

Monophasic vs. Biphasic Stimulation of Single Cardiomyocyte Cell: a Simulation Study

Monica Caselli¹, Stefano Severi¹, Aldo Casaleggio²

¹ University of Bologna, Cesena, Italy, ² IBF – CNR, Genova, Italy

Abstract

Mechanisms involved in the initiation of fibrillation and defibrillation are complex and still not totally understood. This paper computationally investigated the effect of monophasic, biphasic and reversed biphasic stimuli on single cardiomyocyte, with a modified Ten Tusscher model of human ventricular action potential (AP) and calcium dynamics. Three different S1-S2 protocols with variable duration were used: monophasic, biphasic and reversed biphasic. Results were expressed in terms of total response duration (TRD), defined as the interval between the S1 onset and the response generated by S2. TRD was focused both on AP (V_m -TRD) and on Calcium transient (Ca-TRD). Simulations confirmed previous results obtained with the Beeler-Reuter model pointing to the role of I_{Na} in prolonging the refractory period when using a biphasic stimulus. No differential effects of biphasic vs monophasic stimulation when Ca-TRDs are compared instead of V_m -TRDs were found.

1. Introduction

The superiority of biphasic shocks over monophasic ones in defibrillation therapy is nowadays established by experimental evidences that led all implantable as well as external cardioverter defibrillators to use such type of stimulation to defibrillate cardiac tachyarrhythmias [1]. At the same time, electrical stimulation is normally used to induce a tachyarrhythmia during implantable cardioverter defibrillator (ICD) implantation. [2].

In practice the interaction between electrical field and cardiac cells lead to different behavior of cardiac cell and the investigation of possible behavior can lead to important hypotheses about cardiomyocytes.

Still the mechanism justifying such evidences are not perfectly understood and their better understanding could insight on the mechanism involved in the initiation and termination of cardiac tachyarrhythmias, or it could lead to further improvement in the development of new type of tachyarrhythmias induction procedures or defibrillation waveform.

Several theoretical studies has been focused to understand the reason for the superiority of biphasic compared to monophasic electrical shock in defibrillating cardiac muscle; among other we like to mention the work by Popp et al [3] where ventricular myocardium was simulated by means of Priebe-Beuckelmann model; a three-dimensional simulation of heart tissue was constructed and an electrical field of different waveform and amplitude was applied to investigate cardiac response to monophasic rather than biphasic electrical shocks of different amplitudes. Their results provided two observation that would make one to incline in the favor of biphasic electrical shocks; both of them requiring the interaction among cells, thus not expressed by the analysis of single cell simulation. The first of them showed that, when the myocardium was monophasically activated, the real cathode depolarized only a small part of the neighboring area. The tissue in that region was not subsequently excitable. Since the depolarization front, produced at the opposite end did not induce a depolarization in that region, the goal of complete tissue depolarization failed. The second observation was that the biphasic shock reduced very much the time needed for the tissue to pass from one phase to another. The largest amount of depolarized tissue was achieved 240 ms after the monophasic shock was applied, while only 85 ms were needed by the whole tissue to be depolarized after a biphasic impulse was given.

Still this type of investigation was not focused on detailed information about single ion channels activity, and on the effect that an external electrical field would have on them. More recent experimental studies showed that superiority of biphasic over monophasic shocks could be justified by the reactivation of fast sodium channels from the inactivated to the excitable state, and that the extended chronaxie duration for defibrillation versus stimulation may be attributed to the time constant of fast sodium channels reactivation [4]. In other studies the intracellular calcium is considered to play the major role in cardiac defibrillation with biphasic rather than monophasic stimulation. Indeed greater efficacy of biphasic waveform shocks is directly related to the less

heterogeneous effects on shock-induced intracellular Calcium transients. Less heterogeneous intracellular calcium transients reduces the probability of intracellular Ca sinkhole formation, thereby preventing the post-shock re-initiation of ventricular fibrillation [5, 6].

At the same time also the mechanisms involved in cardiac tachyarrhythmias induction have been studied. Among other studies, the simulation of cardiac rabbit heart proposed by Costantino et al. [7] based their analysis on the existence of a submerged “tunnel” propagation of postshock activations through shock-induced intramural excitable areas underlies fibrillation induction and the existence of an isoelectric window. It has been then demonstrated that, during the isoelectric window, an activation originated deep within the ventricular wall, arising from virtual electrodes can propagated fully intramurally through an excitable tunnel induced by the shock, until it emerged onto the epicardium, becoming the earliest-propagated postshock activation. This work provides a novel analysis of the 3D mechanisms underlying the origin of postshock activations in the process of fibrillation induction.

