Ionic Mechanisms of Variability in Electrophysiological Properties in Ischemia: A Population-based Study

A Mincholé S Dutta, J Walmsley, B Rodríguez

Computational Biology Group, University of Oxford, Oxford, UK

Abstract

Electrophysiological heterogeneities in ischemia provide a pro-arrhythmic substrate that can lead to ventricular arrhythmias. However, the mechanisms underlying intersubject variability in the pro-arrhythmic response of the human ventricles to acute ischaemia are unknown. In this initial study, we investigated the ionic basis of variability in cellular electrophysiological properties in normal and acutely ischemic human ventricular cardiomyocytes using a population-based simulation study. Additionally, we analysed the importance of hyperkalemia, $I_{K(ATP)}$ activation and acidosis-induced I_{CaL} and I_{Na} inhibition in modulating these electrophysiological properties within the human cell population. Results show that in the occurrence of APD alternans, the conductance g_{CaL} plays the most important role followed by the Na/K pump whereas under ischemic conditions, other mechanisms also become important such as Na/Ca exchanger and the I_{Kr} and I_{Ks} currents. On the maximum restitution slope, under ischemic conditions, g_{Na} and g_{NaCa} become important while g_{Kr} reduce its influence on it.

1. Introduction

Ventricular arrhythmias caused by myocardial ischemia are a main cause of mortality. Ischemia due to cessation of blood supply in the cardiac tissue results in profound dynamic spatio-temporal electrophysiological changes which promote arrhythmogenesis [1]. Animal studies have shown that ischemia-related pro-arrhythmia is caused by a combination of ionic changes including hyperkalemia (i.e. elevated extracellular potassium concentration $[K]_o$), hypoxia-induced activation of the ATP-dependent potassium current $I_{K(ATP)}$, and a decrease in the conductances of the fast sodium (I_{Na}) and L-type calcium (I_{CaL}) currents caused by acidosis [1]. The effect and severity of ischemia-induced changes in human ventricular electrophysiology is likely to exhibit high inter-subject variability, but its characterisation is challenging due to difficulties in performing appropriate measurements. Hence, the mechanisms underlying inter-subject variability in determining the response to ischemic changes in human are currently unknown.

In the present study, we investigate variability in the human ventricular cardiomyocyte response to ischaemia-induced ionic alterations using a population-based computational approach. Variability underlying the physiological and pathological responses of human cardiomyocytes is investigated using a calibrated population of human ventricular cell models [2, 3]. The human model population is then used to quantify the relative importance of ionic conductances and ischemic changes in determining intersubject variability in each electrophysiological property for each pacing frequency.

2. Methods

2.1. Construction of the population

We constructed a population of human ventricular action potential (AP) models based on the endocardial ten Tusscher model TP06 [4] using the cardiac simulation software Chaste [5]. The model population consisted of an ensemble of cellular models, sharing the same equations as the TP06, but with varying ionic conductances values.

We generated an initial population of 5000 models by sampling the ionic conductances to $\pm$50% of TP06 original values using Latin hypercube sampling (as in [2]). The conductances of the main ionic currents during repolarization and depolarization were varied: the fast sodium (g_{Na}), L-type calcium (g_{CaL}), rapid delayed rectifier potassium (g_{Kr}), slow delayed rectifier potassium (g_{Ks}), inward rectifier potassium (g_{K1}), transient outward (g_{to}) and the Na+/Ca2+ exchanger (g_{NaCa}) currents, and the Na+/K+ pump current permeability (g_{NaK}).

2.2. Calibration of the population

The initial population was calibrated to determine the models that were in agreement with the experimentally observed ranges of APD_{90} and APD_{50} at different cycle lengths (CL) in human. Experimental data used in the

calibration included those obtained by [6–8] in nonfailing hearts and also in vivo [9] in acute ischaemia. Each model was paced for 300 beats at different CLs from 1500 to 300 ms. Models with APD_{90} between 250 to 400ms for the CL of 1000ms and between 225 to 340ms for CL of 500ms, and with APD_{50} between 200 to 350ms for CL of 1000ms, and between 175 to 300ms for CL of 500ms were included in the population (see Figure 1). In addition, the population was calibrated by ensuring the restitution curve was monotonic. The experimentally-calibrated population of models retained 2133 models.

