Omecamtiv Mecarbil Improves Contraction Behaviour in a 3D Electromechanical Tissue Model of Heart Failure

Ilsbeth van Herck[1], Maria Teresa Mora[2], Jordi Llopis-Lorente[2], Henrik Finsberg[1], Cécile Daversin-Catty[1], Javier Saiz[2], Beatriz Trenor[2], Hermenegild Arevalo[1], Samuel Wall[1]

[1]Simula Research Laboratory, Oslo, Norway
[2]Universitat Politècnica de València, València, Spain

Abstract

Inotropic drugs, such as Omecamtiv Mecarbil (OM), are a promising treatment option for patients with heart failure with reduced ejection fraction. However, there are limited computational models available of fully coupled electromechanics (EM) and OM. We present a 3D EM model to simulate inotropic drug effects to assess pharmacological mechanisms and effects on human cardiac tissue. This fully coupled 3D EM open-source solver (SimCardEMS) was used to simulate healthy and failing tissue slabs. A model of OM behaviour was created by using experimental data to parametrize the cell model to replicate stabilisation of the pre-powerstroke state of myosin.

The OM model replicates experimentally observed concentration dependent drug effects such as increased active tension with minimal effect on calcium transient. Therapeutic concentration of OM (0.2 μM) increased active tension by 33% in heart failure tissue. Total displacement was reduced in heart failure, but was partially recovered in the presence of 0.2 μM OM. However, the characteristic delay in time to peak contraction was not reflected in these results. These simulations enable detailed assessment of drug mechanisms and indicate that the model of OM in tissue EM requires further development to better represent the pharmacological effect.

1. Introduction

Development of new pharmacological treatments for cardiovascular diseases is an expensive and time-consuming process. Computational models can contribute and potentially improve the process of drug development and regulatory decision making. However, due to the complex nature of the heart, this requires detailed models that include multiple aspects of cardiac function. Currently, pharmacological assessment in computational models is often performed using cardiac electrophysiology models, lacking the contribution of active contraction.

Meanwhile, heart failure is a disease mainly affecting contraction of the heart, resulting in reduced pumping capacity. Yet the contraction of the heart is an underrepresented component in computational modelling for drug safety. Testing for drug safety and efficacy for heart failure patients would ideally include both contraction and electrophysiological mechanisms of the heart, as well as coupling between these models in a physiological manner.

We have developed a fully coupled electromechanical (EM) model and used it to examine the inotropic drug Omecamtiv Mecarbil (OM). OM selectively targets cardiac contraction, resulting in improved contractility in heart failure patients by increased systolic ejection time and stroke volume while decreasing ventricular diameter [1]. Experimental data shows a lack of effect on electrophysiological biomarkers such as calcium transient and action potential, but improved contractility [2–5]. To simulate these effects in more detail, we used our OM model in a 3D simulation of cardiac tissue to assess its effect on electrophysiological and contraction biomarkers.

2. Methods

A fully coupled 0D ODE based EM model of endocardial ventricular tissue was developed by coupling a modified version of the O'Hara-Rudy electrophysiological model [6] and the Land model [7] for active contraction. Modifications were based on model calibration [8] and experimental data of drug effects [9]. This coupled model used a monodomain representation [10] for electrophysiology and a PDE continuum mechanics model representing cardiac tissue. Passive material properties were described by the Holzapfel model [11] based on biaxial tension data. The final 3D EM solver, SimCardEMS (version 2022.2.0) [12], was implemented by combining existing solvers for electrophysiology [13] and cardiac mechanics [14], which are both based on the open-source framework FEniCS [15] for finite element simulations.

A geometry of 10x2x2 mm was simulated with free movement in the fibre direction on one side. The fibre direction was uniformly aligned along the major axis of the geometry. The mechanical model used a spatial discretization of 1.0 mm as shown in figure 1, and used P2-P1 Taylor Hood elements and a hydrostatic pressure field to enforce incompressibility. The electrophysiology solver requires a finer spatial resolution, and the mechanics mesh was uniformly refined once, resulting in a discretization of 0.5 mm.

