Influence of M-cells on the generation of re-entry in Short QT Syndrome

Ponnuraj Kirthi Priya, Srinivasan Jayaraman

Medical Devices and Diagnostics Group, Tata Consultancy Services Limited, Bangalore, Karnataka, India

Abstract

The distribution of M-cells have always been vital in creating intrinsic spatial heterogeneity thereby acting as a substrate for the development and maintenance of re-entry. Here, a 2D anisotropic transmural tissue made up of endocardial (endo), midmyocardial (mid) and epicardial (epi) layers was constructed by using the ventricular cell model developed by Ten Tusscher et al. Two configurations, the entire column of mid layer and an island within the mid layer of the tissue were considered as M cells. In the latter configuration, slight alterations were introduced in the slow delayed rectifying potassium current and the outward transient current so that the APD is highest in the M-cells followed by the endo, mid and epi cells. The likelihood of reentry generation under conditions of KCNQ1-linked Short QT syndrome type 2 (SQTS2) was then analysed in these two types of tissue configurations. Simulation results show that on including SQTS2 conditions and on pacing the tissue with premature beats in between normal beats, re-entrant waves were generated in the tissue containing a column of M- cells whereas in the tissue including the M-cell island, re-entry was not generated. This study is not in line with those reported earlier due to the variations in the size of the chosen M-cell island as well as the cellular electrophysiological properties. From this investigation, the need for further analysis on the size, location as well as the ionic properties of the M-cells in relation to the neighbouring cells has been emphasized.

1. Introduction

Short QT syndrome (SQTS) is identified by a shortened QT interval and tall peaked T-waves on the electrocardiogram. Individuals with SQTS conditions are prone to reentrant arrhythmias like ventricular tachycardia and fibrillation. Variants in SQTS are associated with a gain in function of the genes encoding different potassium currents or L-type calcium current. A specific variant is the SQTS2 caused due to a mutation in KCNQ1 gene which in combination with KCNE1 encodes the proteins responsible for slow delayed rectifying potassium current (I_{Ks}). KCNQ1 gene mutation has been known to cause an increase in the transmural dispersion of repolarisation (TDR) thereby creating a substrate for reentry. TDR inherently exists in the tissue due to the differences in the electrophysiological properties of the different cells: endocardial (endo), midmyocardial (mid) and epicardial (epi) cells that make up the ventricular wall. Another major contributor to this TDR is the presence of M-cells which are found to be localized in the deep subendocardium to midmyocardium in the anterior wall and throughout the wall in the region of RVOT [1]. The hallmark of these M cells is its substantial ability to prolong the AP more than that of endo or epi cells at slow heart rates or on exposure to certain drugs such as sotalol, quinidine etc.

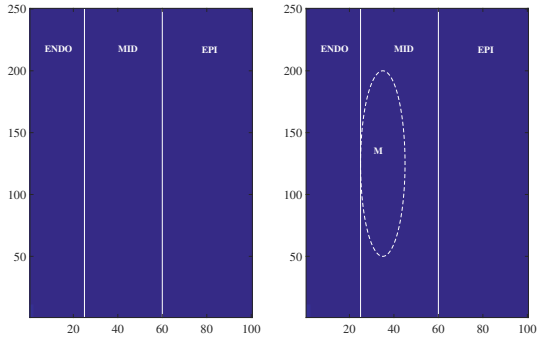
Multi-scale tissue models have been used to critically analyse the ionic mechanisms underlying the different variants of SQTS and as well as its proarrhythmic effect in 2D and 3D realistic anatomical geometries [2,3]. However, the above studies do not critically analyse the properties of M-cells in relation to generating arrhythmia. Along similar lines, Luo et al. [4] studied the functional role of M-cells in presence of SQT2 mutation on generating reentrant arrhythmia. Their results show that reentry was easily initiated and sustained for a longer duration in presence of the M-cell island model compared to the M-cell band model. The heterogeneity in action potential duration (APD) created by the M-cell plays a vital role in increasing the sustenance of reentry during SQTS2 conditions.

