

The Effect of Low Potassium in Brugada Syndrome: A Simulation Study

K Cardona¹, JF Gómez¹, J Saiz¹, W Giles, B Trenor¹

¹Instituto Interuniversitario de Investigación en Bioingeniería y Tecnología Orientada al Ser Humano, Universitat Politècnica de València, Spain

²University of Calgary, Calgary, Canada

Abstract

Brugada Syndrome (BrS) is associated with an increased risk of ventricular arrhythmias. It is caused by ion channel abnormalities and is characterized by coved ST elevation, J wave appearance and negative T waves in the right precordial electrocardiographic lead. The changes in the electrocardiogram (ECG) in the setting of BrS can be due to reduced inward currents, increased outward currents (I_{to}) and fibrosis. Some clinical reports relate hypokalemia to arrhythmic events (in the presence of other pathologies). Hypokalemia contributes to ST-segment elevation and changes in the T-wave morphology. It seems plausible that in patients with BrS, low extracellular potassium concentration ($[K^+]_o$) might increase repolarization gradients, especially in right ventricle (RV), setting the stage for ventricular arrhythmia. The main goal of this study is evaluate the effect of low $[K^+]_o$ in BrS using a mathematical modeling approach. Our results show that transmural dispersion of repolarization (TDR) was augmented in hypokalemic conditions. Furthermore, $T_{peak}-T_{end}$ interval was calculated from the pseudo-ECG and was increased by 14 and 51 % in BrS and in BrS combined with hypokalemia, respectively, with respect to control. Additionally, a prominent J wave was observed in BrS and this increased if hypokalemia was also introduced.

1. Introduction

Brugada Syndrome (BrS) is associated with an increased risk of sudden death due to ventricular arrhythmias. At the molecular level, BrS has been linked to mutations causing decreased inward currents (peak sodium channel current (I_{Na}) and L-type calcium channel current (I_{CaL})) or increased outward currents (especially transient outward potassium current (I_{to})) during phase 1 of the epicardial (epi) action potential (AP), thus accentuating the spike-and-dome morphology of the AP, most prominently in the epicardium of the right ventricular (RV) (1-5).

The electrocardiographic pattern of BrS is characterized by a J-point and ST-segment elevation in the right precordial leads. Experimental studies suggest that prominent J-ST elevation without a deep negative T wave in the electrocardiogram (ECG) indicates severe AP abbreviation in the epicardium and significant dispersion of repolarization creating the substrate for phase 2 reentry and polymorphic ventricular tachycardia (VT) (6-8).

There are clinical reports where hypokalemia was suspected to be related to arrhythmic events in the presence of other pathologies (9). In patients with BrS there also have been reports of induction of VT and ventricular fibrillation (VF) associated with transient hypokalemia (10;11). Low K^+ concentration induces QT prolongation and several ventricular arrhythmias due to an elevation of the resting membrane potential and prolongation of action potential duration (APD). The most common electrocardiographic alterations induced by hypokalemia include an increase of J-wave amplitude, a T-wave depression and a rectification and an increased duration of ST-segment, with consequent increase in QT interval (12). Furthermore, hypokalemia contributes to ST-segment elevation and occurrence of VT. It is plausible that hypokalemia increases transmural or epicardic dispersion of repolarization in RV in patients with BrS (11).

In this simulation study, the most recent human AP mode (13) was used. The original model was modified to simulate BrS and assess the transmural dispersion in RV and BrS with hypokalemia. Also, the changes in the pseudo-ECG observed with BrS and under different levels of K^+ extracellular ($[K^+]_o$) were compared.

2. Methods

Simulations were carried out using the human ventricular AP model by O'Hara et al. (ORD)(13). To improve the behavior of this model under hypokalemic conditions, some changes were made to the original model. Specifically, the inward rectifier potassium current (I_{K1}) was replaced by Grandi et al. formulation (14), and Na^+ and K^+ background currents (I_{NaB} and I_{KB})

were scaled. To reproduce the differences between LV and RV observed experimentally, we increased the densities of I_{to} and the slow delayed rectifier potassium current (I_{Ks}) in the RV. Both currents were increased 2, 1.25 and 2-fold in RV epicardial, midmyocardial and endocardial, cells, respectively (15;16). BrS has been associated with mutation in different genes. The most common were in SCN5A (I_{NaL}) in 11-28%, and CACNA1C and CACNB2b (I_{CaL}) in 7 and 5% respectively (1;2;17). To simulate BrS, we reduced I_{CaL} by 50% and I_{to} was 6-fold increased (1;6).

