Research Article

In Silico Investigation into Cellular Mechanisms of Cardiac Alternans in Myocardial Ischemia

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Myocardial ischemia is associated with pathophysiological conditions such as hyperkalemia, acidosis, and hypoxia. These physiological disorders may lead to changes in the functions of ionic channels, which in turn form the basis for cardiac alternans. In this paper, we investigated the roles of hyperkalemia and calcium handling components played in the genesis of alternans in ischemia at the cellular level by using computational simulations. The results show that hyperkalemic reduced cell excitability and delayed recovery from inactivation of depolarization currents. The inactivation time constant $\tau_f$ of L-type calcium current ($I_{CaL}$) increased obviously in hyperkalemia. One cycle length was not enough for $I_{CaL}$ to recover completely. Alternans developed as a result of $I_{CaL}$ responding to stimulation every other beat. Sarcoplasmic reticulum calcium-ATPase (SERCA2a) function decreased in ischemia. This change resulted in intracellular Ca (Ca$_i$) alternans of small magnitude. A strong Na$^+$-Ca$^{2+}$ exchange current ($I_{NCX}$) increased the magnitude of Ca$_i$ alternans, leading to APD alternans through excitation-contraction coupling. Some alternated repolarization currents contributed to this repolarization alternans.

1. Introduction

The mechanisms underlying ventricular arrhythmias are complex [1]. Ischemia is one of the main causes. Cardiac arrhythmias are produced by electrophysiological disturbances of the heart [1]. Three major pathophysiological conditions linked to acute myocardial ischemia have been identified, including elevated extracellular potassium, acidosis, and anoxia [2]. These conditions cause changes of electrical activities that produce the potent arrhythmia substrate.

T-wave alternans (TWA) can be used for predicting arrhythmogenesis in clinical practice [3]. TWA refers to beat-to-beat alternation in the morphology and amplitude of the ST-segment or T-wave magnitude [3]. Electrical instabilities in ischemia promote the occurrence of TWA. Animal experiments show that ischemia increases the magnitude of TWA [3]. Moreover, TWA alone can be identified as a strong indicator for ischemic cardiomyopathy [4]. It originates from action potential duration (APD) alternans at the cellular level [3].

To understand the mechanism of TWA, the study of APD alternans is necessary. APD alternans can be caused either by voltage instabilities (voltage-driven alternans) or by Ca$^{2+}$ handling dynamics instabilities (Ca$^{2+}$-driven alternans) or their interactions [5]. Because of the bidirectional coupling between membrane voltage kinetics and Ca handling dynamics, it is difficult to identify the exact mechanism of APD alternans [6, 7]. Voltage instabilities or Ca$^{2+}$ handling instabilities affect alternans occurring through changes of ionic currents. Thus, there must exist ionic basis in the genesis of alternans. In order to explore the role of ionic currents in the genesis of alternans, computational simulation methods are applied [8, 9]. Eleven factors have been experimentally reported to be related to cardiac alternans [8]. In order to find out the most relevant factors, investigators compared the differences of these factors between normal and alternans groups [8]. There are significant differences in the following 6 ionic currents between the two groups: the fast sodium current ($I_{Na}$), the L-type calcium current ($I_{CaL}$), the rapid delayed rectifier potassium current, the sodium calcium exchange current ($I_{NCX}$), the sarcoplasmic reticulum (SR) calcium release current ($I_{rel}$), and the SR calcium reuptake current ($I_{up}$) [8, 9].