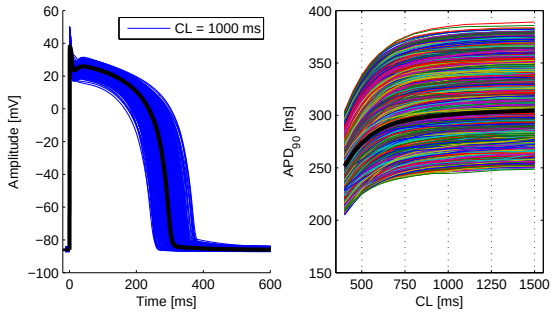

Figure 1. Action potentials (left) and restitution curves (right) simulated using the 2133 human ventricular models in the experimentally calibrated model population. The solid black line corresponds to the original TP06 AP model.

Four different ischemic conditions were applied to the calibrated control population:

- Mild hyperkalemia and hypoxia with $[K]_o = 8mM$ and $f_{K(ATP)} = 10\%$
- Severe hyperkalemia and hypoxia with $[K]_o = 10.8mM$ and $f_{K(ATP)} = 10\%$
- Hyperkalemia with $[K]_o = 10.8mM$
- Simulated ischemia (hyperkalemia, hypoxia and acidosis) with $[K]_o = 10.8mM$, $f_{K(ATP)} = 10\%$ and a reduction of 30% in the g_{CaL} and g_{Na}.

These ischemic changes are in line with experimental recordings [1].

2.3. Electrophysiological properties

In order to determine ischemia-induced electrophysiological effects, we quantified the following properties in the simulations: APD at 90% repolarization, the resting potential, the maximum AP upstroke velocity (dV/dtmax), the maximum APD restitution slope and the occurrence of APD alternans. Alternans were defined as >10 ms difference in APD between consecutive beatsin steady-state conditions. All these electrophysiological properties are known to be modified during the process of ischemia.

2.4. Statistical methods

In order to quantify the relative importance of each ionic conductance on changes of a specific biomarker, a linear regression analysis was performed [3]. Each biomarker computed for each of the models of our calibrated population can be approximated by a linear expression in terms of the eight ionic conductances. The importance of these ionic conductances is given by the regression coefficients.

We further investigated the relative importance of the three pathological components of ischemia: hyperkalemia, activation of $I_{K(ATP)}$ and simulation of acidosis in determining the changes of the different electrophysiological properties. We performed a linear regression with respect to $[K]_o$, $f_{K(ATP)}$ and a categorical variable set to one when representing that the acidosis is present in the model or to zero when it is not.

3. Results and discussion

3.1. Population variability in electrophysiological properties

Figure 2 illustrates the variability in each of the electrophysiological properties obtained in the simulated human ventricular cell population under control and ischaemia-related conditions by showing probability density functions for each biomarker. Figure 2A and 2B shows that firstly the width and height of each distribution is similar in all conditions, indicating that the variability in physiological conditions (control) determines variability under ischaemia-related conditions for APD at both CLs. Secondly, $I_{K(ATP)}$ activation results in significant APD shortening, which is further increased by acidosis-induced inhibition of I_{CaL} and I_{Na} and to a smaller extent by hyperkalemia. This is in agreement with previous results obtained in experimental and theoretical studies [1, 10]. Figures 2C and 2D highlight the importance of hyperkalemia in raising resting potential towards less negative potentials and decreasing dV/dtmax, an effect which is reduced by $I_{K(ATP)}$ activation. Figure 2E shows that all ischaemia-related conditions result in a flattening of the APD restitution, reflected by the decrease in the maximum restitution slope. A narrower distribution than in control is observed in simulated ischemia and severe hyperkalemia with $I_{K(ATP)}$ activation.