In this paper, the focus is on understanding the key role of the distribution on M-cells that can become proarrhythmic. For this, a 2D transmural anisotropic tissue is considered made up of the three different cell: endo, mid and epi layers. M-cells are introduced in the tissue and on pacing the tissue with premature beats, the vulnerability of the tissue to generate arrhythmia under SQTS2 conditions is tested.

2. Methods

The electrical activity of the endo, mid and epi cells is described by the biophysical model developed by Ten Tusscher et al. [5]. Modifications to the parameters this

model were made as in the study of Priya et al.[6] so that the cells develop early after depolarisations (EADs). The stimulus current is applied for 1 ms and has an amplitude of 52 μA. The transmural anisotropic section of a 2D ventricular wall having a length of 250 cells and a thickness of 100 cells interconnected using gap junction conductances (GJCs) that was developed by Priya et al. [6] is considered for evaluation. Two configurations of M-cells are considered as seen in fig. 1. In the first configuration, the entire mid layer is made up of M-cells and in the second configuration, an island of M-cells within the mid layer is considered. The electrophysiological properties of the cells in the second configuration are taken from [7] The tissue is paced at the lower leftmost corner of the tissue (Cells 1:10,1:2) every 800 ms. Normalised Pseudo ECGs are then created based on the equations described by Gima et al. [8]



(i) (ii)

Figure 1: M-cell (i) layer and (ii) island configurations

The mutation induced changes in I_{Ks} current are incorporated by changing the parameters of equations for I_{Ks} based on the experimental data on SQT2 KCNQ1 V307L obtained by Bellocq et al. [9]. Among the reported four different cases: wild type(WT), heterozygous (Het), homozygous and homozygous reduced considered for KCNQ1 V307L mutation induced changes, here the heterozygous mutation alone is considered for evaluation. Eqn. 1 represents the I_{Ks} current in the TP06 model. The heterozygous gene mutation is introduced by varying the time constant and steady state of x_s-gate of I_{Ks} current. The equation for time constant of x_s-gate is different for M-cells compared to the other cells (Eqns. 2-4) since the M-cells have a reduced I_{Ks} current. The I_{Ks} current in epicardial cells is scaled by a factor of 1.5 compared to mid-myocardial cells as reported in the study of Szabo et al. [10], so as to generate a high, symmetrical T-wave as observed in clinical ECG under SQTS conditions.

$$I_{Ks} = G_{Ks} x_s^2 (V_m - E_K) \tag{1}$$

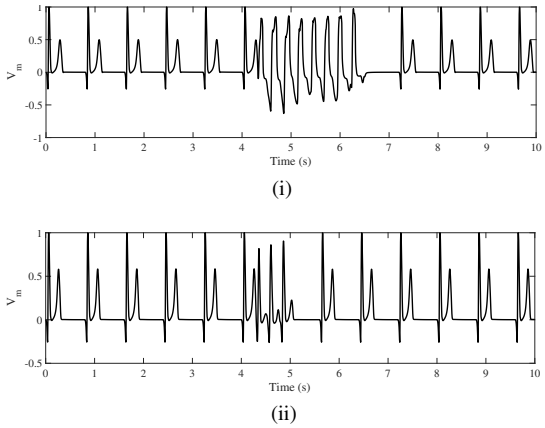
$$Het : x_{s\infty} = \frac{1}{(1 + e^{(-20.62 - V_m)/10.96})} \tag{2}$$

$$M - cell : \tau_{xs} = 0.75 * (\alpha_{xs}\beta_{xs} + 80) \tag{3}$$

$$Othercells : \tau_{xs} = 0.7 * (\alpha_{xs}\beta_{xs} + 80) \tag{4}$$

3. Results

The SQTS2 gene mutation is introduced in all the cells of the tissue and then the tissue is paced with premature beats (PBs) in between the normal pacing pulse in order to check if an arrhythmia is generated. After six normal pacing pulses of 800 ms, three PBs of 270 ms are applied inorder to generate an arrhythmia. Applying single or two PBs doesn't generate an arrhythmia. Fig. 2(i) shows the normalised pseudo ECG on application of this pacing protocol in the M-cell layer configuration. In the ECG, it is observed that the first six beats are normal and appear at regular intervals of 800 ms. The peak amplitude of the first beat is 0.4977 mV and the QT interval is 0.305 s. The three premature beats are applied at 4.27 s, 4.54 s and 4.81 s, after which an arrhythmic type of pattern is observed that is not sustained. The normal pacing pulse is resumed at 7.2 s after a long pause.



