Simulation of Cardiac Contractility Modulation with Single Cell Action Potential Human Models

Chiara Bartolucci[1] and Stefano Severi[1]

[1]University of Bologna, Cesena, Italy

Abstract

Cardiac contractility modulation (CCM) therapy represents a significant advancement in the treatment of heart failure, a condition that remains a leading cause of morbidity and mortality worldwide. This therapy involves the delivery of precisely timed electrical signals to the myocardium during the absolute refractory period.

Computer modelling has become a powerful tool in the study of cardiac electrophysiology as it allows for detailed simulation of heart electrical activity. For this reason, we test the response to a CCM-like stimulation of two single-cell action potential models: the new model of human ventricular cardiomyocytes electromechanics, BPSLand, and the novel electromechanical hiPSC-CM model, hiPSC-CM-CE.

For the first CCM beat in both models, there was an increase in contraction amplitude, stable during CCM. Upon removal of CCM, the amplitude decreased, consistent with the experimental findings. Additionally, only the BPSLand model showed an increased $[Ca^{2+}]_i$ amplitude on the first CCM beat relative to before CCM. These results demonstrate that CCM stimulation modifies intracellular calcium handling properties also in silico.

With this work, we aimed to support the investigation of this new intra-cardiac therapy at the single-cell level using computational models.

1. Introduction

Heart failure (HF) remains a pervasive and challenging health issue, affecting millions of individuals globally and imposing significant healthcare burdens [1]. Conventional therapies for HF, such as pharmacologic treatments and device-based interventions like cardiac resynchronization therapy (CRT), primarily aim to manage symptoms and slow disease progression. However, a substantial subset of patients either do not respond to these treatments or are ineligible for them, underscoring the need for alternative therapeutic options [2].

Cardiac contractility modulation (CCM) therapy has emerged as a promising innovation for managing heart failure, especially in patients with reduced ejection fraction who do not qualify for CRT. CCM involves the delivery of non-excitatory electrical impulses during the absolute refractory period of the cardiac cycle, which enhances myocardial contractility without increasing myocardial oxygen demand [3]. The mechanism of CCM is believed to involve modulation of intracellular calcium handling and improvements in myocardial energetic efficiency, which together enhance the strength of cardiac contractions [4].

Clinical studies have demonstrated that CCM can significantly improve exercise tolerance, quality of life, and functional status in heart failure patients. For instance, a meta-analysis of randomized controlled trials reported that patients receiving CCM therapy experienced marked improvements in peak oxygen consumption and six-minute walk distance, as well as reductions in HF symptoms as measured by the New York Heart Association (NYHA) classification. Additionally, long-term follow-up data suggest that CCM may contribute to favorable cardiac remodeling and reduced hospitalization rates [5]. Given these promising outcomes, CCM therapy represents a valuable addition to the heart failure treatment arsenal.

Since there is a lack of human in vitro tools to evaluate mechanisms of action of CCM, we decided to investigate its effect at the cellular level with the help of action potential (AP) mathematical models. We have tested the CCM-like stimulation in the new model of human ventricular cardiomyocytes electromechanics, BPSLand [6], and the novel electromechanical hiPSC-CM model, hiPSC-CM-CE [7]. These results indicate that CCM stimulation alters intracellular calcium handling properties *in silico* as well.

With this work, we aimed to facilitate the investigation of this new intra-cardiac therapy at the single-cell level through the help of computational models.

2. Methods

The present work used two AP models for testing the effects of a CCM-like stimulation at single cell level. We have employed two models: the human ventricular electromechanics BPSLand [6] and the novel electromechanical hiPSC-CM-CE model [7].

