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RESEARCH ARTICLE

Computational Model based Approach to Analyse Calcium (Ca^{2+}) Channel in Ventricular Cells for Normal and Cardiac Arrhythmias Using Euler Integration Method - A Simulation Study

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ABSTRACT

Aim: In this paper, analysis of ventricular arrhythmias are made with respect to the Calcium (Ca^{2+}) ion channel dysfunction (generating improper electrical activity). Many cases can make arrhythmias and most of them are related to generation or conduction of Action Potential (AP) in cardiac myocardium. **Materials and method:** Human ventricular cell based on the model of the human endocardial cell by Ten Tusscher (TT). The TT model data is modified based on the experimental data of Han, describing the properties of Ca_{2+} currents and its channel dynamics in human ventricular cells. Euler integration method is used to analyse the human ventricular model for different channel failure conditions in the same group of 50 samples. **Results:** Our research findings focus with respect to normal and deviant Ca_{2+} conductance (G_{CaL}). The normal G_{CaL} 0.000175nS and deviant G_{CaL} increase like (10%=0.000218nS, 25%=0.000182nS, 50%=0.000262nS and 100%=0.000350nS) having the normal AP average value ranges between 26.0mV to -74.0mV and 12.0mV to -88.0mV for 10% G_{CaL}, 18.0mV to -78.0mV for 25% G_{CaL}, 18.0mV to -78.0mV for 50% G_{CaL} and 21.0mV to -75.0mV for 100% G_{CaL} deviants. Similarly, deviant G_{CaL} decrease like (10%=0.000158nS, 25%=0.000131nS, 50%=0.000088nS and 100%=0.000001nS) having the deviant AP mean values ranges between 10.0mV to -90.0mV for 10% G_{CaL}, 7.0mV to -92.0mV for 25% G_{CaL}, -9.0mV to -96.0mV for 50% G_{CaL} and -51.0mV to 100.0mV for 100% G_{CaL}. Simultaneously its membrane Ca^{2+} currents are having significant variations. **Conclusion:** The results show clearly for the affirmation for Excitation and Coupling (EC) failures. EC failures lead to a systole phase that is more prolonged, that in turns to produce QT syndrome and hypertrophic cardiomyopathy.

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Introduction

An arrhythmia is a problem with the rate or rhythm of the heartbeat or in general it can be termed as irregular heartbeat. During an arrhythmia the heart can beat too fast, too slow or irregular. In today's industrial world, most of the deaths occur due to sudden cardiac arrest. In that ventricular arrhythmias are abnormal electrical activities that originate in your lower chambers of the ventricular myocardium, called ventricles (Bhardwaj, Choudhary, and Dayama 2012).

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The clinical research for studying cardiac arrhythmia in human ventricular cells are less. In the industrialized world, deaths caused due to arrhythmias and cardiac deaths are more in number and for decades there is no exact explanation or reasons for them. According to a World Health Organisation (WHO) survey nearly 17.9 million deaths due to cardiovascular diseases. Among them 1.8 percent of deaths are due to vascular arrhythmias. In the recent survey 0.57 per 1000 people are affected due to vascular arrhythmia (Khurshid et al. 2018). Ca^{2+} channel is an ion channel which shows selective permeability to Ca^{2+} ions. It is

sometimes synonymous with voltage gated Ca^{2+} channels. In a normal AP contraction phase is related to the Ca^{2+} channel and if there is any problem in the passage of ions between the channels then it leads to slowing down or irregular contraction of myocardium. In arrhythmias the role of Ca^{2+} channel is related to the effect on the sinus and atrioventricular nodes and with regard to how the entry of ions is processed and blockage is done is analysed (Mesirca, Torrente, and Mangoni 2015). Ca^{2+} ions are also responsible for different types of cardiac arrhythmias and they cause potentially cardiac syndromes like congenital long QT syndrome and hypertrophic cardiomyopathy (Landstrom, Dobrev, and Wehrens 2017).