3.2. Occurrence of APD alternans

We also quantified the occurrence of alternans in the human ventricular model population under control and ischemia-related conditions for a range of cycle lengths (Figure 3). Simulation results show that all ischemia-related alterations facilitate the occurrence of alternans at longer CLs. Cells which failed to activate not shown.

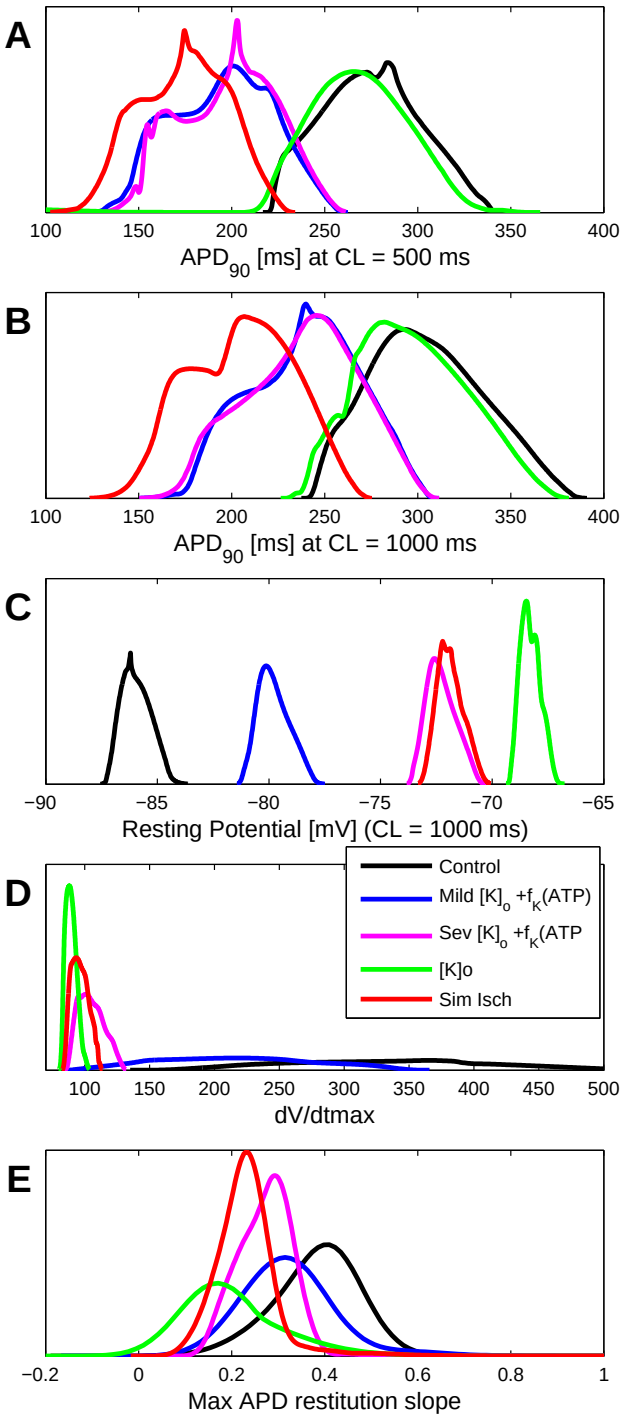

Figure 2. Probability density functions representing population variability in APD (A) at CL of 500 ms and (B) at CL of 1000ms, resting potential (C), dV/dtmax (D) and maximum restitution slope (E) in control (solid black line) and in hyperkalemia (green), mild and severe combined hyperkalemia and hypoxia (magenta and blue lines) and simulated ischaemia (red) for CL=1000ms.