The stimulation was implemented following the protocol proposed by Feaster et al. (2021) [8]. First, the models started at 1Hz steady state, then for other 5s the same stimulus was applied. After that, the CCM starts:

square wave electrical pacing pulses (i.e., monophasic) were generated and the models paced at 1 Hz (2ms stimulus pulse duration; the amplitude of -53A/F and -10A/F for BPSLand and hiPSC-CM-CE respectively). CCM stimulation was delivered as four biphasic pulses of 5ms duration with amplitude -26.5µA/µF and 5A/F for BPSLand and hiPSC-CM-CE respectively, zero interphase interval. The delay between pacing pulses and CCM stimulation was 30ms. For the BPSLand model, the extracellular calcium concentration was set to 0.5mM as in the experiment, while for hiPSC-CM-CE at 1.8mM since 0.5mM was too low for the proper work of the model.

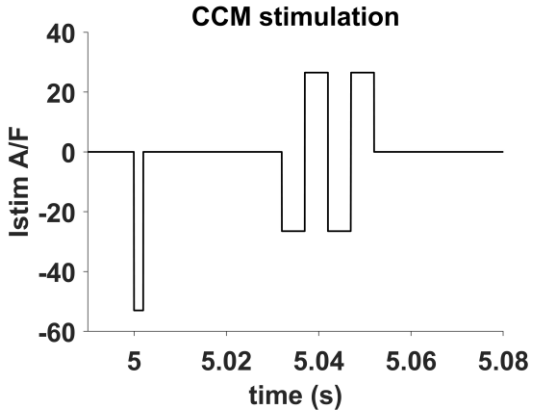

Figure 1. Example of CCM-stimulation.

We considered the following biomarkers computed before the CCM, during the stimulation, and after removing it: for the AP its duration (APD_X measured once membrane voltage reached X% of the resting); for transient calcium and tension the amplitude.

The effects of CCM were also assessed as a function of concentration of extracellular calcium $[Ca^{2+}]_o$ [0.5–2mM].

Model differential equations were implemented in Matlab R2021b (Mathworks Inc., Natick, MA, USA) and solved with a variable order solver (ode15s), based on numerical differentiation formulas, with a max time step of 1ms.

3. Results

For the first CCM beat, there was an increase in contraction amplitude which remained stable during the CCM. In BPSLand model the amplitude of tension passes from 1.8kPa to 3.4kPa for the first beat of the CCM (Figure 2), and then by removing the CCM it decreases back to 1.5kPa. This behaviour agrees with the results reported by Feaster et al. [8] which show a 16 ± 4% increase with CCM. In hiPSC-CM-CE, the increase was absent: the beat before CCM has a tension amplitude of 0.027mN/mm^2 equal to the first CCM beat with no variations when it is removed (Figure 3).

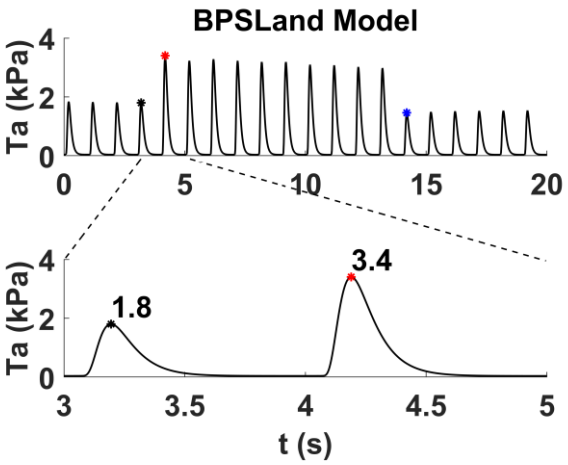

Figure 2. Tension was obtained with BPSLand model during the protocol (top) and zoom of two beats, one before (black asterisk) and the other just after the CCM stimulation (red asterisk) (bottom).