Over the period of past five years the researches went on with regard to Ca^{2+} channel describes about the predominant role of Ca^{2+} in cardiac conduction and excitation. There are many research articles based on ventricular arrhythmias with reference to Ca^{2+} channel and nearly there are 110 papers cited in google scholar and 80 from pub med. Among them the first research is about Cardiac signalling and cardiac arrhythmia which express the regulation of Ca^{2+} channels and its membrane current which leads to arrhythmias (Landstrom, Dobrev, and Wehrens 2017). There after the first research further experimental studies on early afterdepolarization (EAD) and delayed afterdepolarization (DAD) based on Ca^{2+} overload and Ca^{2+}/ calmodulin-dependent kinase II (CaMKII) activation (Skogestad and Aronsen 2018). Third research is about mutation in low tubulous Ca^{2+} channel (LTCC) genes which leads to long QT syndromes and some other cardiac arrhythmias (Zhang et al. 2018). In further researches that are carried on Ca^{2+} channel plays its roles in the plateau phase of AP in excitation and contraction (Betzenhauser, Pitt, and Antzelevitch 2015). From the above research long QT syndromes effect due to Ca^{2+} channel leading to gene mutation changes grasps the attention among them (Zhang et al. 2018).

Previously our team has a rich experience in working on various research projects across multiple disciplines (Sathish and Karthick 2020; Varghese, Ramesh, and Veeraiyan 2019; S.R. Samuel, Acharya, and Rao 2020; Venu, Raju, and Subramani 2019; M. S. Samuel et al. 2019; Venu, Subramani, and Raju 2019; Mehta et al. 2019; Sharma et al. 2019; Malli Sureshbabu et al. 2019; Krishnaswamy et al. 2020; Muthukrishnan et al. 2020; Gheena and Ezhilarasan 2019; Vignesh et al. 2019; Ke et al. 2019; Vijayakumar Jain et al. 2019; Jose, Ajitha, and Subbaiyan 2020). Now the growing trend in this area motivated us to pursue this project.

Till now many researches are performed on Ca^{2+} channel and its role in the plateau phase of AP in excitation and contraction, but there is lack of proper information on excitation and contraction with respect to Ca^{2+} channel in real time. In order to understand more information about Ca^{2+} plateau phase AP and its excitation and contraction process, we implemented the mathematical model (Innovative computational approach) which is very useful in providing the information about that limitation of existing real time researches.

Materials and Methods

The research is carried out in the digital signal processing laboratory in the department of Biomedical Engineering. Our research analysis is carried out in a single group with different channel arrhythmic conditions. Sample size was calculated by using previous study results (Ramírez et al. 2020), in Clinicalc.com by keeping threshold 0.05, G Power 80%, confidence interval 95% and enrolment ratio as 1. Number of samples considered is 50 for each analysis.

Preparation of sample group: Normal G_{CaL}=0.000175nS is considered to be normal AP. Then for dysfunction Ca^{2+} channels, G_{CaL} increase is 0.000350nS for 100%, G_{CaL} increase is 0.000262nS for 50%, G_{CaL} increase is 0.000218nS for 25%, G_{CaL} increase is 0.000182nS for 10%. In the same process even the decrease analysis is done (G_{CaL} value with 100% decrease is 0.000001nS, G_{CaL} value with respect to 50% decrease is 0.000088nS, G_{CaL} value with 25% decrease is 0.000131nS, G_{CaL} value with respect to 10% decrease is 0.000158nS). In this research, the Ten Tusscher model of human ventricular cells is used for simulation analysis (ten Tusscher and Panfilov 2004). The electrophysiological study of a single cell can hence be described with the following differential equation.

$$C_m\,(dV/dt) = -\,(I_{ion} + I_{stim})$$

Where, V is membrane potential (mV), C_m is membrane capacitance (μF), I_{ion} is total ionic current (pA), I_{stim} is stimulation current (pA). The data is collected from the literature survey of different research studies. The model is computed by using the Euler integration innovative approach with MATLAB software (R2015a). Finally we are validating our result of normal and dysfunction channel potentials and currents mean values, standard deviation of dependent variables with the Statistical Package for the Social Sciences (SPSS) software using Paired Sample T Tests.

