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Population of Human Ventricular Cell Models Calibrated with in vivo Measurements Unravels Ionic Mechanisms of Cardiac Alternans

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Abstract

Cardiac alternansis an important risk factor in cardiac physiology, and is related to the initiation of many pathophysiological conditions. However, the mechanisms underlying the generation of alternans remain unclear. In this study, we used a population of computational human ventricle models based onthe O'Hara model [1] to explore the effect of 11 key factors experimentally reported to be related to alternans. In vivo experimental datasets coming from patients undergoing cardiac surgery were used in the calibration of our in silico population of models. The calibrated models in the population were divided into two groups (Normal and Alternans) depending on alternans occurrence.

Our results showed that there were significant differences in the following 5 ionic currents between the two groups: fast sodium current, sodium calcium exchanger current, sodium potassium pump current, sarcoplasmic reticulum (SR) calcium release flux and SR calcium reuptake flux. Further analysis indicated that fast sodium current and SR calcium uptake were the two most significant currents that contributed to voltage and calcium alternans generation, respectively.

1. Introduction

Cardiac alternans is a repetitive beat-to-beat fluctuation between subsequent action potentials (APs), and is regarded as an important risk factor for ventricular arrhythmia and fibrillation. It can be observed in many pathophysiological conditions under significant metabolic stress and chronotropic stimulations [2]. Two major hypotheses have been developed to explain the generation of alternans in cardiac myocytes: the voltage-driven and the calcium-driven hypothesis.

According to the first hypothesis, the alternation in sarcolemmal currents, membrane voltage, and AP morphology can lead to beat-to-beat fluctuations in intracellular calcium concentration [3]. Modulation of sarcolemmal K^+ and Ca^{2+} currents based on changes of AP morphology has been reported to have a significant effect on the stability of Ca^{2+} cycling and the transition to stable alternans[4].Some other transmembrane proteins, such as the Na^+/Ca^{2+} exchanger and the Na^+/K^+ pump, may also play a role in the generation and maintenance of these alternans.

The second hypothesis suggests alternation of intracellular Ca^{2+}concentration as the primary event, leading to changes in AP morphology and sarcolemmal currents [3]. Calcium storage in the intracellular subspace plays a crucial role in the maintenance of myocyte physiological activity. The sarcoplasmic reticulum (SR) is a subspace in muscle cells that is responsible for the release and storage ofCa^{2+} ions. The amount of Ca^{2+} release from the SR to initiate contraction must match the amount of Ca^{2+} reclaimed from cytoplasm. Under this hypothesis, cardiac alternans occur when heart rate exceeds the capability of cardiac myocytes to recycle calcium. In this process, SR Ca^{2+} release by ryanodine receptors (RyRs) and re-uptake by sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA) are the two major processes that affect the dynamic changes of intracellular Ca^{2+} concentration [3].Recent experimental data tends to support the idea that the perturbation in the intracellular Ca^{2+}cycling may be the fundamental event in the generation of alternans [3].

2. Methods

In order to simulate the variability and uncertainty of biological problems, one parameter set in a single model is insufficient. Instead, we base our analysis on a population of models of human ventricular electrophysiology based on the O'Hara model [1].Within this population, cell models share the same equations representing ionic

current kinetics but different conductance values[5, 6].

2.1. Variation of key parameters

A population of models was constructed based on the sampling of the following 11 key parameters related to alternans: GNa (fast Na channel conductance), PCa (Ca channel permeability),GKs (Ks channel conductance),GK1 (K1 channel conductance);GKr (Kr channel conductance), Gto (Transient outward potassium channel conductance), GNaL (late Na channel conductance), GNaCa (Na^+/Ca^{2+} exchanger conductance), GNaK (Na^+/K^+ pump), Jrel(Ca^{2+} release via ryanodine receptors to myoplasm) and Jup(Ca^{2+} uptake via SERCA from the myoplasm) .

2.2. Latin hypercube sampling

Due to the complexity of cardiac cell models and the large number of parameters, considering every possible combination of parameter values is computationally intractable. Latin hypercube sampling (LHS) methods [7] allow us to generate parameter sets over large number of parameters efficiently and without bias [6].

To generate a sample size N from K parameters, the range of each parameter is divided into N non overlapping intervals. From each interval one value is selected randomly according to the probability density of the interval. The N values of the first parameter are paired in a random way with the N values of the second parameter, and these N pairs are then paired randomly with values of the third parameter and so on until N groups of K parameters are formed.

LHS was used in this study to generate scaling factors uniformly distributed between 0 and 2. Base model parameters in [1] were then multiplied by these scaling factors to generate a population of 10000 ionic models.