(i)

(ii)

Figure 2: Pseudo ECG generated in M-cell (i) layer (ii) island configuration under SQTS heterozygous mutation

The normalised pseudo ECG generated on applying similar pacing protocol to the M-cell island configuration tissue and on introducing SQTS2 gene mutation conditions is shown in Fig. 2(ii). After six normal pacing pulses, the three PBs are applied every 260 ms at 4.26 s, 4.52 s and 4.78 s. It is observed that the peak value of the normal QRS complex is 0.581 mV and QT interval is 0.28 s. The application of three PBs doesn't generate an arrhythmic rhythm and the normal pacing sequence is resumed after a pause at 5.6 s.

3.1. Voltage Snapshots M-Cell Layer

Fig.3 shows the voltage snapshots after applying the pacing protocol in the M-cell layer configuration. On stimulating the endo pacing site at 0.01 s, a convex depolarisation wavefront originating from the lower leftmost corner is generated that reaches the mid layer at 0.022 s. This wavefront reaches the mid-epi interface after 0.045 s and is delayed here due to the lowered gap junction conductances. The depolarisation proceeds towards the end of the epi cells at 0.07 s and then continues to move upwards. All the cells get depolarised after 0.1 s (not shown here). Repolarisation proceeds from the epi and endo cells from the bottom to the top of the tissue. The M-cells located in the top of the mid layer are the last to repolarise and all the cells finally repolarise at 0.385 s. Fig. 3(a) shows the tissue after the application of the first PB. At this time, the M-cells in the mid layer of the tissue are still in repolarising state. Therefore, the depolarisation wavefront moves upwards along the endo layer as seen in Fig. 3(b). Once all the M-cells return to their resting state, the depolarisation wavefront moves from the endo to the mid layer and the epi layer assuming a parallel wavefront as seen in Figs. 3(c). Fig. 3(d) shows the state of the tissue after the application of the second PB. It is seen that the cells in the mid and epi layer are in repolarising state. Thus, the depolarisation wavefront from this stimulus also travels upwards along the endo layer and then moves into the mid and epi layers as seen in Fig. 3(e-f) similar to the one seen on the application of the earlier beat. Fig. 3(g) shows the tissue on application of the third PB at 4.81 s. The cells in the mid and epi layer are in a depolarised state and therefore the wavefront moves upwards along the endo layer and then reenters into the mid layer and epi layer at the top portion as seen in Figs. 3(h-i). In Figs. 3(j-l), it is seen that this depolarisation wavefront travels downward along the epi layer and then reenters into the endo layer. This wavefront continues to circulate within the tissue creating a reentrant arrhythmia until 6.43 s (Figs. 3(m)). At 6.475 s, it is observed that the depolarisation wavefront at the bottom mid cells doesn't reenter into the endo cells as seen in Figs. 3(n-o). Therefore, all the cells in the tissue get repolarised. At 7.2 s, the normal pacing pulse is resumed and this is shown in Fig. 3(p).