A 2 ms stimulus was applied to the entire mesh at 1 Hz frequency. The electrophysiological model was solved with a temporal resolution of 0.05 ms, and adaptive time stepping applied for solving the mechanics. This adaptive scheme monitored the ODE model states representing cross-bridge cycling and solved the nonlinear mechanics problem when a threshold in these states was reached.

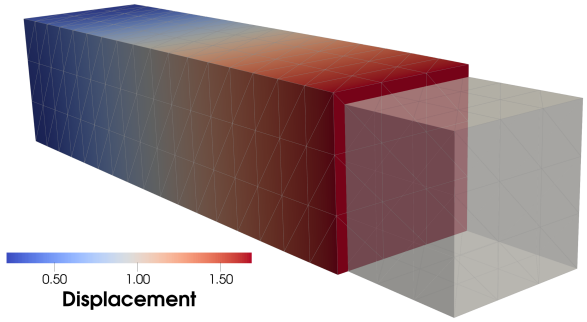

Figure 1: Geometry for EM simulations with spatial discretization for mechanics model. Colour indicates magnitude of displacement, with the unloaded geometry in grey.

Heart failure in the electrophysiological model was modelled as presented by Gomez et al. [16]. Calcium sensitivity in the contraction model (Ca-T50) was reduced to 60% based on experiments [17,18] and heart failure remodelling on late sodium current was set to 130% due to scaling applied in the model of healthy tissue.

OM was modelled to increase cardiac myocyte contractility without changing the calcium transient [2]. Data from human engineered heart tissues [3] was used to build the model of concentration dependent OM effect, and was validated by comparison with human primary cardiomyocytes [4]. The model simulated a stabilization of the pre-powerstroke state by increasing parameter *kuw* and decreasing parameter *kws* in the corresponding ODEs in the contraction model. Both parameters were scaled with a Hill equation:

$$sf = 1 + \frac{a}{1 + \frac{0.47}{[OM]}^{1.4}}$$

with a=3.1554 and a=0.0875 for *kuw* and *kws* respectively.

All quantitative analysis was performed on traces from the centre node of the geometry. The following biomarkers were analysed in simulation results of healthy tissue, heart failure tissue, and heart failure tissue in presence of OM in range 0.1-2 µM: action potential duration at 90% repolarization (APD_{90}), action potential triangulation, peak $[Ca^{2+}]_i$, peak active tension (Ta), peak displacement, time to peak displacement ($ttp_{displacement}$) and displacement duration at 90% repolarization ($twitchD_{90}$).

3. Results

SimCardEMS simulated the EM tissue model successfully, and increased efficiency by two methods: 1) reduced number of elements for mechanics by 8-fold, and 2) adaptive time stepping for the contraction model resulting in 3.5-fold speedup.

Bidirectional coupling of cardiac electrophysiology and mechanics alters electrophysiological traces such as voltage and calcium transient as shown in figure 2. In addition, the simulations provided a new set of biomarkers on contraction to assess drug effects. The heart failure model shows expected changes in endocardial electrophysiological biomarkers [16], such as increased APD_{90} and decreased peak $[Ca^{2+}]_i$.

Experimental data on OM show that it has no effect on calcium transient in rat myocytes [2] or action potential

