Finite Element Analysis of Myocardial Work in Cardiomyopathy

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Abstract. Analysis of myocardial work is essential in determination of left ventricle ejection fraction (LVEF) and non-invasive assessment of different types of cardiomyopathies. Two major classifications of cardiomyopathy are: hypertrophic (HCM) and dilated (DCM) cardiomyopathy. Although there are clinical improvements in cardiomyopathy risk assessment, patients are still under high risk of severe events. Computational modelling and computer-aided drug design can significantly advance the understanding of cardiac muscle activity in HCM and DCM, speed up the drug discovery and reduce the risk of severe events, aiming to improve the treatment of cardiomyopathy. This study is devoted to modelling of HCM using coupled macro and micro simulation through finite element (FE) modelling of fluid-structure interaction (FSI) and molecular drug interaction with the cardiac cells. FSI is used for modelling the HCM with nonlinear material model for heart wall. Analysis of myocardial work and changes of pressure and volume within the LV parametric model of HCM are presented at basic condition and after simulated effects of administered drugs. The obtained results provide better insight into the myocardial work of HCM patients as well as in estimated effects of drug therapy, leading to improved patient monitoring and treatment.

Keywords: Hypertrophic Cardiomyopathy, Parametric Model of Left Ventricle, Computational Modelling, Finite Element Method, Myocardial Work

1 Introduction

1.1 Motivation

Myocardial work provides incremental information of left ventricle ejection fraction (LVEF) and strain which are sensitive to left ventricle (LV) afterload and related to non-invasive assessment of different types of cardiomyopathies. According to the guidelines of the European Society of Cardiology [1], cardiomyopathies are defined as structural and functional abnormalities of the ventricular myocardium.

Two major classifications of cardiomyopathy are: hypertrophic (HCM) and dilated (DCM) cardiomyopathy. HCM is characterized by enlargement of the heart with increased LV wall thickness, often with asymmetrical hypertrophy of the septum that separates the LV from the right ventricle (RV) and can lead to left ventricular outflow tract obstruction (LVOTO). Fig. 1 represents comparison between healthy heart and HCM, with marked thickening of the left ventricular myocardium [2].

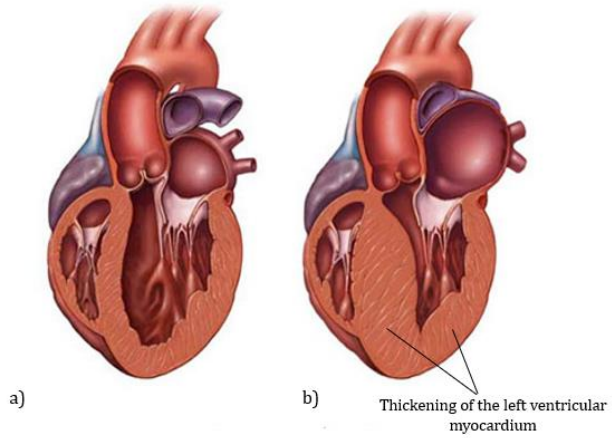

Fig. 1. a) Illustration of a healthy heart; b) Illustration of a heart with hypertrophic cardiomyopathy, with marked thickening of the walls of the left ventricle; cut views [2].

Although there are clinical improvements in cardiomyopathy risk assessment, patients are still exposed to high risk of severe events. Computational modeling and computer-aided drug design can significantly advance the understanding of cardiac muscle activity in cardiomyopathy, speed up the drug discovery and reduce the risk of severe events. The main motivation for such approach relies on application of computational modeling in testing the effects of pharmacological treatment, aiming to contribute to clinical practice, reduce animal experiments and human clinical trials.

1.2 Research Questions

In silico clinical trials are the future of medicine, whereas the virtual testing and simulations are the future of medical engineering. Currently, there is a lack in using the computational platforms and solutions which can assist in a daily clinical practice. In analysis of cardiomyopathy, understanding of disease progression is still limited, as well as the effects of drugs interactions on cardiac tissue.