These 6
currents play an important role in the development of alternans. Voltage-driven alternans is related to APD restitution properties [1, 9]. APD restitution curve results from collective effects of the recovery properties of all the ionic currents and their interactions with membrane voltage [1, 5]. Sarcolemmal K\(^+\) and Ca\(^{2+}\) currents have an influence in the genesis of voltage-driven alternans. Transmembrane proteins such as Na\(^+\)-Ca\(^{2+}\) exchange and Na\(^+\)-K\(^+\) pump also take an effect [8]. Ca\(_3\) alternans is subsequently induced by the effect of voltage-dependent \(I_{\text{Cal}}\) current [6, 7]. Ca\(^{2+}\)-driven alternans originates from steep fractional Ca\(^{2+}\) release relationship [10] or a generic mechanism of RyR properties, refractoriness, randomness, and recruitment [11]. \(I_{\text{rel}}, I_{\text{up}}, I_{\text{Cal}},\) and \(I_{\text{NCX}}\) have an effect on the genesis of Ca\(^{2+}\)-driven alternans [6, 7]. A strong \(I_{\text{NCX}}\) can translate Ca\(_3\) alternans to voltage alternans [12].

Some of the 6 factors are related to instabilities of electrical activities in ischemia. Intracellular and extracellular acidosis affect ionic currents as channel proteins function like enzymes [13]. Conductibility of \(I_{\text{NCX}}, I_{\text{Cal}},\) and \(I_{\text{rel}}\) current is reduced significantly by acidosis [13]. SERCA2a is regulated by energy metabolism and its function is greatly decreased in ischemia [14]. A population-based study shows that the conductance \(g_{\text{Cal}}\) contributes most to the occurrence of APD alternans. Under ischemic conditions, there are also other currents such as \(I_{\text{NCX}}, I_{\text{rel}},\) and \(I_{\text{Cal}}\) that play a role [15].

Pathophysiological conditions in ischemia, such as hyperkalemia, acidosis, and hypoxia, promote alternans occurrence by affecting ionic currents at the cellular level. While many experimental and numerical studies reveal voltage- or Ca\(^{2+}\)-dependent cellular mechanism, how ischemic conditions cause alternans remains unclear. In this work, we aim to investigate how electrical changes in ischemia promote alternans using computer simulations.

2. Methods

2.1. Hyperkalemic Condition. The epicardial ten Tusscher model (TNNP) [16] was employed in this study. In the epicardial cell model, we simulated hyperkalemic condition by increasing the extracellular potassium concentration \([K^+]_o\). We changed \([K^+]_o\) to investigate its independent role in the development of alternans. \([K^+]_o\) concentration was set to increase from 5.4 to 15 mM. Cycle length was applied at 400 ms.

2.2. SERCA2a Function Decreased in Ischemia. A thermodynamic model of the cardiac SERCA2a [17] was integrated into the TNNP model. The thermodynamic model based on biophysical kinetic is sensitive to metabolism compromised in ischemia.

\[
2\text{Ca}^{2+} + \text{MgATP} + \text{H}_2\text{O} \leftrightarrow 2\text{Ca}^{2+} + \text{MgADP} + \text{Pi} + \text{H}^+ \tag{1}
\]

The process of Ca uptake from the cytoplasm to SR can be presented by the above reaction equation. The equation shows that translating two Ca\(^{2+}\) needs the hydrolysis of one ATP. At the same time, the products MgADP, Pi, and H\(^+\) are released. This reversible reaction is modeled by El-E2 model [18, 19] which consisted of two conformational changes of Ca\(^{2+}\)-binding sites.

The cardiac SERCA2a model applied in our study was a three-state model. The three-state model (Figure 1) is simplified from the El-E2 model [18, 19] using rapid equilibrium assumption. In the positive direction, state \(S_3\) transforms to \(S_2\) via the hydrolysis of ATP. State \(S_2\) indicates Ca\(^{2+}\)-binding sites binding Ca\(^{2+}\) and the Ca\(^{2+}\)/H\(^+\) countertransport transporting H\(^+\) from SR to the cytoplasm, state \(S_3\) represents the Ca\(^{2+}\)-binding sites releasing Ca\(^{2+}\) to the SR and Ca\(^{2+}\)/H\(^+\) countertransport binding H\(^+\) to SERCA. The rate constants (\(\alpha\)) are functions of intracellular Pi, ATP, ADP, and H\(^+\) concentrations. See Appendix for formulas of these rate constants [17].