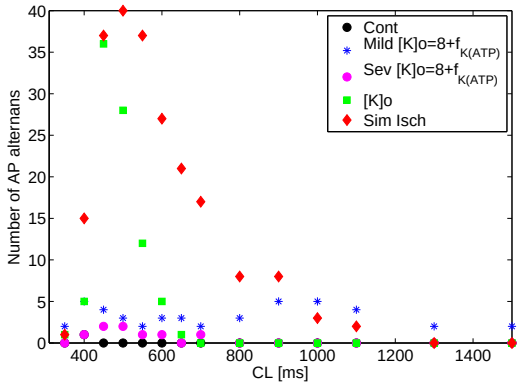

Figure 3. Number of human models in the population exhibiting APD alternans in control (solid black line) and in hyperkalemia (green), mild and severe combined hyperkalemia and hypoxia (magenta and blue lines) and simulated ischaemia (red) for each CL tested from 350 to 1500ms.

3.3. Ionic basis of variability

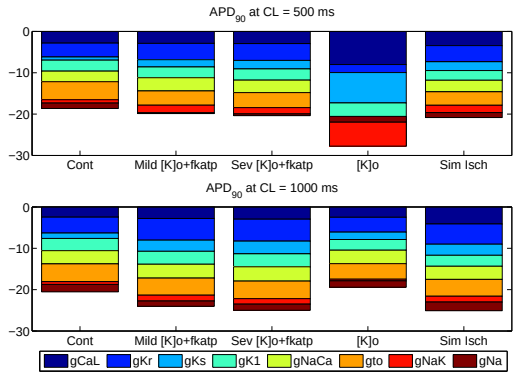

Figure 4. Relative importance of ionic conductances in determining APD values for CL= 500ms (top) and 1000ms (bottom) for the human ventricular cell population in control, and in the four ischemic conditions. Each bar plot shows regression coefficients obtained for each conductance.

Linear regression analysis was conducted on the simulated population results to quantify the relative importance of ionic conductances and ischemia-related changes in determining human electrophysiological variability. Figure 4 indicates that 1) g_{Kr}, g_{to} and g_{NaCa} are the main determinants of APD variability in most simulated conditions; 2) The importance of g_{Kr} in APD increases under conditions of combined hyperkalemia and hypoxia. Finally, for CL of 500 ms, we observe a higher importance of g_{Ks}, g_{CaL} and the NaK pump during hyperkalemia.

In the occurrence of APD alternans, g_{CaL} is the conductance that plays the most important role followed by the NaK pump. Under ischemic conditions, other mecha-

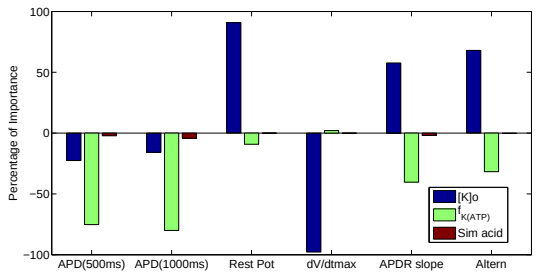

Figure 5. Relative importance of ischaemia-induced alterations in determining electrophysiological properties: APDs at CLs of 500 and 1000 ms, resting potential, dV/dtmax, APD restitution slope and the APD alternans. Y axis corresponds to normalised regression coefficient for each condition (control, hyperkalemia and acidosis).

nisms also become important such as NaCa exchanger and the I_{Kr} and I_{Ks} currents.

The main mechanism that modifies the resting potential is the NaK pump permeability followed by g_{K1} in control. Under ischemic conditions, g_{K1} reduces its relative importance whereas g_{CaL} increases in importance.

Regression shows that under ischemic conditions, g_{Na} and g_{NaCa} become important while g_{Kr} reduces its influence on the maximum restitution slope. Acidosis, an early ischemia response, inhibits I_{Na} dynamically, affecting the restitution slope in turn. All the regression coefficients increase under hyperkalemia resulting in a wider distribution as shown in Figure 2E and, therefore in a higher variability. On the other hand, the regression coefficients in the other ischemic conditions decrease, reducing the variability of maximum APD restitution slopes.