The main advantage and novelty of presented study are coupled macro and micro simulations into the integrated Fluid Solid Interaction (FSI) system and its application for examination of heart behavior and drug interactions. In contrary to detailed and patient-specific models where FSI analyses are very time-consuming, our models are parametric and based on dimensions of specific LV components. In this way, the

simulations can be performed for a large number of patients reducing time needed for developing new models.

1.3 Related Work

Recently established computational platform (SILICOFCM) [3] for *in silico* clinical trials integrates patient-specific data (genetic, biological, pharmacological, clinical, imaging and patient specific cellular data) and allows the testing and optimization of medical treatment to maximize positive therapeutic outcomes. Also, it has been used for risk prediction of cardiac hypertrophic disease [4,5]. In addition, recently developed computational models, such as the MUSICO platform [6], have significantly advanced our understanding of cardiac muscle activity in HCM and DCM cardiomyopathies.

The idea of an integrative multiscale modelling [7] might help in identifying the symptoms and outcomes of patients with multiple genetic disorders. For the simulation of total heart health or pathology, molecular, cellular, tissue, and organ levels have to be integrated. Simulation of FSI in whole heart during the total heart cycle demands usage of a large number of finite elements (FEs) due to complex heart geometry. Instead of patient-specific geometry, we are employing parametric 3D models of the LV, which are suitable for running large number of simulations by varying selected parameters.

The paper is organized as follows: the applied multiscale modelling is briefly descried in Section II. The results (Pressure-Volume diagrams) with administered two drugs for HCM and comparison with the initial condition (no drug) is presented in Section III. Section IV discusses relevant work and concludes the paper.

2 Materials and Methods

2.1 Myocardial Work

Myocardial work is a novel technique used in the advanced assessment of LVEF. It includes LV pressure and provides incremental information to LVEF and strain which are sensitive to LV afterload. Fig. 2 schematically represents the pressure-volume relationship, i.e. P-V (Pressure-Volume) diagram in the LV during a normal cardiac cycle [8].

The PV diagram includes the diastolic and systolic phases, which are marked by points from A to D. The phase of diastole, or protodiastole, begins at point A, which also represents the end of systole. At that moment, the leaflets of the arterial valves are still open, and they begin to separate from the arterial walls. The phase of isovolumetric relaxation (A-B, Fig. 2.) is the second phase of diastole, where the arterial valves close, while the atrioventricular valves have not opened yet. During this phase, the blood volume and pressure in the ventricles are at their lowest values. Then follows the phase of filling the chambers (B-C, Fig. 2).

The opening of the atrioventricular valves and the sudden transfer of blood from the atria to the relaxed ventricles represents the early phase of rapid filling. The rapid transfer of blood from the atria to the ventricles leads to the pressure drop in the atria and a sudden increase of the ventricles volume. The slow filling phase (diastasis) represents

the longest period in the normal duration of the cardiac cycle. The presystolic phase (late rapid filling phase) occurs as a result of atrial systole. Since the contraction of the atria in this phase led to rapid filling of the ventricles with blood, the volume and pressure in them suddenly increase and the atrioventricular valves close. This phase is called isovolumetric contraction (C-D, Fig. 2) and it is the first phase when begins ventricular systole (the atrioventricular valves have closed and the arterial valves have not yet opened).

The ejection phase (D-A, Fig, 2), that is, the blood pumping phase, occurs when the pressure in the LV rises above the pressure in the aorta, which leads to the opening of the aortic valve and the pumping of blood from the LV into the aorta. At the same time, blood is pumped from the right heart (pulmonary blood flow). The ejection phase includes the fast and slow pumping of blood. Slow pumping represents late systole, when relaxation of the ventricles begins and pressure drops in them (returning to point A again, and starting a new cycle).