\[
V_{\text{cycle}} = \frac{\alpha_1\alpha_2\alpha_3 - \alpha_2\alpha_4\alpha_5}{\Sigma}, \tag{2}
\]

where \(V_{\text{cycle}}\) is clockwise cycle rate per pump at steady state. By modifying physiological parameters we could simulate metabolism compromised. In ischemia pH was decreased accompanied with a decrease of intracellular ATP. We set pH at 6 and ATP concentration at 4.2 mM. At the same time the concentrations of intracellular ADP and Pi [20] were simulated to increase to 100 nM and 30 mM [21], respectively. Values of other parameters in the formulas were the same as in the original three-state model [17].

\[
I_{\text{up}} = N \ast V_{\text{cycle}} \tag{3}
\]

The value of \(I_{\text{up}}\) was in proportion to the whole-cell pump flux. The whole-cell pump flux was determined by \(V_{\text{cycle}}\) and the numbers of SERCA pumps on the SR membrane. In order to calculate \(I_{\text{up}}\) under compromised metabolism conditions, we multiplied \(V_{\text{cycle}}\) by the constant \(N\) as a scale factor. The value of \(N\) was the ratio of maximum \(I_{\text{up}}\) obtained by original TNNP model simulation and maximum \(V_{\text{cycle}}\) under normal conditions.
Figure 2: APD computed at the cycle length of 400 ms. (a) APs in control condition with $[K^+]_o = 5.4$ mM. (b) Alternate APs in hyperkalemia with $[K^+]_o = 15$ mM.

Figure 3: Gating variables of $I_{Na}$ in hyperkalemia. (a) Fast inactivation gate $h$; (b) slow inactivation gate $j$; (c) activation gate $m$.

3. Results

3.1. The Effects of Hyperkalemia on APD and Ionic Currents. While the cycle length was applied at 400 ms, no APD alternans existed under normal conditions (Figure 2(a)). There existed no alternans except for the elevated resting potential and decreased amplitude of action potential when the $[K^+]_o$ values were in between 5 mM and 14.7 mM. APD alternans occurred in hyperkalemia with $[K^+]_o$ ranging from 14.7 to 15 mM. The $[K^+]_o$ values in this range correspond to severe hyperkalemia. Moreover, significantly elevated $[K^+]_o$ values may also occur in ischemic hearts as well as in isolated hearts in experiments. The longer AP manifested two depolarization phases. These two depolarization phases were
maintained by $I_{Na}$ and $I_{CaL}$. The availability of $I_{CaL}$ in shorter APs was reduced, resulting in small depolarization phases during the next beats (Figure 2(b)).

To investigate the process of alternans occurring, depolarization currents were selected to be studied. $I_{Na}$ decreased significantly in hyperkalemia. Open possibilities of inactivation gates, $h$ and $j$, came near to be zero (Figures 3(a) and 3(b)). In contrast, the open possibility of activation gate $m$ increased at depolarized resting voltage (Figure 3(c)).

The amplitude of $I_{CaL}$ showed alternans (Figure 4(a)). Activation gate $d$ was voltage-dependent and manifested alternans from beat to beat (Figure 4(b)). The intracellular calcium-dependent inactivation gate, $f_{cal}$, was nearly in closed state. Voltage-dependent inactivation gate $f$ needed two cycle lengths to recover completely (Figure 4(c)). Moreover, the inactivation time constant $\tau_f$ of the gate $f$ became larger during shorter APs (Figure 4(d)). That further verified the gate $f$ could not recover instantly from inactivation, leading to decreased availability of $I_{CaL}$ during shorter APs. While $\tau_f$ was decreased by 70 ms (Figure 5(a)), the gate $f$ recovered instantly (Figure 5(b)) and alternans in APD disappeared (Figure 5(c)).