We simulated the electrical activity of a strand of 165 cells and the transmural heterogeneities of ion channel densities were considered to represent the 3 ventricular cell types: endocardial (cell 1 to 60), midmyocardial (cell 61 to 105) and epicardial (cell 106 to 165). Stimuli were applied at the endocardial end with a basic cycle length (BCL) of 1000 ms. Parameters corresponding to the last stimulation were measured, after steady state was reached.

Transmural dispersion of repolarization (TDR) was computed as the difference between the maximum and minimum repolarization time along the multicellular strand. The epicardial dispersion of repolarization (EDR) was computed as the TDR but only within epicardial cells (cells 106 to 165). The APD at 90% of repolarization (APD_{90}) was computed in all cells of the strand.

With respect to the pseudo-ECG, the T and J wave amplitudes were measured for BrS in normal $[K^+]_o$ levels and under hypokalemic conditions. The T wave is always coincident with the repolarization of epicardium, whereas the end of the T wave is dictated either by the repolarization of M cells, or by the repolarization of the endocardium. The time interval from T_{peak} to T_{end} represents the maximal TDR of the ventricle and quantifies dispersion. Additionally, we measured QT interval and ST-segment.

3. Results and discussion

Figure 1 shows transmural AP heterogeneities in the RV and the corresponding pseudo-ECG in control (black line). The red line shows the AP and pseudo-ECG when BrS is simulated. The biggest alteration with respect to control can be observed in epicardial cells. The reduced plateau level of the AP in the epicardium gives rise to an increase in the transmural voltage gradient, causing an increase in the amplitude and areas of the J wave (Figure 1D). Under these conditions, a prominent increase in the epicardial dispersion of repolarization and TDR is obtained as was observed experimentally by Szel (4). Table 1 shows the values of TDR, which was significantly increased when BrS was simulated. In control, TDR was 26 ms, for BrS TDR increased to 47 ms. Furthermore, when $[K^+]_o$ was lowered to 4.2 and 3.5 mM TDR further increased to 52 and 53 ms, respectively.

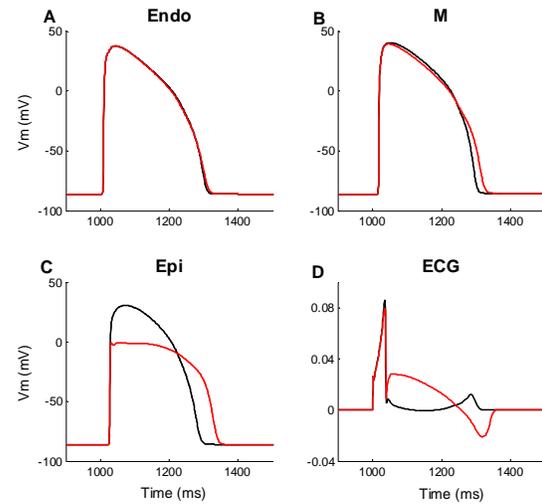


Figure 1. Action potential in endocardium, M-cells and epicardium (A-C) and its ECG (D) in control (black line) and for Brugada Syndrome (red line).

Experimentally, it has been observed how the shift in the balance of currents in the early phase of AP leads to loss of the action potential dome at some epicardial sites but not others resulting in the development of an epicardial dispersion of repolarization, which enhances the risk of reentry (7). In our simulations (figure 1 and table 1), EDR was increased by 6% in BrS with respect to control. Under hypokalemic conditions combined with BrS EDR increased by 30%. Both the increment in EDR and TDR provides the stage for the development of polymorphic ventricular tachycardia and fibrillation.

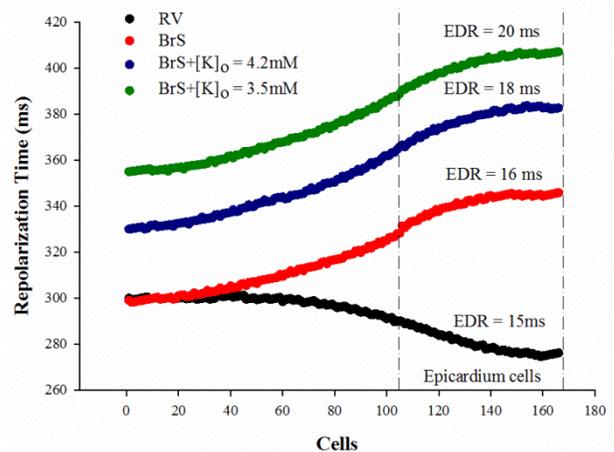


Figure 2. Transmural dispersion of repolarization (TDR) in right ventricle in control (black line), for Brugada Syndrome (BrS) (red line), and for BrS combined with two values of hypokalemia: $[K^+]_o=4.2$ and 3.5 mM (blue and green lines, respectively).