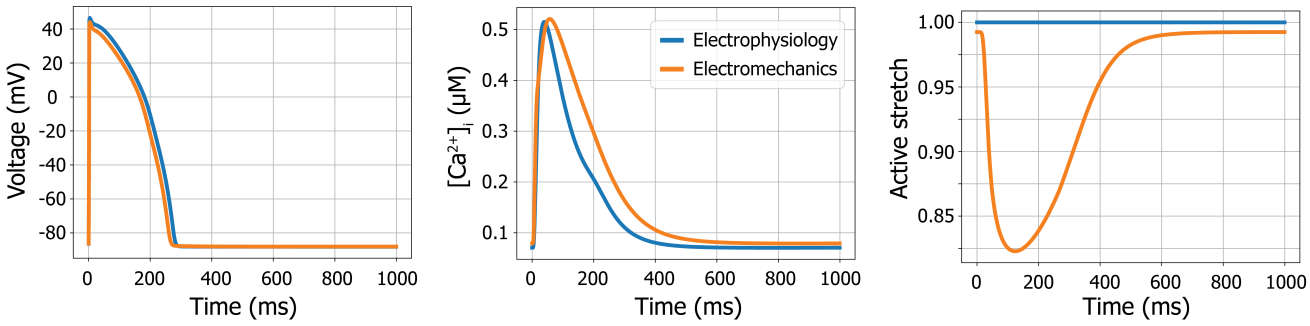

Figure 2: Voltage, $[Ca^{2+}]_i$ and active stretch traces extracted from the center of a tissue slab, highlighting the impact of bidirectional coupling with the mechanical model.

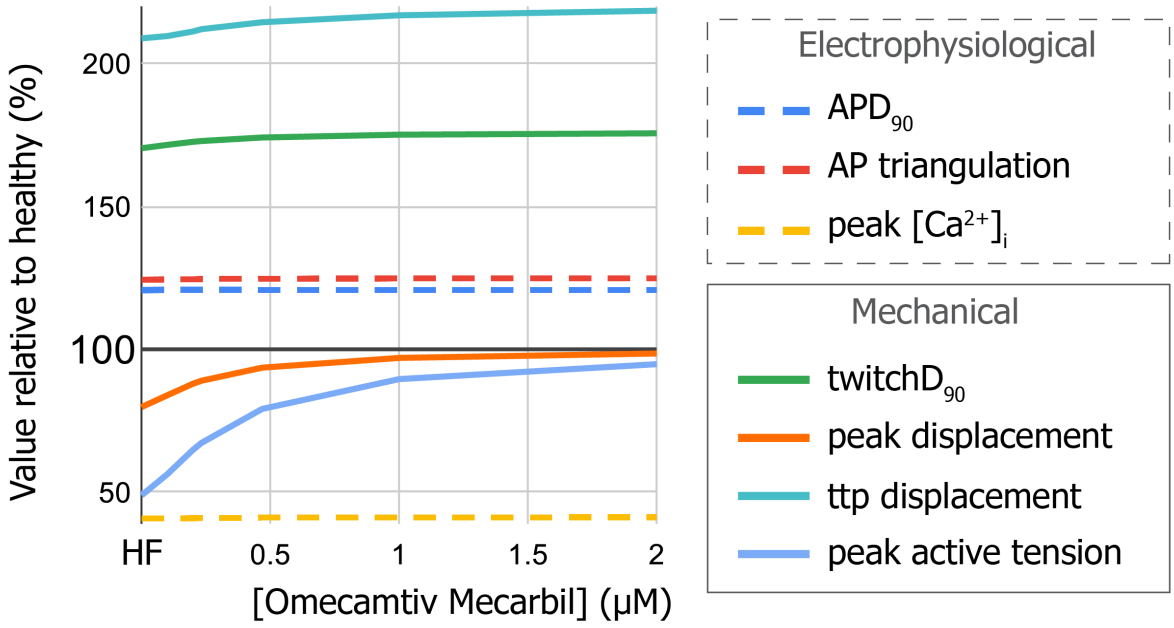

Figure 3: Biomarker values expressed relative to its equivalent in healthy tissue. Electrophysiological biomarkers (dashed lines) remain unchanged, while mechanical biomarkers (solid lines) increase with increasing concentration of OM.

as measured in canine ventricular cardiomyocytes [5]. The model of OM in failing tissue replicates the trends observed in experimental and clinical data in a concentration dependent manner. Table 1 and figure 3 show a lack of effect on all electrophysiological biomarkers of the heart failure model. In contrast, the biomarkers describing contractility (peak Ta, peak displacement, $ttp_{displacement}$ and $twitchD_{90}$) increased with [OM]. The $ttp_{displacement}$ and $twitchD_{90}$ increase with increasing concentration of OM, and move further from the values simulated in healthy tissue. Peak Ta and peak displacement decreased from healthy to heart failure tissue, but were recovering back to healthy biomarker values with increasing concentration of OM. Therefore, these simulations showed that failing tissue contractility could be increased with OM in a concentration dependent manner, matching increased contractility of heart failure patients upon application of OM [1].