Results

Table 1 shows Paired Sample T Test analysis of mean and standard deviation value for AP pair 1 (normal and 100% dysfunction G_{CaL} increase), pair 2 (normal and 50% dysfunction G_{CaL} increase), pair 3 (normal and 25% dysfunction G_{CaL} increase), pair 4 (normal and 10% dysfunction G_{CaL} increase), pair 5 (normal and 100% dysfunction G_{CaL} decrease), pair 6 (normal and 50% dysfunction G_{CaL} decrease), pair 7 (normal and 25% dysfunction G_{CaL} decrease), pair 8 (normal and 10% dysfunction G_{CaL} decrease) and accordingly standard error means are plotted for each pairs and that mean shows the difference in action potential variations.

Table 1. Mean, standard deviation and standard error mean for different dysfunction pairs. 50 samples are selected and paired T test analysis is done for different sets of pairs with normal AP.

Paired Samples Statistics

		Mean	N	Std deviation	Std error mean
Pair 1	Normal ap hninc ap	-27.9295178	50	49.03255606	7.150232519
Pair 2	Normal ap ffinc ap	-32.9391477	50	49.03673755	7.150232519
Pair 3	Normal ap twinc ap	-32.9295166	50	49.03462345	7.150232519
Pair 4	Normal a teninc ap	-34.9492578	50	48.03523908	6.150232519
Pair 5	Normal ap hndec ap	-36.9295178	50	24.03234897	3.420232519
Pair 6	Normal ap ffdec ap	-75.9595178	50	49.03543669	7.150232519
Pair 7	Normal ap twdec ap	-50.9295568	50	46.03214567	6.150232519
Pair 8	Normal ap tendec ap	-42.9795176	50	47.03434567	6.150232519

Table 2. Samples, correlation and significance values for normal and different dysfunction pairs. All paired conditions show significance value (P<0.001).

Paired Samples Correlations

		N	correlation	Sig.
Pair 1	Normal ap hninc ap	50	.974	<.001
Pair 2	Normal ap ffinc ap	50	.942	<.001
Pair 3	Normal ap twinc ap	50	.942	<.001
Pair 4	Normal ap teninc ap	50	.907	<.001
Pair 5	Normal ap hndec ap	50	.466	<.001
Pair 6	Normal ap ffdec ap	50	.766	<.001
Pair 7	Normal ap twdec ap	50	.853	<.001
Pair 8	Normal ap tendec ap	50	.879	<.001

Table 2 shows the Paired Sample T test analysis done for each normal and dysfunction parameter, where the major changes are seen in correlation values of each pair of set and the highest variation is seen to normal and 100% decreased dysfunction parameter with 0.466 and in normal it is observed to be 0.974. This is for one single AP.