3.2. The Effects of $I_{up}$ and $I_{NCX}$ on Ca Transient and APD. As the component of cardiac Ca handling, $I_{up}$ decreased under ischemic conditions. This change was simulated by modifying the physiological parameters of the SERCA pump model [17]. Thus the direct role of $I_{up}$ in the onset of Ca$_i$ alternans could be investigated. Decreased $I_{up}$ slowed down the rate of SR Ca uptake and could not balance Ca$^{2+}$ flux released from SR. As Figure 6(b) showed, Ca$^{2+}$ transients alternated obviously during early beats and reached a steady state finally. In contrast to alternate Ca$^{2+}$ transients, APD remained unchanged (Figure 6(a)).

$I_{NCX}$ decreased under acidic conditions [13]. Decreased $I_{NCX}$ was also added in the simulation after investigating the effect of $I_{up}$ on Ca$_i$ alternans. As Figure 7 showed, the magnitude of Ca$^{2+}$ transient alternans decreased. The result suggested that decreased $I_{NCX}$ could inhibit Ca$_i$ alternans. Based on this observation, we expected that Ca$_i$ alternans magnitude would increase as $I_{NCX}$ current increased. Figure 8(b) confirmed the guess. Results showed that APD alternans was accompanied with Ca$_i$ alternans of large magnitude (Figure 8(a)).

To compare the differences in the durations of repolarization between APs, we placed the 6 beats in the coordinate axes in Figure 9(a). Previous study suggested that $I_{Kr}$ and $I_{Ks}$ played a role in the occurrence of APD alternans. We selected $I_{Ks}$ and $I_{Kr}$ to investigate their roles in the process. $I_{Kr}$ and $I_{Ks}$ alternated from beat to beat as shown in Figures 9(b) and 9(c).
4. Discussion

4.1. The Mechanism of Alternans in Hyperkalemia. Depolarization alternans in hyperkalemia arises from changes in depolarization currents. In order to find out the key factors relating to alternans occurring in hyperkalemia, we selected depolarization currents for analysis. Our simulation results suggest that $I_{Na}$ is too small to affect the process of depolarization during both longer and shorter APs. $I_{CaL}$ may be the key factor in the development of alternans. Cycle lengths are fixed and the longer AP is followed by the shorter duration. $I_{CaL}$ cannot recover completely from inactivation in the shorter duration. Its availability decreases in the following depolarization phase. Thus the next depolarization phase maintained by $I_{Na}$ alone is small. Small depolarization phase leads to shorter AP. Subsequently, the longer duration provides enough time for $I_{CaL}$ to recover completely. Shorter APs are following longer APs and alternans develops. In order to further verify the role of $I_{CaL}$, $\tau_f$ of voltage-dependent inactivation gate $f$ is decreased in simulation. Decreased $\tau_f$ indicates that the gate $f$ needs shorter time to recover completely. Then the availability of $I_{CaL}$ increases in APs. Alternans disappears due to complete response of $I_{CaL}$ in every beat.

In contrast, some studies investigate alternans mechanisms in ischemia at the tissue level. Previous study supports that the depolarization alternans is linked to conduction abnormalities in the ischemia region [22]. The conduction block occurs under hyperkalemic conditions. Moreover, the depolarization phase is fragmented in the current simulation of hyperkalemia as is consistent with previous observations. Results show that depolarization alternans in ischemia region can be produced by hyperkalemic conditions [23].

Alternate conduction block induced by hyperkalemia leads to APD alternans [24]. The areas of conduction blocks become larger and alternans occurs at slower pacing frequency while increasing the inactivation time constant $\tau_f$ [24]. According to the observation, smaller areas are expected to be blocked if $\tau_f$ decreases and APD alternans will be depressed in the areas with no block any more. In other words, decreased $\tau_f$ can abolish alternans through eliminating conduction block. That is consistent with our observations. Hyperkalemia increases $\tau_f$ by depolarizing the resting voltage and thus promotes APD alternans.

4.2. The Direct Role of $I_{up}$ in $Ca_i$ Alternans. The slow rate of SR Ca uptake contributes to the occurrence of $Ca_i$ alternans.
Figure 7: Ca transient after decreasing $I_{\text{up}}$ and $I_{\text{NCX}}$ currents. Ca$_i$ alternans disappeared after decreasing $I_{\text{NCX}}$.