Table 1. Values for transmural dispersion of repolarization (TDR) and epicardial dispersion of repolarization (EDR) on the right ventricle (RV) in control, for Brugada Syndrome (BrS), and BrS combined with low K^+ conditions.

	$[K^+]_o$ (mM)	TDR (ms)	EDR(ms)
RV	5.4	26	15
BrS	5.4	47	16
BrS	4.2	52	18
BrS	3.5	53	20

BrS is also characterized by ST segment elevation in the ECG followed by a negative T wave. Figure 3 plots the pseudo-ECG in control RV, for BrS and BrS with combined hypokalemic conditions. Our results show how the transmural voltage gradient caused by differences in the level of the AP plateau within the cellular strand leads to ST-segment elevation. The loss of the dome in the epicardial AP is due to a prominent I_{to} and has been described in several experimental studies (2;4;6). Under this pathologic condition, the J wave may progressively get larger (accentuation of the AP notch) during the transition to ST-segment elevation. In our case, the inversion of the T wave was obtained because the repolarization in epicardial cells takes place after repolarization in endocardial cells as shown in figure 2. Different studies have demonstrated how the accentuation of the notch and prolongation of the epicardial action potential lead to a negative T wave (2;18;19). In BrS the negative T wave is increased and it is associated with the increment in TDR. Amplification of TDR contributes to create the substrate for the development of VT/VF. A large negative T wave is also associated with the development of phase 2 reentry.

Antzelevitch (20) demonstrated how the interval from the peak to end of T wave is able to offer an important non-invasive index of changes in spatial dispersion of repolarization as is TDR. In our work, the $T_{peak}-T_{end}$ in control was 35 ms, in BrS it increased to 40 ms. Decreasing $[K^+]_o$ from 4.2 to 3.5 mM resulted in an increase to 50 and 53 ms, respectively. As TDR, $T_{peak}-T_{end}$ was increased in presence of BrS and low K^+ concentration.

The most common electrocardiographic alterations caused by hypokalemia are an increased J wave amplitude and an elevation of ST-segment. Clinical reports have shown how hypokalemia may also augment ST segment elevation and is proarrhythmic in BrS(10;11). Consistent with experimental findings, our results show that the J wave amplitude and ST-segment were increased in the presence of hypokalemic conditions (Table 2). J wave was elevated by 213% when both pathologic conditions were simulated.

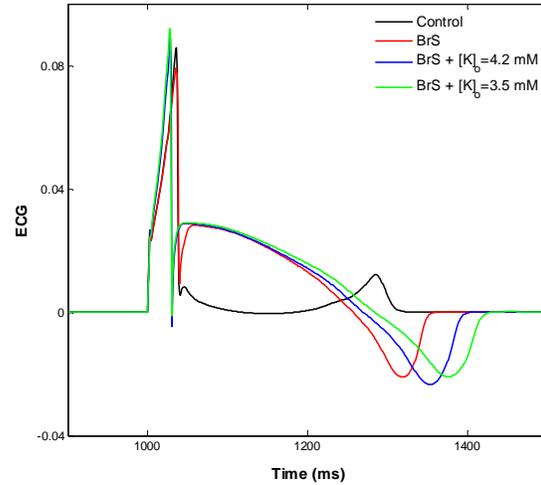


Figure 3. Pseudo-ECG for control right ventricle (black line), Brugada Syndrome (BrS) (red line), and combined BrS with hypokalemia ($[K^+]_o=4.2$ and 3.5 mM, blue and green lines, respectively).

Table 2. Values of different parameters of the pseudo-ECG in control right ventricle (RV), for Brugada Syndrome (BrS), and for BrS combined with and low K^+ conditions.

	$[K^+]_o$ (mM)	ST-segment (ms)	$T_{peak}-T_{end}$ (ms)	J wave (mV)
Control	5.4	143	35	9.3×10^{-3}
BrS	5.4	198	40	2.83×10^{-2}
BrS	4.2	222	50	2.89×10^{-2}
BrS	3.5	235	53	2.92×10^{-2}

4. Conclusion

The results of the present simulation study show how hypokalemia increases repolarization gradients in BrS patients, increasing the risk of VT/VF. The altered AP waveform in epicardial cells increased TDR and EDR, which is reflected in the rise of $T_{peak}-T_{end}$ in the pseudo-ECG.