2.3. Data acquisition and signal analysis

In vivo information from 23 patients (7 female, 16 male) undergoing AVR (Aortic Valve Replacement) or CABG (Coronary Artery Bypass Grafting) was used in this study. Multielectrode activation and repolarization maps on the whole heart epicardial surface at multiple cycle lengths (CLs) were used to calculateactivation-recovery intervals (ARIs) [8]. ARIs have been validated theoretically and experimentally as a measure of APD_{90} (AP duration to 90% repolarization); therefore, we used ARIs to constrain APD_{90} [9].For each CL, the minimum ARI was evaluated to be 183ms, and the maximum values for different CLs are given in Table1. Any parameter sets that generated a model with unphysiological APD_{90} were excluded from the population.

Table 1.Maximum ARI values for different cycle lengths (CL) used in the calibration of the models.

CL (ms)	600	550	500	450	400	350
ARI_{max}(ms)	350	345	340	335	330	320

2.4. Electrophysiological simulations

All numerical simulations were performed using our open source simulation software Chaste [10] on a 512 core cluster Intel processors at the Oxford Supercomputing Centre (OSC). Cell models were stimulated for 1000 paces at each of the following CLs in a step protocol: 600, 500,450, 400, 350 and 300 ms.

3. Results

3.1. Calibration of models

10000 models were generated by varying 11 different parameters using Latin hypercube sampling as described in Methods. 3548 models were accepted after the calibration (Figure 1).

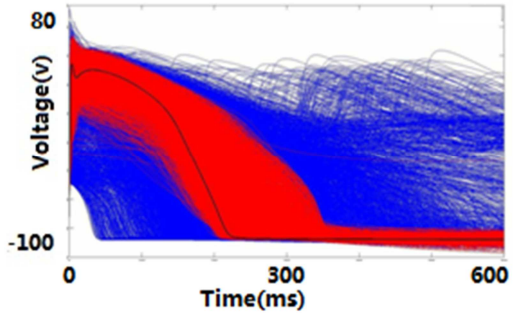

Figure 1.Population of models of human ventricular electrophysiology, paced at a CL=600 ms. Black: original model; blue: rejected models; red: accepted models.

3.2. Analysis of cardiac alternans

The occurrence of voltage and Ca^{2+}alternans was defined as a difference of greater than 5ms between the APD_{80} (AP duration to 80% repolarization) or $CaTD_{80}$ (Ca^{2+} transients duration to 80% of repolarization) in the penultimate and final APs. Linear regression analysis indicates, at all CLs under study, a significant correlation between both types of alternans (Figure 2, linear fit). This is with the exception of models exhibiting large magnitudes of voltage alternans in the absence of Ca^{2+} fluctuations (Figure 2, points in green circle). These results therefore suggest that some of the observed voltage alternans were contributed by Ca^{2+}alternans, while others were contributed by a different mechanism.

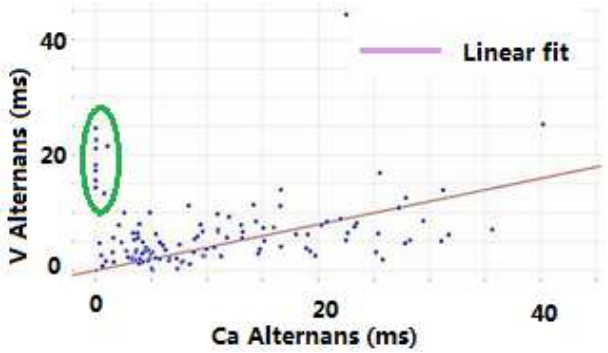

Figure 2. Correlation in the magnitude between voltage and calcium alternans, for a CL=350ms.

Parameter sets were divided into two groups (Normal and Alternans) depending on alternans occurrence. Both Normal (non-alternating) and Alternans group parameters were distributed across the whole sampling range (Fig. 3).

Statistical analysis (Student's t-test) was used to compare the differences between the two groups of parameters. For GNa, GNaCa, GNaK,Jrel and Jup, the differences were statistical significant (Figure3). GNa and Jup were much smaller in the Alternans group, while GNaCa, GNaK and Jrel were relatively larger in the Alternans group. Among the above five parameters, GNa and Jup exhibited the greatest differences, which suggested the importance of the fast sodium current and the Ca^{2+} uptake flux in alternans generation(Figure 3 a,e).

After a comparison of the contributions of GNa and Jup, we concluded that smaller GNa mainly contributed to the larger amplitudes of voltage alternans while it had little effect on the amplitude of calcium alternans (Figure 4a). Small values of Jup had greater effect on the amplitude of calcium alternans compared to voltage alternans (Figure 4b). These results suggested that GNa and Jup may affect the generation of alternans, but through different mechanisms.

4. Discussion and Conclusions

In this study we built a population of models of human ventricular electrophysiology based on the O'Hara model, and calibrated the population of models using *in vivo* epicardial ARI values. Within the accepted models in the population, we detected the generation of voltage and calcium alternans and compared all the parameters sets depending on their contributions to alternans occurrence. Significant differences between GNa, GNaCa,GNaK, Jrel and Jup were observed.