3.2. M-cell Island

Fig. 4 shows the voltage snapshots of the M-cell island tissue configuration after the application of the pacing protocol. The normal pacing site is excited creating a depolarisation wavefront that propagates from the endo cells reaching the mid layer at 0.02 s. The depolarisation reaches the end of the epi layer at 0.07 s after a small delay at the mid-epi interface and then moves from bottom to the top of the tissue. Repolarisation starts from the epi and the endo layer and the M-cells located as an island in the mid layer are the last to repolarise. Due to the apex-base variation in APD of endo cells, the cells located at the base (top) of the tissue repolarise later than those located at the endo apex (bottom) of the tissue. All cells repolarise at 0.345 s. Fig.4(a) shows the voltage snapshot after the application of the first PB, at this instant, the M-cells are still in the repolarising state. By the time the depolarisation wavefront reaches the M-cells, they have returned to their refractory state and are ready to be reexcitable again. Thus, the depolarisation wavefront arising from this stimulus propagates as described earlier although with a small delay through the M-cell island as seen in Fig.4(b). All the cells get depolarised in Fig.4(c) and repolarisation starts. The second PB is applied at 4.52 s and the wavefront generated from it is shown in Figs.4(d-e). The cells repolarise from bottom to top with the M-cells repolarising last as seen in Fig.4(f). When the third PB is applied at 4.78 s, all the cells are in repolarised state and the depolarisation wavefront arising from this PB is seen in Fig.4(g) at 4.81 s. This wavefront propagates in a regular fashion and all the cells repolarise such that a normal upright T-wave is created as seen in Figs.4(h-i). Therefore, no arrhythmia is generated and the normal pacing pattern is resumed.

4. Discussions and Conclusion

The existence of M-cells in the transmural layer of the heart and its functional role in the formation of T-wave and arrhythmogenesis has been a matter of debate [10]. A number of studies validate as well as dispute their existence and role in various species. This controversy in M-cell findings may be due to differences in measuring techniques, samples on which the experiments are conducted (wedge or intact heart), anesthetic agent used and the age or species of the sample. In this paper, the existence of M-cells is assumed and it's effect on the shape and duration of the T-wave is assessed. On introducing heterozygous SQTS2 gene mutation and on pacing the tissue with premature beats, it is observed that arrhythmia is generated only when the entire mid layer is made up of M-cells. The presence of an M-cell island doesn't generate arrhythmia. This finding contradicts those reported by Luo et al. [11], where the presence of the M-cell island caused the reentrant arrhythmia to circulate around this island. This could be due to the differences in the electrophysiological properties of the considered M-cell island and surrounding cells. The use of a 3D anatomically accurate model in place of the simplified model used here would bring in differences in the propagation direction and therefore changes in the repolarisation pattern and subsequently in the morphology of the T-wave. Such in-depth analysis of the properties and topography of the M-cells in relation to

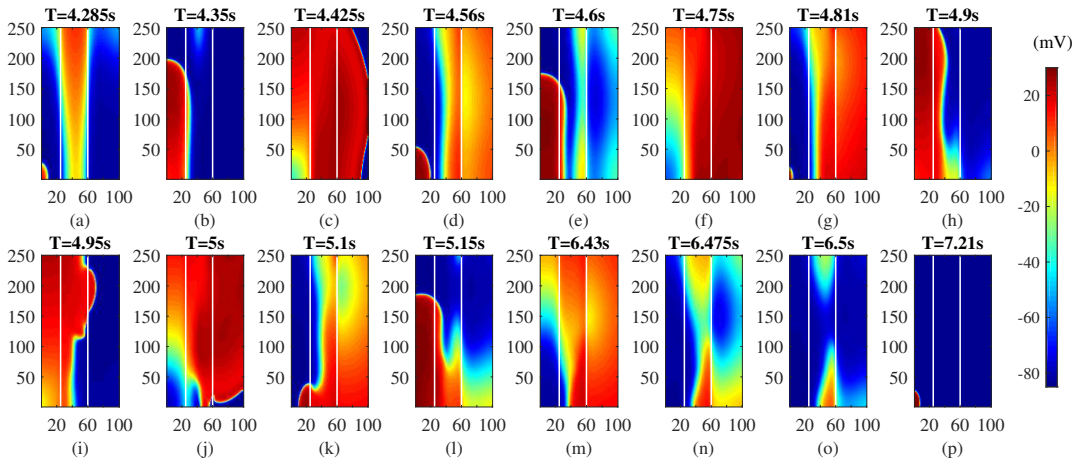


Figure 3: (i) Pseudo ECG and (ii)voltage snapshots in TM-25 configuration and heterozygous mutation