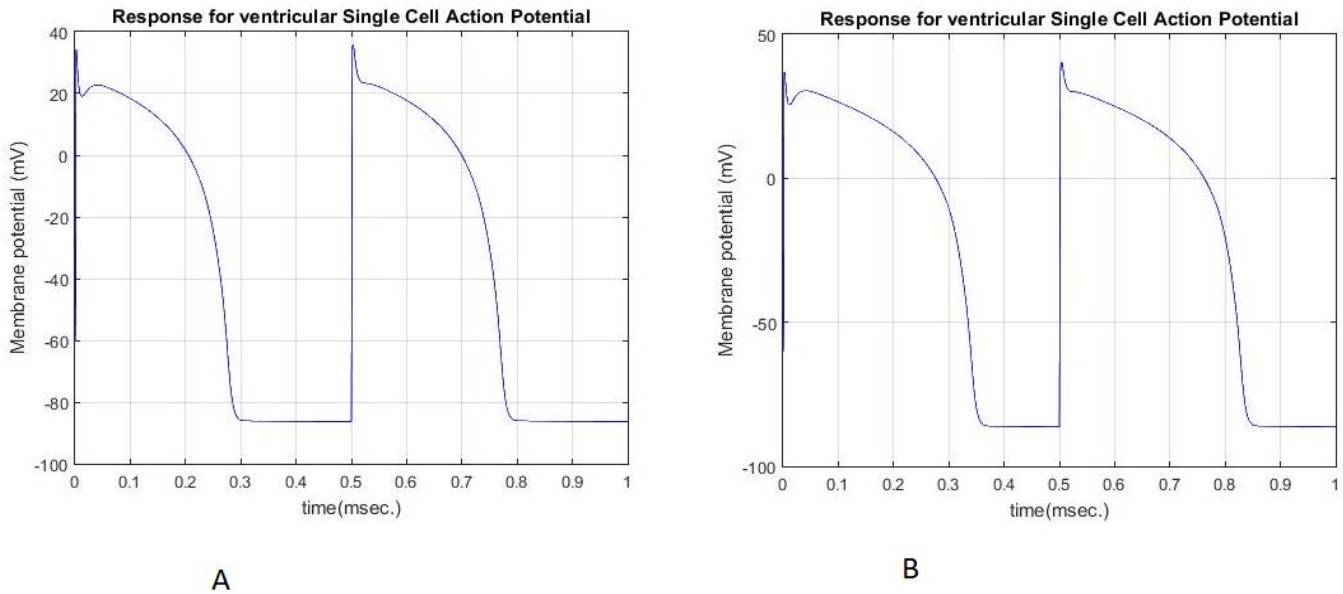

Fig. 1. (A) AP in mV of a single ventricular cell with G_{CaL}=0.000175nS. (B) AP in mV of a single ventricular cell with G_{CaL}=0.000350nS.

Figure 1(a) and 2(a) shows the normal AP of a single ventricular cell with Ca^{2+} conductance (G_{CaL}=0.000175nS). In that it has a maximum amplitude of 29.3mV, maximum diastolic potential is -85mV and AP duration is 290ms. In AP of dysfunction Ca^{2+} conductance level with increased G_{CaL}=0.000350nS having AP duration is 350mS is shown in Fig. 1(b). Similarly, AP of dysfunction Ca^{2+} conductance level with decreased G_{CaL}=0.000001nS having AP duration is 120mS is shown in Fig. 2(b).