We also analysed the importance of hyperkalemia, $I_{K(ATP)}$ activation and acidosis-induced I_{CaL} and I_{Na} inhibition in determining electrophysiological properties within the human cell population. Results shown in Figure 5 indicate that $I_{K(ATP)}$ activation is the strongest determinant of APD for both CLs, hyperkalemia determines resting potential and dV/dtmax and both factors play a critical role in determining the APD restitution slope and the occurrence of alternans. Our quantitative results are in agreement with results obtained in previous studies [11].

4. Conclusions

In this study, we investigated the ionic basis of variability in the response of the human ventricles to acute ischaemia using a population-based computation approach. Results suggest that some electrophysiological properties such as APD or resting potential do not increase in variability relative to control whereas maximum upstroke velocity or maximum restitution slope have reduced in variability during different ischemia-related conditions. Further studies should be done to investigate the potential implications of variability in electrophysiological properties during acute ischemia.

Acknowledgments

AM holds a Marie Curie Intra-European fellowship (FP7-PEOPLE-2011-IEF and acknowledges support of grant TEC2010-19410 from MINECO, Spain. BR holds Medical Research Council Career Development, Industrial Partnership and MRC Centenary Awards. SD acknowledges EPSRC. JW acknowledges MRC Centenary Awards.

References

[1] Carmeliet E. Cardiac ionic currents and acute ischemia: from channels to arrhythmias. Physiol Rev 1999; 79(3):917–1017.

[2] Britton O, Bueno-Orovio A, Van Ammel K, Lu H, Towart R, Gallacher D, Rodriguez B. Experimentally-calibrated population of models predicts and explains inter-subject variability in cardiac cellular electrophysiology. PNAS 2013;.

[3] Walmsley J, Rodriguez J, Mirams G, Burrage K, Efimov I, Rodriguez B. mrna expression levels in failing human hearts predict cellular electrophysiological remodelling: A population-based simulation study. PLoS ONE 2013;8(2):e56359.

[4] ten Tusscher K, Panfilov A. Alternans and spiral breakup in a human ventricular tissue model. Am J Physiol Heart Circ Physiol 2006;291(3):H1088–100.

[5] Mirams GR, Arthurs CJ, Bernabeu MO, Bordas R, Cooper J, Corrias A, Davit Y, Dunn SJ, Fletcher AG, Harvey DG, Marsh JM, Osbourne JM, , Pathmanathan P, Pitt-Francis J, Southern J, Zemzemi N, Gavaghan DJ. Chaste: An open source c++ library for computational physiology and biology. PLoS Comput Biol 2013;9(3):e1002970.

[6] Glukhov AV, Fedorov VV, Lou Q, Ravikumar VK, Kalish P, Schuessler RB, Moazami N, Efimov IR. Transmural dispersion of repolarization in failing and nonfailing human ventricle. Circ Res 2010;106:981–991.

[7] Li GR, Lau CP, Leung TK, Nattel S. Ionic current abnormalities associated with prolonged action potentials in cardiomyocytes from diseased human right ventricles. Heart Rhythm 2004;1(4):460–468.

[8] Lou Q, Fedorov VV, Glukhov AV, Moazami N, Fast VG, Efimov IR. Transmural heterogeneity and remodeling of ventricular excitation-contraction coupling in human heart failure. Circ 2011;123:1881–1890.

[9] Sutton PM, Taggart P, Opthof T, Coronel R, Trimlett R, Pugsley W, Kallis P. Repolarisation and refractoriness during early ischaemia in humans. Heart 2000;84:365–369.

[10] Rodriguez B, Trayanova N, Noble D. Modeling cardiac ischemia. Annals of the New York Academy of Sciences 2006;1080(1):395–414.

[11] Shaw R, Rudy Y. Electrophysiologic effects of acute myocardial ischemia: a theoretical study of altered cell excitability and action potential duration. Cardiovasc Res 1997;35(2):256–272.