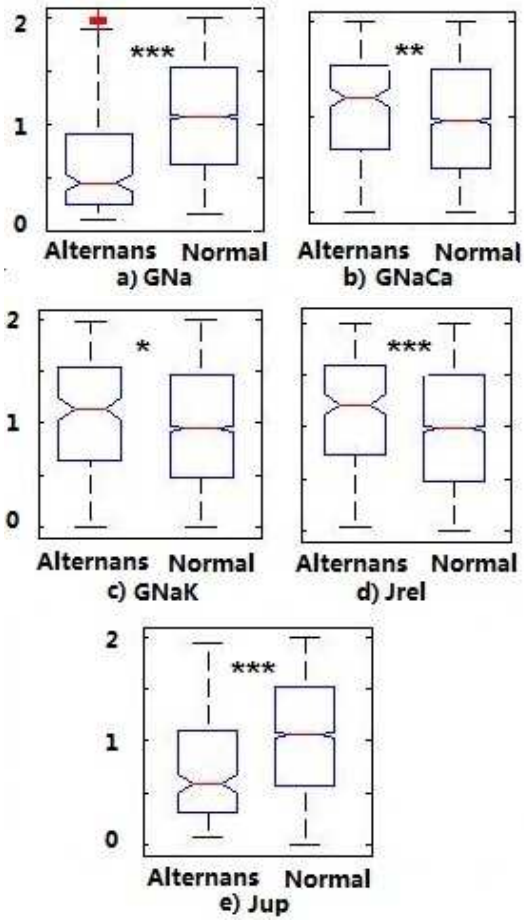

Figure 3.Comparison of parameters between two groups. Central marks: distribution medians; box edges: 25th and 75th percentiles. Symbols indicate statistical differences: *** (p<0.001); ** (p<0.01); * (p<0.05).

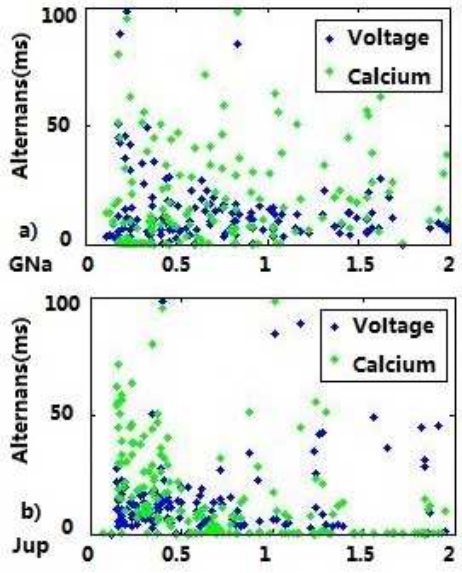

Figure 4.Relationship between two types of alternans and the distribution of GNa and Jup parameters (CL= 350ms).

Among the five, GNa and Jup exhibited the greatest differences. Smaller GNa mainly contributed to large voltage alternans at fast pacing rates. As GNa plays an important role in the depolarization period (phase 0) of the AP, modulation of GNa may lead to alternans caused by the depolarization period rather than repolarization. Importantly, this type of alternans caused by depolarization effects was also observed in our patients (Figure 5).

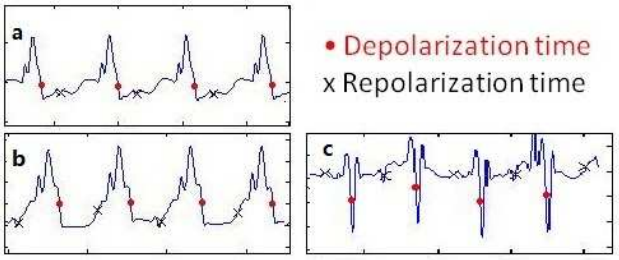

Figure 5 Electrograms of a patient showing no alternans (a), repolarization alternans (b) and depolarization alternans (c)

The other parameters, however, affected alternans generation in a different way. Insufficient Jup flux or excess Jrel flux in cardiac myocytes may cause an increase of the cytosolic Ca^{2+} concentration and so, disturb the balance between SR Ca^{2+} release and SR Ca^{2+} re-uptake and hence lead to Ca^{2+}alternans. It has also been found experimentally that over-expression of SERCA2a can improve the resistance to APD alternans [11]. GNaCa and GNaK may also be involved in this process by affecting the intracellularCa^{2+} cycle.

The results in this study were based on the initial analysis of *in vivo* data from a relatively small number of individuals. Currently, we only used the overall ARI ranges from all patients to calibrate the population of models. Future work may extend this approach by developing further subpopulations based on gender, age and the condition of patients. One limitation of this study is that only APD_{90}information was used to calibrate the population of models; additional physiological information may be incorporated into the calibration method to make the results closer to physiological reality. A more thorough statistical analysis should also be applied to the analysis of alternans in future studies.

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