Table 1: Biomarker values from traces extracted at centre of 3D tissue slab.

Biomarker	Healthy	HF	HF+0.2 μM OM
APD_{90} (ms)	256	309	310
AP triangulation	76.4	95.0	95.2
peak $[Ca^{2+}]_i$ (μM)	0.521	0.213	0.213
peak Ta (kPa)	5.17	2.53	3.36
peak displacement	0.886	0.707	0.780
$ttp_{displacement}$ (ms)	124	259	262
$twitchD_{90}$ (ms)	438	746	756

4. Discussion and Conclusion

We present a solver for fully coupled 3D cardiac EM to simulate drug effects and assess drug safety. In agreement with experimental data, the application of OM to *in silico* heart failure tissue did not affect electrophysiological biomarkers, but selectively increased contraction. However, the model of OM did not induce the delay in peak contraction as typically seen in experiments at the sarcomere and cell level. A better fit to the experimental data would cause additional delay in contraction of the already delayed heart failure tissue. Therefore, the model of OM requires further validation to match experimental data at the sarcomere and cell level, as well as predict the effect of OM in this 3D cardiac tissue model of heart failure.

The bidirectional coupling facilitates further investigation into the multifactorial effect of pharmacological compounds on *in silico* human heart tissue. This enables simulation of both mechanical and physiological function of the heart to aid mechanistic understanding and development of safe and efficient treatment.

Acknowledgments

The simulations were performed on resources provided

by Sigma2 - the National Infrastructure for High Performance Computing and Data Storage in Norway. We thank the European Union's Horizon 2020 Framework Programme (SimCardioTest project, grant agreement 101016496).

References

[1] J. R. Teerlink *et al.*, "Acute treatment with omecamtiv mecarbil to increase contractility in acute heart failure: The ATOMIC-AHF study," *J Am Coll Cardiol*, vol. 67, no. 12, pp. 1444–1455, Mar. 2016, doi: 10.1016/J.JACC.2016.01.031.

[2] F. I. Malik *et al.*, "Cardiac myosin activation: A potential therapeutic approach for systolic heart failure," *Science (1979)*, vol. 331, no. 6023, pp. 1439–1443, Mar. 2011, doi: 10.1126/science.1200113.

[3] S. Shen, L. R. Sewanan, D. L. Jacoby, and S. G. Campbell, "Danicamtiv enhances systolic function and frank-starling behavior at minimal diastolic cost in engineered human myocardium," *Journal of the American Heart Association*, vol. 10, no. 12. American Heart Association Inc., Jun. 15, 2021. doi: 10.1161/JAHA.121.020860.

[4] N. Abi-Gerges *et al.*, "Multiparametric mechanistic profiling of inotropic drugs in adult human primary cardiomyocytes," *Sci Rep*, vol. 10, no. 1, Dec. 2020, doi: 10.1038/s41598-020-64657-2.

[5] B. Horváth *et al.*, "Frequency-dependent effects of omecamtiv mecarbil on cell shortening of isolated canine ventricular cardiomyocytes," *Naunyn Schmiedebergs Arch Pharmacol*, vol. 390, no. 12, pp. 1239–1246, Dec. 2017, doi: 10.1007/s00210-017-1422-z.

[6] T. O'Hara, L. Virág, A. Varró, and Y. Rudy, "Simulation of the undiseased human cardiac ventricular action potential: model formulation and experimental validation," *PLoS Comput Biol*, vol. 7, no. 5, May 2011, doi: 10.1371/JOURNAL.PCBI.1002061.