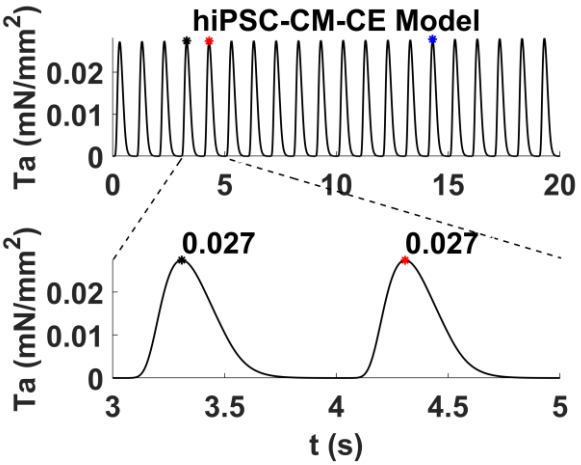

Figure 3. Tension was obtained with hiPSC-CE-CM model during the protocol (top) and zoom of two beats, one before (black asterisk) and the other just after the CCM stimulation (red asterisk) (bottom).

Moreover, only the BPSLand model has shown that on the first CCM beat, the $[Ca^{2+}]_i$ amplitude was increased (0.22µM) relative to before CCM (0.19µM). Additionally, the effects of CCM on intracellular calcium handling remained for the entire duration of CCM stimulation and were eliminated at the end of CCM (Figure 4).

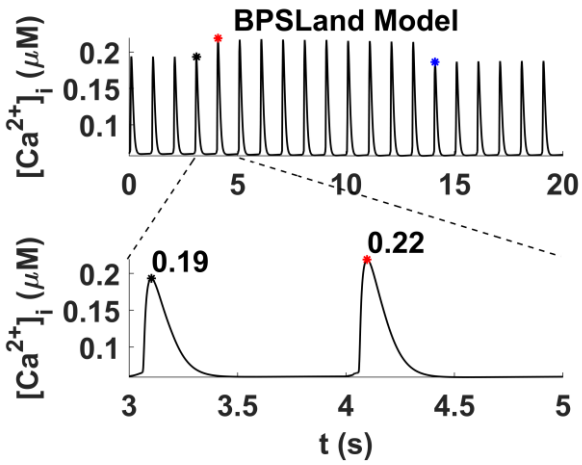

Figure 4. Calcium transient was obtained with BPSLand model during the protocol (top) and zoom of two beats, one before (black asterisk) and the other just after the CCM stimulation (red asterisk) (bottom).

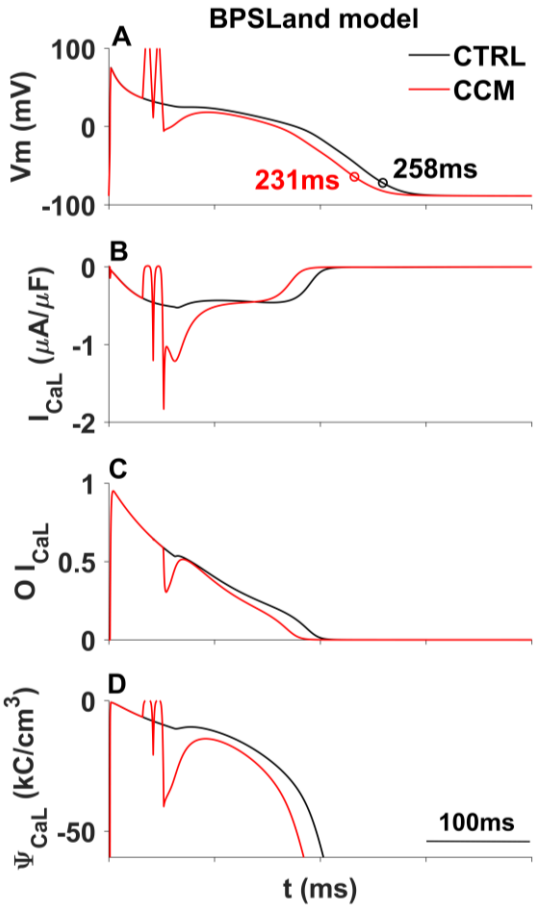

Figure 5. A: AP of the last beat before CCM (black) and the first beat of CCM stimulation (red) with the corresponding APD_{90} values. **B:** I_{CaL} currents of the last beat before CCM (black) and the first beat of CCM stimulation (red). **C:** open probability of I_{CaL} for the last beat before CCM (black) and the first beat of CCM stimulation (red). **D:** driving force of I_{CaL} for the last beat before CCM (black) and the first beat of CCM stimulation (red).