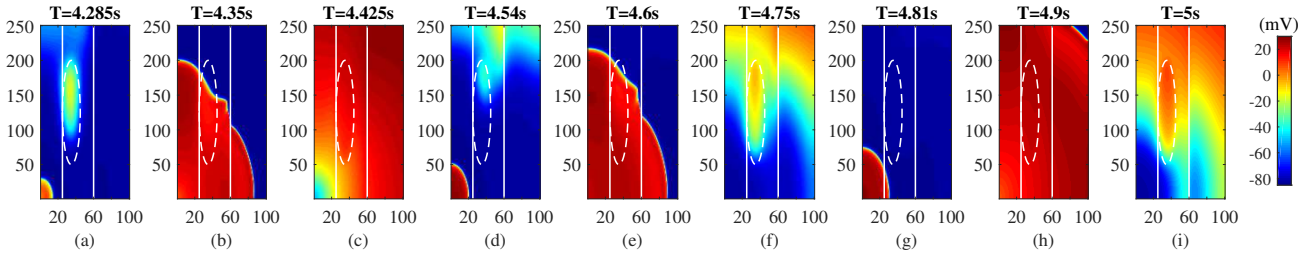


Figure 4: (i) Pseudo ECG and (ii) voltage snapshots in M-cell island configuration and heterozygous mutation

the surrounding cells in 3D tissue models would need to be carried out.

References

[1] Antzelevitch C. M cells in the human heart. Circulation research 2010;106(5):815–817.

[2] Adeniran I, Whittaker DG, El Harchi A, Hancox JC, Zhang H. In silico investigation of a KCNQ1 mutation associated with short qt syndrome. Scientific reports 2017;7(1):8469.

[3] Zhang H, Kharche S, Holden AV, Hancox JC. Repolarisation and vulnerability to re-entry in the human heart with short QT syndrome arising from KCNQ1 mutation—a simulation study. Progress in biophysics and molecular biology 2008;96(1-3):112–131.

[4] Luo C, Wang K, Zhang H. Functional effects of island-distribution of mid-cardiomyocytes on re-entrant excitation waves in the KCNQ1-linked short QT syndrome. In 2016 Computing in Cardiology Conference (CinC), volume 43. IEEE, 2016; 933–936.

[5] Ten Tusscher KH, Panfilov AV. Alternans and spiral breakup in a human ventricular tissue model. American Journal of Physiology Heart and Circulatory Physiology 2006;291(3):H1088–H1100.

[6] Priya PK, Reddy MR. Study of factors affecting the progression and termination of drug induced torsade de pointes in two dimensional cardiac tissue. Journal of electrocardiology 2017;50(3):332–341.

[7] Priya PK, Reddy MR. Simulation study of the ionic mechanisms underlying torsade de pointes in a 2D cardiac tissue. Computers in biology and medicine 2017;89:293–303.

[8] Gima K, Rudy Y. Ionic Current Basis of Electrocardiographic Waveforms A Model Study. Circulation Research 2002;90(8):889–896.

[9] Bellocq C, van Ginneken AC, Bezzina CR, Alders M, Escande D, Mannens MM, Baro I, Wilde AA. Mutation in the KCNQ1 gene leading to the short QT-interval syndrome. Circulation 2004;109(20):2394–2397.

[10] Nattel S, Antzelevitch C, Noble D. Resolving the m-cell debate: why and how. Heart Rhythm 2011;8(8):1293–1295.

[11] Luo C, Wang K, Liu Y, Xia Y, Zhang H. Effects of quinidine on short QT syndrome variant 2 in the human ventricle: A modelling and simulation study. In 2017 Computing in Cardiology (CinC). IEEE, 2017; 1–4.

Address for correspondence:

Name: Ponnuraj Kirthi Priya
Full postal address: D-Block, Gopalan Global Axis, Opp. Satya Sai Hospital, Rd Number 9, KIADB Export Promotion Industrial Area, Whitefield, Bengaluru 560066, Karnataka, India.
E-mail address: p.kirthipriya@tcs.com