All these studies are focused on the interaction among cells that comes together with the interaction between an external electrical field and the cardiac tissue.

In the present paper we have a limited aim, which is to use the computational approach proposed by Jones et al [8] to investigate the effect of an electrical field with different types of stimulation and amplitude on a single cardiomyocyte (CM) cell, simulated using a modified Ten Tusscher model of human ventricular action potential (AP) [9, 10]. The considered stimulations include monophasic, biphasic and biphasic with reversed polarity (reversed biphasic) stimuli, while the field amplitude is chosen higher than the stimulus able to initiate an action potential with the same cell. A deeper analysis over a single cell allows a more detailed investigation of the effect of an external electrical field on single cell dynamics for intracellular calcium concentration and fast sodium channel activation.

2. Methods

Following the paper by Jones et al [8] in this study the response of a single cell to electrical stimulation is investigated. As outcome the total response duration defined as the interval between the initial stimulation and the end of the AP originated by a second stimulation is considered. Furthermore the ionic currents across the membrane and the transmembrane potential and intracellular calcium concentration are examined.

Stimulation protocol is characterized by two following stimuli (S1-S2) of variable form and duration: the S1 is always a positive pulse of 10 msec duration and amplitude 5.4 [A/F] (equal to 1.5 times the threshold to initiate an AP); in Monophasic the stimulus simulation S2

is like S1; in Biphasic stimulus simulation it is a double pulse with zero mean and with negative first semi-wave; and in Reversed Biphasic it has the same S2 waveform as in Biphasic, but with reversed polarity (Fig. 1).

S1-S2 duration is variable and related to the refractory period of cell.

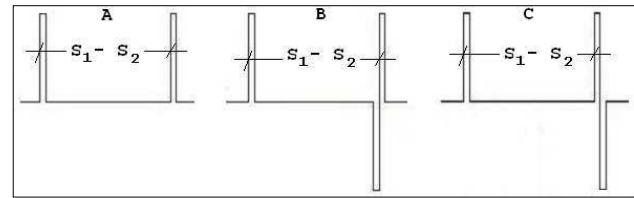


Figure 1. Stimuli definition; (A) Monophasic, (B) Biphasic, (C) Reversed Biphasic stimuli.

3. Model

Ventricular action potential (AP) was simulated using the Ten Tusscher model of human epicardial ventricular myocyte as modified by Grandi et al. to correctly reproduce the experimental APD inverse dependence on extracellular calcium concentration (Fig. 2).

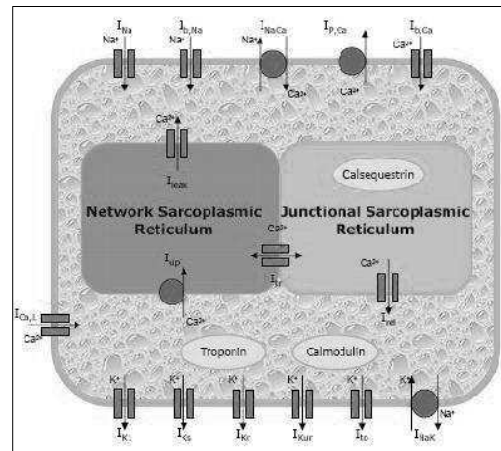


Figure 2. Schematic diagram of the ventricular cell model. The model describes the main membrane currents and active transport mechanisms participating in the AP and the processes that regulate intracellular Ca^{2+} concentration.

The model was used to simulate the effects of a monophasic or biphasic stimulus by imposing a current-clamp stimulation. Stimulation protocol is characterized by two following stimuli (S1-S2) of variable form and duration: the S1 is a positive pulse, S2 is like S1 in monophasic simulation, and it is a double pulse with zero mean in biphasic simulation; S1-S2 duration is variable and related to the refractory period of CM cell.

Action potential duration (APD) was measured as the

interval between the AP upstroke and the 90% repolarization level (APD_{90}). To quantify the effect of S1-S2 on CM AP and the total response duration (TRD) defined as the interval between the S1 onset and the end of the action potential generated by S2 are considered.

Model differential equations were implemented in Simulink (Mathworks Inc., Natick, MA, U.S.A.). A variable order solver based on the numerical differentiation formulas (NDFs) was used to numerically solve the model equations (ode15s) [6].

4. Results

Transmembrane potential (TmP) and intracellular calcium concentration (Ca_i) are shown in Fig. 3 for the three considered type of stimulations and for different choices of S1-S2 intervals durations, while Fig. 4 presents TRD of TmP and Ca_i for increasing choices of the S1-S2 intervals between 300 and 380 msec and the three stimuli.