Regarding the effect on the APD_{90}, with the BPSLand we observed a shortening of 27ms (258ms vs 231ms) upon CCM stimulation following the experimental findings of Feaster et al. [8] (Figure 5), and restoration when it is removed (APD_{90} = 260ms). In panels B, C and D of Figure 5 we reported the I_{CaL} behaviour, its open probability and the driving force, respectively. We can note that the increase in force, resulting from the rise in $[Ca^{2+}]_i$ is due to the L-type calcium current. In fact, a lower plateau during phase 2 of the AP provides a greater driving force for I_{CaL}.

Therefore, with the hiPSC-CE-CM model we obtained a reduction of APD_{90} (493ms vs 504ms) (Figure 6) even if less pronounced.

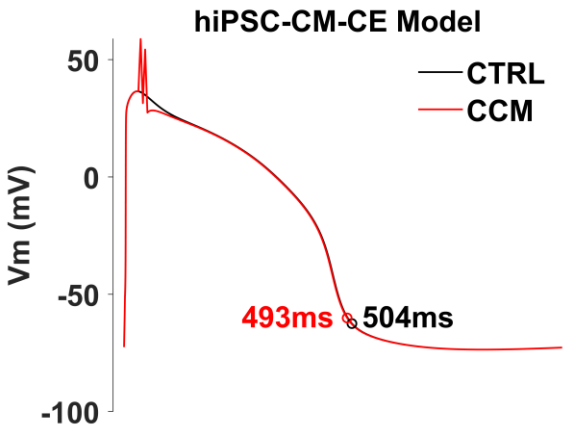

Figure 6. AP of the last beat before CCM (black line) and the first beat of CCM stimulation (red line) with the corresponding APD_{90} values.

The effects of CCM were evaluated based on the concentration of extracellular calcium $[Ca^{2+}]_o$ [0. 5–2 mM]. CCM stimulation increased calcium sensitivity, as evidenced by a leftward shift in the contraction versus calcium concentration curve compared to before CCM stimulation (Figure 6). This indicates greater contraction amplitude at lower extracellular calcium concentrations, suggesting that during CCM stimulation, the myofilament becomes more sensitive to calcium.

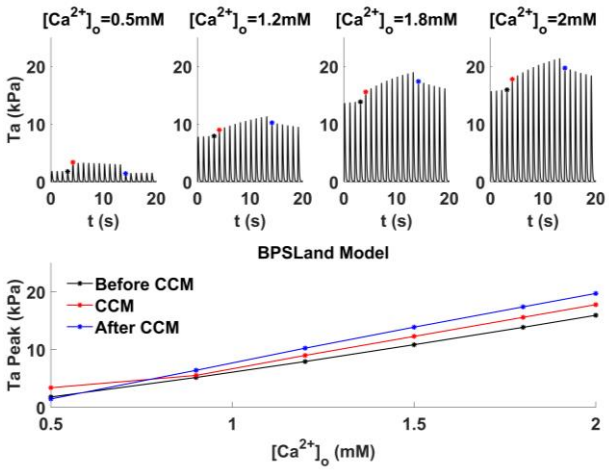

Figure 7. Effect of extracellular calcium modulation on cardiac contractility modulation (CCM) response. **Top**: Representative contraction traces by increasing concentrations of $[Ca^{2+}]_o$=0.5-2mM. **Bottom**: Peak tension in function of extracellular calcium concentration before, during and after CCM.