Ca content in diastole decreases compared to the last Ca transient. Fluctuations in cytoplasmic Ca content in diastole originate from unbalance in Ca$^{2+}$ flux between $I_{\text{up}}$ uptake and $I_{\text{rel}}$ releasing. Transient Ca$_i$ alternans are consequently caused by the fluctuations. According to the unified theory presented by Qu et al. [26], we could add ischemic changes of $I_{\text{rel}}$ to the cell model to obtain stable calcium alternans. Ca content fluctuation in SR plays a role in producing Ca$^{2+}$ transients alternans [10]. But our results show that SR load decreases from beat to beat (Figure 6(c)). That suggests SR load may not be the direct factor in the development of Ca$_i$ alternans.

4.3. The Role of $I_{\text{NCX}}$ in the Alternans Translation from Ca to APD. Larger $I_{\text{NCX}}$ increases Ca$_i$ alternans magnitude. Our results suggest that Ca$_i$ alternans can lead to APD alternans while the Ca$_i$ alternans magnitude is large enough. However, decreased $I_{\text{up}}$ and increased $I_{\text{NCX}}$ are not sufficient to produce stable alternans in our simulations. Previous study also shows that $I_{\text{NCX}}$ is the key factor that translates alternans from Ca to APD [12]. More precisely, the balance of $I_{\text{NCX}}$ and $I_{\text{Ca}}$ determines coupling in phase of Ca$_i$ alternans to APD alternans [27]. Alternans presented by Wan et al. can arise from the shifted balance of $I_{\text{NCX}}$ and $I_{\text{Ca}}$ at higher pacing
rates. In our simulation, the extent of unbalance between these currents shifted by increasing $I_{NCX}$ at cycle length of 400 ms could be too small to produce stable alternans [27]. $I_{Kr}$ and $I_{Ks}$ contribute to the occurrence of APD alternans in ischemia [15]. $I_{Kr}$ contributes most due to its larger amplitude.

**5. Conclusion**

In silico simulations have been carried out to investigate cellular mechanisms of cardiac alternans under pathological disorders including hyperkalemia, acidosis, and hypoxia. Pathophysiological changes in ischemia play a significant role in the development of cardiac alternans by affecting ionic currents. Hyperkalemic conditions delay the recovery of depolarization current $I_{CaL}$. Thus depolarization alternans occurs. Decreased $I_{up}$ of Ca handling in ischemia promotes Ca$_i$ alternans. A large $I_{NCX}$ has the ability to translate alternans from Ca to APD. Studying changes of these ionic currents can help further understand cellular mechanisms of the genesis of alternans and form the basis of study of TWA in ischemia.

**Appendix**

The rate constants used in (2) are as follows:

\[
\alpha_1^+ = k_1^- [\text{MgATP}],
\]

\[
\alpha_2^+ = \frac{k_2^+ \text{Ca}^{2+} \bar{C}_a}{\text{Ca}_i^{2+} (1 + \bar{H}_i) + \bar{H}_i (1 + \bar{H}_1)},
\]

\[
\alpha_3^- = \frac{k_3^- \text{H}_i}{\bar{H}_i (1 + \text{Ca}_i^{2+}) + \bar{H}_i (1 + \bar{H}_1)},
\]

\[
\alpha_1^- = \frac{k_1^- \bar{H}_i}{\text{Ca}_i^{2+} (1 + \bar{H}_i) + \bar{H}_i (1 + \bar{H}_1)},
\]

\[
\alpha_2^- = \frac{k_2^- [\text{MgADP}] \bar{C}_a \bar{H}_i}{\bar{H} (1 + \text{Ca}_i^{2+}) + \bar{H}_i (1 + \bar{H}_1)},
\]

\[
\alpha_3^- = k_3^- [\text{Pi}],
\]