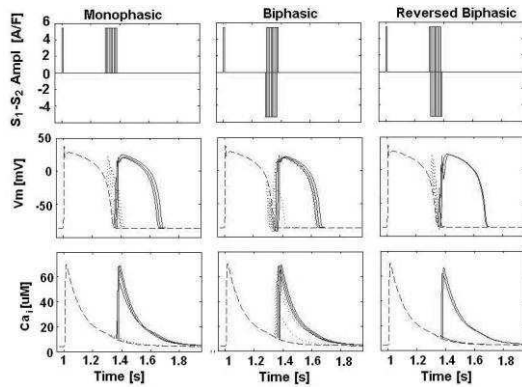


Figure 3. Simulated AP and intracellular calcium transient for variable S1-S2 interval. The S1 action potential is shown by the dashed line. (A) Monophasic S2. The dotted lines show nonrefractory response having a plateau. The solid lines show refractory-type response without a plateau. (B, C) Biphasic and Reversed Biphasic S2. Responses at short coupling intervals that were refractory to monophasic stimulation (solid lines) exhibit a plateau with biphasic S2 stimulation.

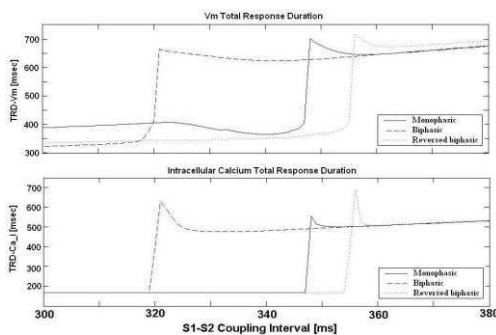


Figure 4. Total response duration of transmembrane potential (panel A) and intracellular calcium concentration (panel B) for

increasing S1-S2 intervals between 300 and 380 msec.

TmP, Ca_i as well as sodium and calcium currents are shown in Fig. 5 and 6 for two peculiar choices of the S1-S2 interval durations: the first is S1-S2 = 325 msec when only biphasic stimulus was generating a complete AP, while the second is obtained with S1-S2 = 350 msec when all types of S2-stimulus are able to induce a new AP.

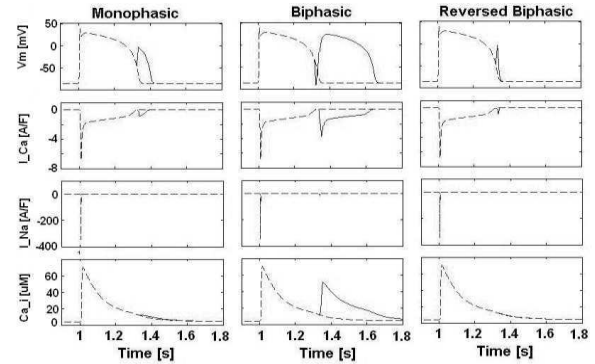


Figure 5. Simulated AP, calcium transient, Sodium and Calcium currents for S1-S2 = 325 msec.

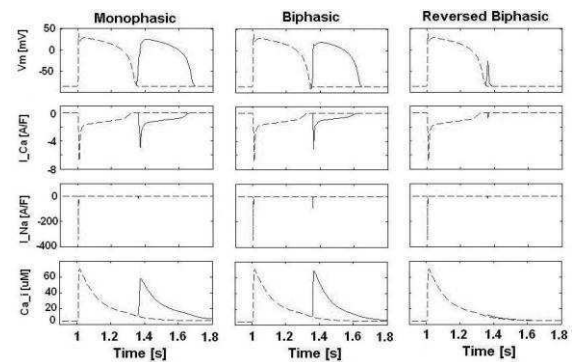


Figure 6. Simulated AP, calcium transient, Sodium and Calcium currents for S1-S2 = 350 msec.

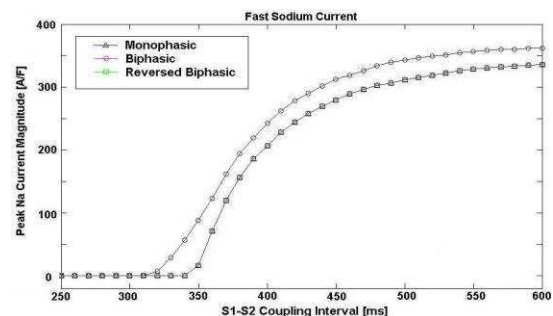


Figure 7. Peak of Fast-Sodium currents for different S1-S2 intervals between 250 and 600 msec and for the three stimulation waveforms.