4. Discussion and Conclusions

In this study, we want to support with in silico simulation a robust in vitro method [8], to quantify the effect of acute CCM stimulation on human cardiomyocytes and improve regulatory decision-making capabilities. CCM is an intracardiac therapy approved for treating heart failure with reduced ejection fraction. However, the immediate effects of standard clinical CCM pulse parameters on human cardiomyocytes remain incompletely understood.

With the simulations, we demonstrate the acute CCM stimulation effects in significant increase of contraction, calcium handling, and electrophysiological properties. We also hypothesize the role of I_{CaL} driving force as a mechanism behind the CCM effects on contraction that should be supported experimentally. The difference between human-CMs and hiPSC-CMs CCM profile may also result from species differences in simulation.

One limitation is related to the CCM pulse parameters tested, we selected to best mimic that of the clinical CCM device while we did not explore how different pulse parameters might influence the specificity of the observed CCM response. Moreover, our stimulation is given in current and not in voltage as experimentally performed.

Acknowledgments

C.B. and S.S. have received funding from the European Union - NextGenerationEU through the Italian Ministry of University and Research under PNRR - M4C2- I1.3 Project PR 00000019 "HEAL ITALIA" to S.S. CUP J33C22002920006.

References

[1] G. Savarese, P. M. Becher, L. H. Lund, P. Seferovic, G. M. C. Rosano, and A. J. S. Coats, "Global burden of heart failure: a comprehensive and updated review of epidemiology," Dec. 01, 2022, *Oxford University Press*. doi: 10.1093/cvr/cvac013.

[2] L. H. Lund *et al.*, "Prevalence, correlates, and prognostic significance of QRS prolongation in heart failure with reduced and preserved ejection fraction," *Eur Heart J*, vol. 34, no. 7, pp. 529–539, Feb. 2013, doi: 10.1093/EURHEARTJ/EHS305.

[3] C. M. Campbell, R. Kahwash, and W. T. Abraham, "Optimizer smart in the treatment of moderate-to-severe chronic heart failure," *Future Cardiol*, vol. 16, no. 1, pp. 13–25, 2020, doi: 10.2217/FCA-2019-0044.

[4] M. Imai *et al.*, "Therapy with cardiac contractility modulation electrical signals improves left ventricular function and remodeling in dogs with chronic heart failure," *J Am Coll Cardiol*, vol. 49, no. 21, pp. 2120–2128, May 2007, doi: 10.1016/J.JACC.2006.10.082.

[5] M. Ruzzolini *et al.*, "Cardiac contractility modulation in patients with heart failure: the added value of cardiac rehabilitation in identification, management, and follow-up," *International Journal of Cardiology Cardiovascular Risk and Prevention*, vol. 21, p. 200284, 2024, doi: 10.1016/j.ijcrp.2024.200284.

[6] C. Bartolucci, M. Forouzandehmehr, S. Severi, and M. Paci, "A novel in silico electromechanical model of human ventricular cardiomyocyte," *Front Physiol*, vol. 13, Jun. 2022, doi: 10.3389/fphys.2022.906146.

[7] M. Forouzandehmehr, J. T. Koivumäki, J. Hyttinen, and M. Paci, "A mathematical model of hiPSC cardiomyocytes electromechanics," *Physiol Rep*, vol. 9, no. 22, Nov. 2021, doi: 10.14814/phy2.15124.

[8] T. K. Feaster, M. Casciola, A. Narkar, and K. Blinova, "Acute effects of cardiac contractility modulation on human induced pluripotent stem cell–derived cardiomyocytes," *Physiol Rep*, vol. 9, no. 21, Nov. 2021, doi: 10.14814/phy2.15085.

Address for correspondence:

Chiara Bartolucci
Department of Electrical, Electronic
and Information Engineering, University of Bologna,
Via dell'Università 50, 47522 Cesena (FC), Italy
chiara.bartolucci4@unibo.it