where

\[
\bar{C}_a = \frac{[\text{Ca}^{2+}]}{K_{d,Ca}},
\]

\[
\bar{H}_i = \frac{[\text{H}^+]}{K_{d,H}},
\]

\[
\bar{H}_1 = \frac{[\text{H}^+]_{\text{Ca}_{sr}}}{K_{d,H}},
\]

\[
\bar{C}_a_{sr} = \frac{[\text{Ca}^{2+}]_{\text{Ca}_{sr}}}{K_{d,Ca}_{sr}},
\]

\[
\bar{H}_{sr} = \frac{[\text{H}^+]_{\text{Ca}_{sr}}}{K_{d,H}_{sr}},
\]

\[
\bar{H} = \frac{[\text{H}^+]}{K_{d,H}}.
\]

**Competing Interests**

The authors declare that there is no conflict of interests regarding the publication of this paper.

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References

[1] Z. Qu and J. N. Weiss, “Mechanisms of ventricular arrhythmias: from molecular fluctuations to electrical turbulence,” *Annual Review of Physiology*, vol. 77, pp. 29–55, 2015.

[2] R. M. Shaw and Y. Rudy, “Electrophysiologic effects of acute myocardial ischemia: a theoretical study of altered cell excitability and action potential duration,” *Cardiovascular Research*, vol. 35, no. 2, pp. 256–272, 1997.

[3] R. L. Verrier, T. Klingenheben, M. Malik et al., “Microvolt T-wave alternans: physiological basis, methods of measurement, and clinical utility—consensus guideline by international society for Holter and noninvasive Electrocardiology,” *Journal of the American College of Cardiology*, vol. 58, no. 13, pp. 1309–1324, 2011.

[4] T. Chow, D. J. Kereiakes, C. Bartone et al., “Prognostic utility of microvolt T-wave alternans in risk stratification of patients with ischemic cardiomyopathy,” *Journal of the American College of Cardiology*, vol. 47, no. 9, pp. 1820–1827, 2006.

[5] Z. Qu, Y. Xie, A. Garfinkel, and J. N. Weiss, “T-wave alternans and arrhythmogenesis in cardiac diseases,” *Frontiers in Physiology*, vol. 1, article 154, 2010.

[6] D. Sato and C. E. Clancy, “Cardiac electrophysiological dynamics from the cellular level to the organ level,” *Biomedical Engineering and Computational Biology*, vol. 5, pp. 69–75, 2013.

[7] Y.-L. Zang and L. Xia, “Cellular mechanism of cardiac alternans: an unresolved chicken or egg problem,” *Journal of Zhejiang University: Science B*, vol. 15, no. 3, pp. 201–211, 2014.

[8] X. Zhou, A. Bueno-Orovio, M. Orini et al., “Population of human ventricular cell models calibrated with in vivo measurements unravels ionic mechanisms of cardiac alternans,” in *Proceedings of the IEEE Computing in Cardiology Conference (CinC’13)*, Zaragoza, Spain, September 2013.

[9] M. L. Koller, S. K. G. Maier, A. R. Gelzer, W. R. Bauer, M. Meesmann, and R. F. Gilmour Jr., “Altered dynamics of action potential restitution and alternans in humans with structural heart disease,” *Circulation*, vol. 112, no. 11, pp. 1542–1548, 2005.

[10] M. E. Díaz, S. C. O’Neill, and D. A. Eisner, “Sarcoplasmic reticulum calcium content fluctuation is the key to cardiac alternans,” *Circulation Research*, vol. 94, no. 5, pp. 650–656, 2004.

[11] R. Rovetti, X. Cui, A. Garfinkel, J. N. Weiss, and Z. Qu, “Spark-induced sparks as a mechanism of intracellular calcium alternans in cardiac myocytes,” *Circulation Research*, vol. 106, no. 10, pp. 1582–1591, 2010.

[12] X. Zhou, A. Bueno-Orovio, M. Orini et al., “In vivo and in silico investigation into mechanisms of frequency dependence of
[13] E. Carmeliet, "Cardiac ionic currents and acute ischemia: from channels to arrhythmias," Physiological Reviews, vol. 79, no. 3, pp. 917–1017, 1999.