Finally Fig. 7 shows the Peak Fast-Sodium current obtained for varying S1-S2 intervals and different types of stimuli.

5. Discussion

Results indicate that S2-induced response changes with S1-S2 duration and type of S2 stimulus as follows:

Monophasic S2. Refractory-type responses without AP / Calcium transient activation (Fig. 3, dotted lines, and Fig. 5) are observed for $S1-S2 \leq 350$ msec (Fig. 4); nonrefractory responses with a second AP / Calcium transient activation (Fig. 3, solid lines, and Fig. 6) are obtained for longer S1-S2.

Biphasic S2. Responses are activated with S1-S2 duration that were refractory to monophasic stimulation (Fig. 3, dotted lines, Fig. 4 and 6).

Reversed Biphasic S2. Nonrefractory responses with a second AP / Calcium transient activation are obtained only for S1-S2 longer than 360 msec (Fig. 3, solid line, and Fig. 4 and 6)

Peak I_{Na} is larger for biphasic vs monophasic S2 stimuli (Fig. 7) even for very long coupling intervals since the negative semi-wave makes available a fraction of sodium channels, which are inactivated at normal resting potential. No differences were observed between monophasic and reversed biphasic stimuli.

Minor differences can be observed in AP vs calcium transient Total Response Durations.

6. Conclusion

Simulations with an updated human model qualitatively confirmed previous results obtained with the Beeler-Reuter model [8] pointing to the role of I_{Na} in prolonging the refractory period when using a biphasic stimulus.

Simulations with a single cell AP model did not highlight a differential effect of biphasic vs monophasic stimulation when Ca-TRDs are compared instead of V_m -TRDs. Reproduction of experimentally observed [5] effects on shock-induced Ca_i transients heterogeneity would require a more detailed description of intracellular calcium handling and/or propagation in the heterogeneous cardiac tissue.

References

- [1] RD.White New concepts in transthoracic defibrillation. *Emerg Med Clin N Am* 20 785–807 2002.
- [2] Swerdlow CD, Russo AM, Degroot PJ. The dilemma of ICD implant testing. *Pacing Clin Electrophysiol.* 2007 May; 30(5):675-700.
- [3] Popp L, Seemann G, Dossel O. A simulation study of the reaction of human heart to biphasic electrical shocks. *BMC Cardiovascular Disorders* 4:9, 2004
- [4] Lawo T, Deneke T, Schrader J et al. A Comparison of Chronaxies for Ventricular Fibrillation Induction, Defibrillation, and Cardiac Stimulation: Unexpected Findings and Their Implications. *J Cardiovasc Electrophysiol* 20:307-314, 2009
- [5] Hwang GS, Tang L, Joung B, Morita N, Hayashi H, Karagueuzian HS, Weiss JN, Lin SF, Chen PS. Bi Vs Monophasic Waveform - Superiority of Biphasic Over Monophasic Defibrillation Shocks Is Attributable to Less Intracellular Calcium Transient Heterogeneity *J Am Coll Cardiol* 52:828-835, 2008;
- [6] Daubert JP, Sheu SS. Mystery of Biphasic Defibrillation Waveform Efficacy Is it Calcium? *J Am Coll Cardiol* 52:836-838, 2008.
- [7] Constantino J, Long Y, Ashihara T, Trayanova N: Tunnel propagation following defibrillation with ICD shocks: Hidden postshock activations in the left ventricular wall underlie isoelectric window. *Heart Rhythm* 7 (7):953-961, 2010
- [8] Jones JL, Jones RE, Milne KB. Refractory Period Prolongation by Biphasic Defibrillator Waveforms is Associated with Enhanced Sodium Current in a Computer Model of the Ventricular Action Potential *IEEE Trans Biomed Engi*, 41:60-68, 1994,
- [9] Grandi E, Pasqualini FS, Pes C, Corsi C, Zaza A, Severi S: Theoretical investigation of action potential duration dependence on extracellular Ca^{2+} in human cardiomyocytes. *Journal of Molecular and Cellular Cardiology* 46:332-342, 2009
- [10] KHwj Ten Tusscher, D. Noble, PJ Noble, AV Panfilov “A model for human ventricular tissue” *Am J Physiol Heart Circ Physiol* 286: H1573-H1589

Stefano Severi
Biomedical Engineering Laboratory
D.E.I.S., University of Bologna
Via Venezia 52, I - 47023 Cesena – ITALY
E-mail: stefano.severi@unibo.it