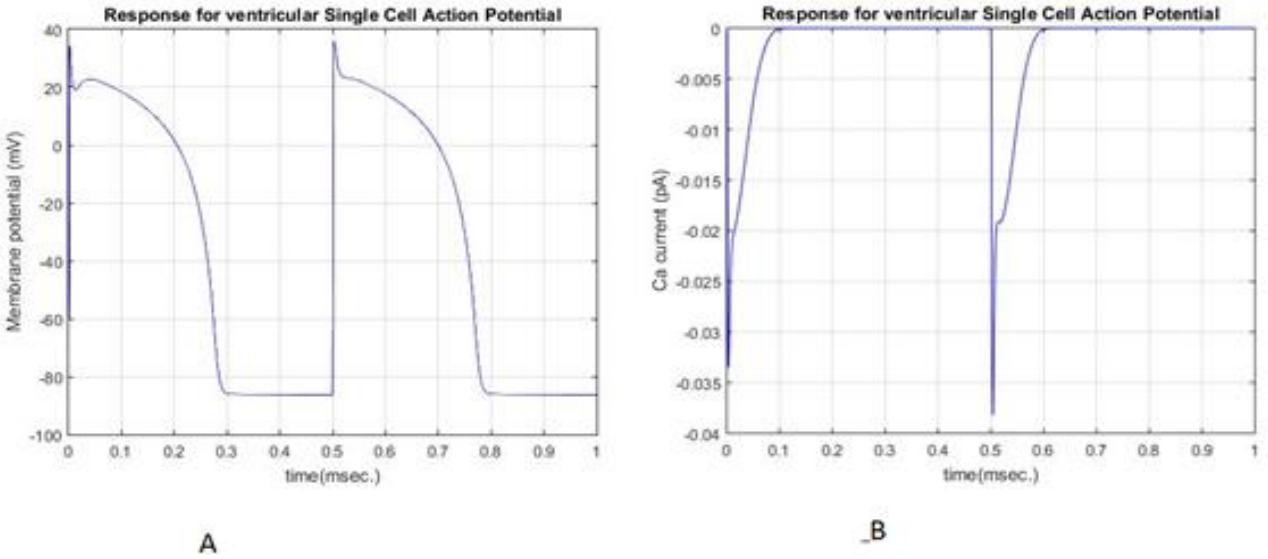

Fig. 2. (A) AP in mV of a single ventricular cell with G_{CaL}=0.000175nS. (B) AP in mV of a single ventricular cell with G_{CaL}=0.000001nS

Figure 3(a) and 4(a) shows the response of normal I_{CaL} current at G_{CaL} =0.000175nS. In that peak value of I_{CaL} is varied from 0 pA to -4.5 pA over the time period of 500ms. In the same manner Fig 3(b) shows, peak value of I_{CaL} is varied from 0 pA to -8 pA at G_{CaL}=0.000350nS. Similarly, Fig. 4(b) shows peak value of I_{CaL} variations from 0 pA to -0.033 pA at G_{CaL}=0.000001nS.

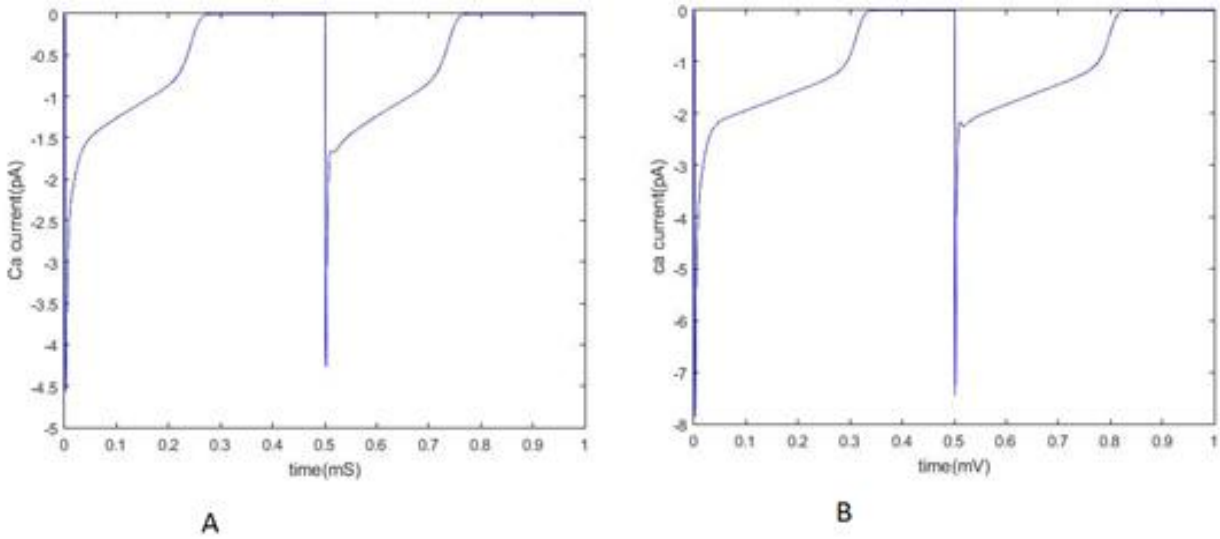

Fig. 3. (A) I_{CaL} in pA of a single ventricular cell with G_{CaL}=0.000175nS. (B) I_{CaL} in pA of a single ventricular cell with G_{CaL}= 0.000350nS

