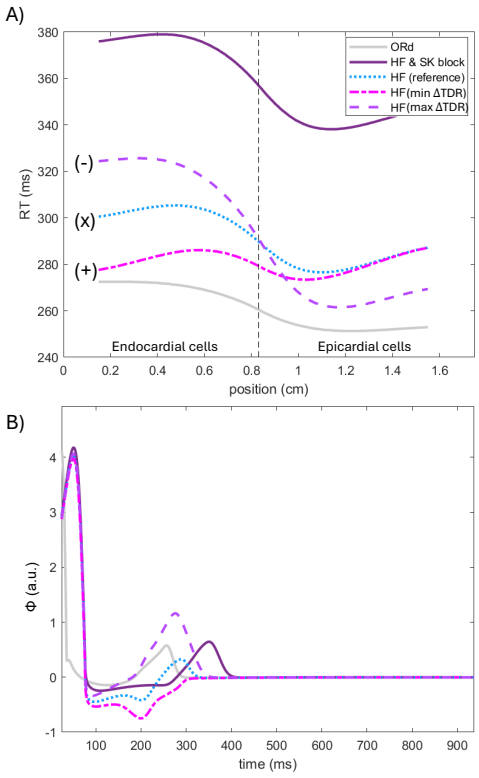

Figure 2. Repolarization time (A) and pseudo-ECG (B) in normal conditions, failing conditions with I_{SK} block and failing conditions for the reference, maximum and minimal values of ΔTDR ((x), (+) and (-), respectively) in the second fiber.

4. Discussion and conclusions

The pathophysiological role of SK channels in ventricular electrophysiology remains to be fully characterized. In this work, we explore the effects of small variations in the conductance of SK channels of endocardial and epicardial cells using 1-D transmural ventricular models. Simulations were performed for combinations of conductance values in each of the two cell types. For each of the combinations, the increase in TDR and the QT prolongation were evaluated when SK channels were blocked.

First, a fiber composed of endocardial, mid-myocardial and epicardial cells was built to simulate the electrical activity of a transmural fiber under failing conditions. As Table 1 illustrates, SK channel block increased TDR and prolonged the QT interval for most variations in SK current conductance (21 of 25 cases), with these two manifestations considered to be predisposing factors for ventricular arrhythmia [13]. A second fiber without mid-myocardial cells was generated to corroborate those findings. As shown in Table 2, SK channel block also increased TDR and prolonged the QT interval in most cases (19 of 25),

except when G_{SK} was substantially higher in the epicardial layer than in the endocardial layer. Given that experimental evidence on SK channel conductance distribution is limited, especially in human ventricular tissue, conclusions are difficult to draw. However, the available data suggest that SK conductance tends to be lower in epicardial cells compared to endocardial cells [14]. Based on this, the scenarios in which SK channel block did not increase proarrhythmic markers may not represent typical physiological conditions.

In conclusion, this study demonstrates that the block of SK channels generally increases TDR and prolongs the QT interval in simulated human ventricular failing tissues even when accounting for physiological variability in endocardial and epicardial SK current conductance. Since these manifestations are considered predisposing factors for ventricular arrhythmia, our results suggest that SK channel inhibition may generally have proarrhythmic effects in failing ventricles, and highlight the need to consider SK channels to better understand the ventricular electrophysiology in patients with HF. These findings may have clinical relevance, as they reinforce the need for SK channel modulators to be further investigated for the treatment of atrial fibrillation in hearts with HF, in line with experimental studies challenging SK channels as specific targets for atrial drug therapies [6].

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