[14] S. Krause and M. L. Hess, "Characterization of cardiac sarcoplasmic reticulum dysfunction during short-term, normothermic, global ischemia," Circulation Research, vol. 55, no. 2, pp. 176–184, 1984.

[15] M. S. Dutta, J. Walsma, and B. Rodriguez, "Ionic mechanisms of variability in electrophysiological properties in Ischemia: a population-based study," in Proceedings of the IEEE Computing in Cardiology Conference (CinC ’13), pp. 691–694, Zaragoza, Spain, September 2013.

[16] K. H. W. J. Ten Tusscher, D. Noble, P. J. Noble, and A. V. Panfilov, "A model for human ventricular tissue," American Journal of Physiology—Heart and Circulatory Physiology, vol. 286, no. 4, pp. H1573–H1589, 2004.

[17] K. Tran, N. P. Smith, D. S. Loiselle, and E. J. Crampin, "A thermodynamic model of the cardiac Sarcoplasmic/Endoplasmic Ca\(^{2+}\) (SERCA) pump," Biophysical Journal, vol. 96, no. 5, pp. 2029–2042, 2009.

[18] M. Makinose, "Possible functional states of the enzyme of the sarcoplasmic calcium pump," FEBS Letters, vol. 37, no. 2, pp. 140–143, 1973.

[19] L. D. Meis and A. L. Vianna, "Energy interconversion by the Ca\(^{2+}\)-dependent ATPase of the sarcoplasmic reticulum," Annual Review of Biochemistry, vol. 48, pp. 275–292, 1979.

[20] J. P. Ebus, Z. Papp, R. Zaremba, and G. J. M. Stienen, "Effects of MgATP on ATP utilization and force under normal and simulated ischaemic conditions in rat cardiac trabeculae," Pflügers Archiv, vol. 443, no. 1, pp. 102–111, 2001.

[21] A. F. De Castro, A. Giovanni, J. F. Rodriguez, and J. M. Ferrero, "Dynamic computational simulations of alternans in acute myocardial ischemia," in Proceedings of the 41st IEEE Computing in Cardiology Conference (CinC ’14), pp. 877–880, September 2014.

[22] I. Martišiene, J. Jurevičius, R. Vosylute et al., "Evolution of action potential alternans in rabbit heart during acute regional ischemia," BioMed Research International, vol. 2015, Article ID 951704, 12 pages, 2015.

[23] J. Carro, J. F. Rodriguez, P. Laguna, and E. Pueyo, "A human ventricular cell model for investigation of cardiac arrhythmias under hyperkalaemic conditions," Philosophical Transactions of the Royal Society of London, Series A: Mathematical, Physical and Engineering Sciences, vol. 369, no. 1954, pp. 4205–4232, 2011.

[24] O. Bernus, C. W. Zemlin, R. M. Zaristsky, S. E. Mironov, and A. M. Pertsov, "Alternating conduction in the ischaemic border zone as precursor of reentrant arrhythmias: a simulation study," Europace, vol. 7, no. S2, pp. S93–S104, 2005.

[25] L.-H. Xie, D. Sato, A. Garfinkel, Z. Qu, and J. N. Weiss, "Intracellular Ca alternans: coordinated regulation by sarcoplasmic reticulum release, uptake, and leak," Biophysical Journal, vol. 95, no. 6, pp. 3100–3110, 2008.

[26] Z. Qu, M. B. Liu, and M. Nivala, "A unified theory of calcium alternans in ventricular myocytes," Scientific Reports, vol. 6, Article ID 35625, 2016.

[27] X. Wan, M. Cutler, Z. Song et al., "New experimental evidence for mechanism of arrhythmogenic membrane potential alternans based on balance of electrogenic INCX/ICa currents," Heart Rhythm, vol. 9, no. 10, pp. 1698–1705, 2012.