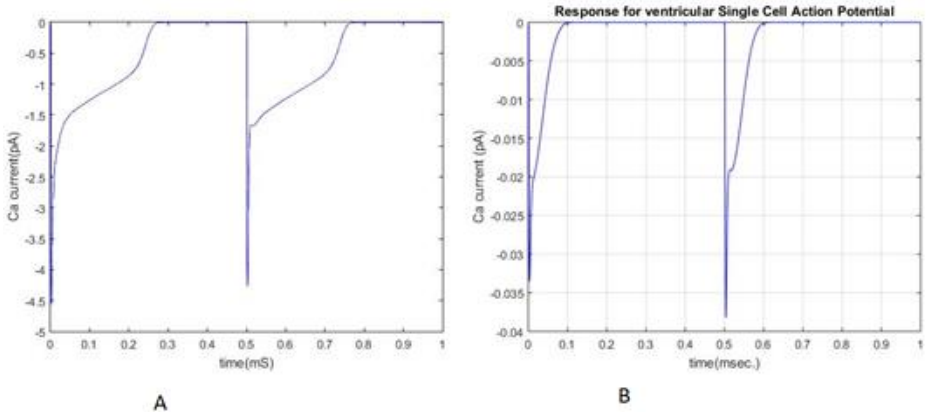

Fig. 4. (A) I_{CaL} in pA of a single ventricular cell with G_{CaL}=0.000175nS. (B) I_{CaL} in pAof a single ventricular cell with G_{CaL}= 0.000001nS

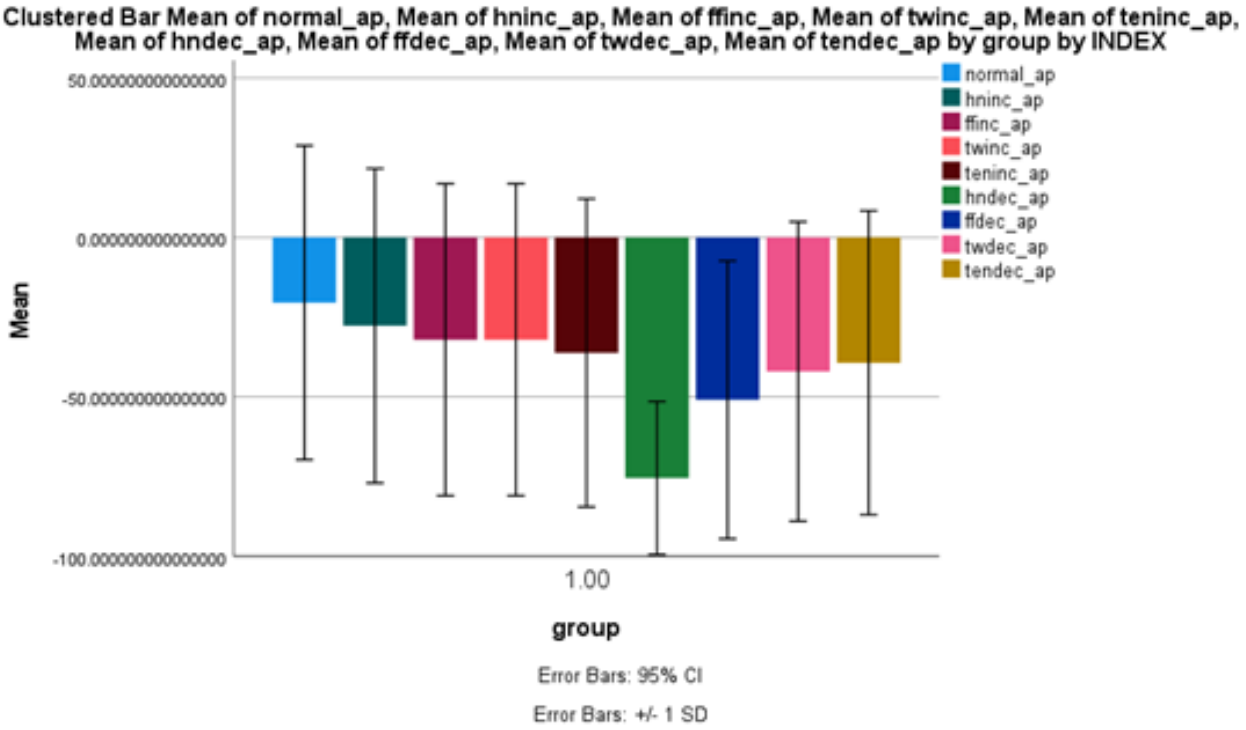

Fig. 5. Comparison of normal AP with different G_{CaL} parameters AP, in terms of mean and standard deviation value plotted in the graph. X axis: Mean of AP in mV and Y axis: normal and dysfunction different G_{CaL} parameters in same group. Mean accuracy of detection ± 1 SD