[7] S. Land, S. J. Park-Holohan, N. P. Smith, C. G. dos Remedios, J. C. Kentish, and S. A. Niederer, "A model of cardiac contraction based on novel measurements of tension development in human cardiomyocytes," *J Mol Cell Cardiol*, vol. 106, pp. 68–83, May 2017, doi: 10.1016/J.YJMCC.2017.03.008.

[8] F. Margara *et al.*, "In-silico human electro-mechanical ventricular modelling and simulation for drug-induced pro-arrhythmia and inotropic risk assessment," *Prog Biophys Mol Biol*, vol. 159, pp. 58–74, Jan. 2021, doi: 10.1016/J.PBIOMOLBIO.2020.06.007.

[9] J. Llopis-Lorente, J. Gomis-Tena, J. Cano, L. Romero, J. Saiz, and B. Trenor, "In silico classifiers for the assessment of drug proarrhythmicity," *J Chem Inf Model*, vol. 60, no. 10, pp. 5172–5187, Oct. 2020, doi: 10.1021/ACS.JCIM.0C00201.

[10] J. Sundnes, G. T. Lines, X. Cai, B. F. Nielsen, K.-A. Mardal, and A. Tveito, *Computing the electrical activity in the heart*. Springer Berlin Heidelberg, 2006. doi: 10.1007/3-540-33437-8.

[11] G. A. Holzapfel and R. W. Ogden, "Constitutive modelling of passive myocardium: a structurally based framework for material characterization," *Philos Trans A Math Phys Eng Sci*, vol. 367, no. 1902, pp. 3445–3475, Sep. 2009, doi: 10.1098/RSTA.2009.0091.

[12] "ComputationalPhysiology/simcardems: Simula Cardiac ElectroMechanics Solver." https://github.com/ComputationalPhysiology/simcardems (accessed Oct. 03, 2022).

[13] M. E. Rognes, P. E. Farrell, S. W. Funke, J. E. Hake, and M. M. c. Maleckar, "cbcbeat: an adjoint-enabled framework for computational cardiac electrophysiology," *J Open Source Softw*, vol. 2, no. 13, p. 224, May 2017, doi: 10.21105/JOSS.00224.

[14] H. N. T. Finsberg, "pulse: A python package based on FEniCS for solving problems in cardiac mechanics," *J Open Source Softw*, vol. 4, no. 41, p. 1539, Sep. 2019, doi: 10.21105/JOSS.01539.

[15] A. Logg, K. A. Mardal, and G. N. Wells, "Automated solution of differential equations by the finite element method," *Lecture Notes in Computational Science and Engineering*, vol. 84 LNCSE, pp. 1–736, 2012, doi: 10.1007/978-3-642-23099-8_1.

[16] J. F. Gomez, K. Cardona, L. Romero, J. M. Ferrero, and B. Trenor, "Electrophysiological and structural remodeling in heart failure modulate arrhythmogenesis. 1D simulation study," *PLoS One*, vol. 9, no. 9, Sep. 2014, doi: 10.1371/JOURNAL.PONE.0106602.

[17] J. van der Velden, J. W. de Jong, V. J. Owen, P. B. J. Burton, and G. J. M. Stienen, "Effect of protein kinase A on calcium sensitivity of force and its sarcomere length dependence in human cardiomyocytes," *Cardiovasc Res*, vol. 46, no. 3, pp. 487–495, Jun. 2000, doi: 10.1016/S0008-6363(00)00050-X.

[18] P. G. Vikhorev and N. N. Vikhoreva, "Cardiomyopathies and related changes in contractility of human heart muscle," *Int J Mol Sci*, vol. 19, no. 8, Aug. 2018, doi: 10.3390/IJMS19082234.

Address for correspondence:

Ilse van Herck
Kristian Augusts Gate 23, 0164 Oslo, Norway
ilse@simula.no