Acknowledgements

This work was supported by: (i) VI Plan Nacional de Investigación Científica, Desarrollo e Innovación Tecnológica from the Ministerio de Economía y Competitividad of Spain (TIN2012-37546-C03-01) and the European Commission (European Regional Development Funds—ERDF—FEDER), (ii) the Dirección General de Política Científica de la Generalitat

Valenciana (grant number GV/2013/119), (iii) Programa Prometeo (PROMETEO/2012/030) de la Conselleria d'Educació Formació I Ocupació, Generalitat Valenciana.

References

- [1] Antzelevitch C, Yan GX. J wave syndromes. *Heart Rhythm* 2010;7:549-58.
- [2] Morita H, Zipes DP, Wu J. Brugada syndrome: insights of ST elevation, arrhythmogenicity, and risk stratification from experimental observations. *Heart Rhythm* 2009;6(Suppl):S34-S43.
- [3] Morita H, Zipes DP, Morita ST, Wu J. Genotype-phenotype correlation in tissue models of Brugada syndrome simulating patients with sodium and calcium channelopathies. *Heart Rhythm* 2010;7:820-7.
- [4] Szel T, Koncz I, Antzelevitch C. Cellular mechanisms underlying the effects of milrinone and cilostazol to suppress arrhythmogenesis associated with Brugada syndrome. *Heart Rhythm* 2013;10:1720-7.
- [5] Dong M, Niklewski PJ, Wang HS. Ionic mechanisms of cellular electrical and mechanical abnormalities in Brugada syndrome. *Am J Physiol Heart Circ Physiol* 2011;300:H279-H287.
- [6] Yan GX, Antzelevitch C. Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST-segment elevation. *Circulation* 1999;100:1660-6.
- [7] Wilde AA, Postema PG, Di Diego JM, Viskin S, Morita H, Fish JM, et al. The pathophysiological mechanism underlying Brugada syndrome: depolarization versus repolarization. *J Mol Cell Cardiol* 2010;49:543-53.
- [8] Cantalapiedra IR, Penaranda A, Mont L, Brugada J, Echebarria B. Reexcitation mechanisms in epicardial tissue: role of I(to) density heterogeneities and I(Na) inactivation kinetics. *J Theor Biol* 2009;259:850-9.
- [9] Genaro NR, Anselm DD, Cervino N, Estevez AO, Perona C, Villamil AM, et al. Brugada Phenocopy Clinical Reproducibility Demonstrated by Recurrent Hypokalemia. *Ann Noninvasive Electrocardiol* 2013.
- [10] Mok NS, Tong CK, Yuen HC. Concomitant-acquired Long QT and Brugada syndromes associated with indapamide-induced hypokalemia and hyponatremia. *Pacing Clin Electrophysiol* 2008;31:772-5.
- [11] Araki T, Konno T, Itoh H, Ino H, Shimizu M. Brugada syndrome with ventricular tachycardia and fibrillation related to hypokalemia. *Circ J* 2003;67:93-5.
- [12] Gazzoni GF, Borges AP, Bergoli LC, Soares JL, Kalil C, Bartholomay E. Brugada-like electrocardiographic changes induced by hypokalemia. *Arq Bras Cardiol* 2013;100:e35-e37.
- [13] O'Hara T, Virag L, Varro A, Rudy Y. Simulation of the undiseased human cardiac ventricular action potential: model formulation and experimental validation. *PLoS Comput Biol* 2011;7:e1002061.
- [14] Grandi E, Pasqualini FS, Bers DM. A novel computational model of the human ventricular action potential and Ca transient. *J Mol Cell Cardiol* 2010;48:112-21.
- [15] Cieniawa J, Baszak J, Olchowik G, Widomska J. Modeling gender effects on electrical activity of single ventricular myocytes. *Comput Biol Med* 2013;43:1063-72.
- [16] Potse M, Vinet A, Opthof T, Coronel R. Validation of a simple model for the morphology of the T wave in unipolar electrograms. *Am J Physiol Heart Circ Physiol* 2009;297:H792-H801.
- [17] Nielsen MW, Holst AG, Olesen SP, Olesen MS. The genetic component of Brugada syndrome. *Front Physiol* 2013;4:179.
- [18] Antzelevitch C, Belardinelli L. The role of sodium channel current in modulating transmural dispersion of repolarization and arrhythmogenesis. *J Cardiovasc Electrophysiol* 2006;17 Suppl 1:S79-S85.
- [19] Fish JM, Antzelevitch C. Cellular mechanism and arrhythmogenic potential of T-wave alternans in the Brugada syndrome. *J Cardiovasc Electrophysiol* 2008;19:301-8.
- [20] Antzelevitch C. Ionic, molecular, and cellular bases of QT-interval prolongation and torsade de pointes. *Europace* 2007;9 Suppl 4:4-15.

Address for correspondence.

Karen Cardona
kcardona@gbio.i3bh.es