In the bar graph it is shown in Fig. 5, that the mean of normal AP ranges with different dysfunction Ca^{2+} channel conductance AP (Paired Sample T test). The deviation in mean can be clearly observed, when it is compared to each pair set from normal AP to 10%, 25%, 50% and 100% increased and decreased values of AP. (increased 10% G_{CaL}=0.000182nS, increased 25% G_{CaL}=0.000218nS, increased 50% G_{CaL}=0.000262nS, increased 100% G_{CaL}=0.000350nS) (decreased 10% G_{CaL}=0.000158nS, decreased 25% G_{CaL}=0.000131nS, decreased 50% G_{CaL}=0.000088nS, decreased 100% G_{CaL}=0.000001nS). Similarly its I_{CaL} mean ranges are illustrated in Fig. 6.

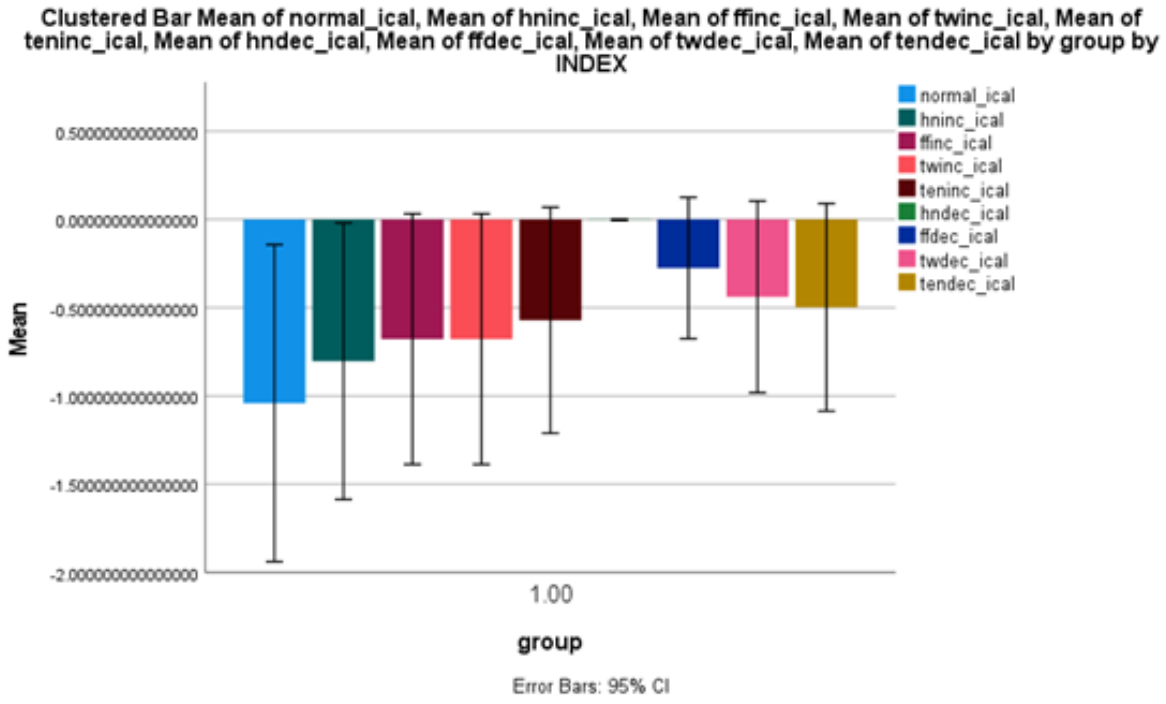

Fig. 6. Comparison of normal I_{CaL} with different G_{CaL} parameters I_{CaL}, in terms of mean and standard deviation value plotted in the graph. X axis: Mean of I_{CaL} in pA and Y axis: normal and dysfunction different G_{CaL} parameters in the same group. Mean accuracy of detection ± 1 SD.

