Mechanisms underlying interactions between low-frequency oscillations and beat-to-beat repolarization variability under sympathetic provocation

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1. Introduction

Enhanced beat-to-beat variability of ventricular repolarization (BVR) is a strong predictor of sudden cardiac arrhythmic death, however the mechanism remains unclear. Recent experimental studies have shown that BVR presents low-frequency (LF) oscillations during sympathetic provocation in humans [1]. In this work human ventricular computational cell models coupling mechanics, electrophysiology, and β-adrenergic stimulation are developed to reproduce the observed interactions between BVR and its LF oscillations and to assess underlying mechanisms.

2. Materials and Methods

A population of 35 action potential (AP) models based on O'Hara *et al*. [2] and Pueyo *et al*. [3] was built to represent a wide range of feasible human ventricular AP characteristics, both at baseline and in response to sympathetic provocation (higher levels of β-adrenergic and mechanical stretch). AP duration (APD) series were calculated and both BVR (measured by APD standard deviation, SD) and LF oscillation (measured by LF power of APD between 0.04 and 0.15 Hz, PLF) were characterized.

3. Results

Fig.1A illustrates the spectral analysis for the APD series of a simulated cell, with a large peak at the stimulation fundamental frequency in the LF band and other minor peaks related to intrinsic ion channel gating stochasticity. In Fig. 1.B, both SD and PLF present a large increase under sympathetic provocation for all simulated cells, with significant Spearman correlation between them (p-value<0.001). Partial correlation analysis revealed I_{Kr} and I_{K1} downregulation as the main drivers of increased SD and PLF under sympathetic provocation (p-value<0.01 in all cases).

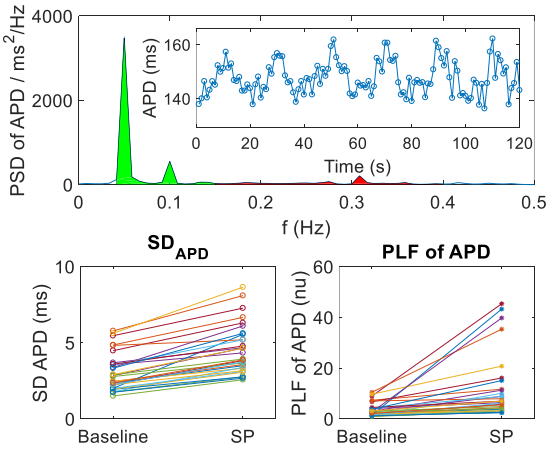

Fig. 1. A) Spectral analysis of APD series for a simulated cell. B) Increases in SD and PLF under sympathetic provocation (SP).

4. Discussion and Conclusions

The presented computational approach allows reproducing the interactions between BVR and LF oscillations of human ventricular repolarization reported in literature. I_{Kr} and I_{K1} are key in determining variations in both phenomena following increased sympathetic activity.

5. References

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