Discussion

The computational approach in the ventricular cell that AP and its currents for normal and abnormal dysfunction channel conductance are shown clearly in Fig 1,2 and Fig 3,4. In that normal AP duration (APD) is 290ms, with increased dysfunction Ca^{2+} channel conductance (G_{CaL}(100%) =0.000350nS) having APD is 350ms. Similarly in decreased dysfunction Ca^{2+} channel conductance (G_{CaL}(100%) = 0.000001nS) having APD is 120ms. As per the literature survey normal AP is mentioned as the same (ten Tusscher and Panfilov 2004), in the same way with reference to normal APD (Scarle and Clayton 2009) shows it in 250ms. Even when the currents are also compared with normal and abnormal AP there are changes (G. and R. 2018), for a ventricular cell its membrane Ca^{2+} currents are varied with normal (-0.13pA to -1.96pA) and abnormal (-0.02pA to -1.6pA for 100%). The main observation with reference to every literature survey is, there are changes in normal APD to abnormal ones and even the inhibiting processes are also present to analyse early ventricular arrhythmias (Rodríguez-Mañero et al. 2018). This APD alternant is a potential threat for cardiac contraction and relaxation (Qu et al. 2019). Furthermore, the results are analysed by SPSS software, in that the mean of normal AP ranges between 26.0mV to -74.0mV, whereas in abnormal case of increasing parameters (G_{CaL}(100%)=0.000350nS) its mean ranges from 21.0mV to -75.0mV for 100% and in the case of decreasing parameters (G_{CaL}(100%)=0.000001nS) is -51.0mV to 100.0mV for 100% are shown clearly in Fig 5 . Its membrane Ca^{2+} currents are also shown in Fig 6 with their respective mean and significant values.

Our institution is passionate about high quality evidence based research and has excelled in various fields ((Vijayashree Priyadharsini 2019; Ezhilarasan, Apoorva, and Ashok Vardhan 2019; Ramesh et al. 2018; Mathew et al. 2020; Sridharan et al. 2019; Pc, Marimuthu, and Devadoss 2018; Ramadurai et al. 2019). We hope this study adds to this rich legacy.

The major problem of using the Euler integration method is prediction of accurate stiffness is not possible and also it is having lesser accuracy when step size (dt=0.001ms) is increased. When we increase step size the number of computational time will also be increased. To overcome this stiffness and lesser accuracy problem, we can use higher numerical methods like Runge Kutta and back propagation methods for future basis.

To improve our research to understand Ca^{2+} channel behaviour more in computational approach by 1-Dimensional, 2-Dimensional and 3-Dimensional. To perform the computational study in advanced mechanisms between two different cardiac cells which helps in easy understanding of AP generation and propagation.

Conclusion

In a normal AP the contraction phase occurs with respect to Ca^{2+} channel and from this research it is observed that change in electrophysiological conduction between ion channels affects the duration of time and that leads to the irregular contraction. This is observed with reference to the Ca^{2+} channel and its Ca^{2+} gated parameters. For a normal AP the conductivity is in the range between 26.0mV to -74.0mV but for an abnormal condition it ranges between 12.0mV to -88.0mV. This affects the duration of time for a phase of heartbeat and Excitation and Coupling (EC) failures lead to a systole phase that is more prolonged, that in turns produce QT syndrome and hypertrophic cardiomyopathy.

Declarations

Conflict of Interests

No conflict of interest in this manuscript.

Authors Contributions

Author SSB was involved in literature survey in mathematical model, Euler integration matlab code development, Arrhythmias analysis and manuscript writing. Author GG involved in conceptualization, data validation and critical review of manuscript.

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