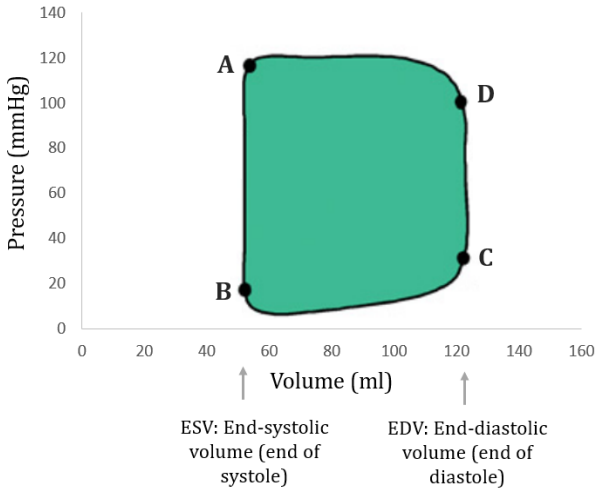

Fig. 2. Schematic representation of the PV diagram in the left heart chamber. A-B isovolumetric relaxation, B-C filling phase, C-D isovolumetric contraction, D-A ejection phase [8].

The green area within the loop (Fig. 2) is equal to the stroke volume, which refers to the amount of blood pumped out of the LV in one cardiac cycle. The effects of isolated changes in preload are best demonstrated in the PV diagram, which relates ventricular volume to the pressure inside the ventricle throughout the cardiac cycle. The maximum right point in the diagram is denoted as the end-diastolic volume (EDV), while the minimum left point represents the end-systolic volume (ESV). Also, as EDV increases, the proportion of blood ejected from the heart slightly increases; this is the ejection fraction (EF) calculated by the following equation [9]:

$$EF = \frac{EDV\text{-}ESV}{EDV} \quad (1)$$

2.2 PAK FE Solver and FSI Analysis

The presented study gives the insight into the model-based simulation of myocardial work under HCM, employing the PAK FE software coupled with multi-scale model of muscle contraction. FSI algorithm within the PAK software is used for modelling the LV with nonlinear material model, together with stretches integration along muscle fibers. The methods are integrated within the SILICOFCM platform [3], with aim to propose an advanced approach for the assessment of work indices and biomechanical characteristics of HCM and drugs effects, based on computational modelling.

The parametric LV model for HCM, with specific parametric parts: base part, valves (aortic and mitral) and connecting part (connection between base and valves) has been implemented (Fig. 3). The FE simulations of LV model of HCM using PAK FE solver [10] enable quantitative assessment of the effect of administered drugs on cardiac output including increase in both systolic and diastolic pressures, and the LVEF. The applied boundary conditions are related to adopted nominal inlet and outlet velocities for mitral and aortic valves of LV, as well as applied calcium concentrations for Mavacamten and Disopyramide.

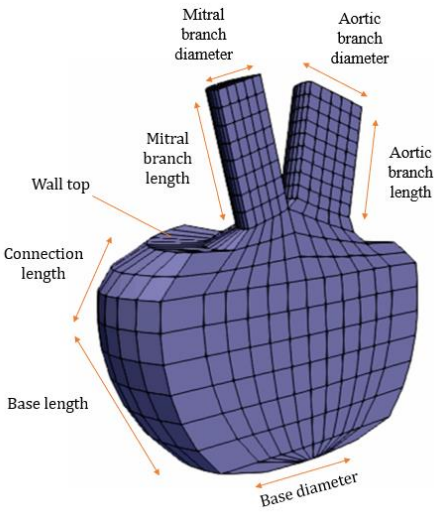

Fig. 3. Parametric 3D model of HCM heart LV with specific parametric parts: base part, valves (aortic and mitral) and connecting part (connection between base and valves).

2.3 Drugs Simulations

There are two major groups of specific drugs by their principal mechanisms of acting. The first group of drugs modulates calcium transients, while the second group changes

kinetics of contractile proteins. We have considered the major representative drugs in these two groups: Disopyramide which modulates calcium transients and Mavacamten which changes kinetics of contractile proteins. Both types of selected drugs are used in the treatment of HCM.

3 Results and Discussion

Simulations of the effect of drugs on improving performance of HCM LV parametric model include the drugs that affect calcium transients (Disopyramide) and changes in kinetic parameters (Mavacamten). All simulations are performed using PAK FSI, FE solver and coupled with multi-scale model of muscle contraction. Myocardial work is presented through changes of pressures and volumes (P-V diagrams) for HCM LV model at basic condition (without administered drug) and with using Disopyramide and Mavacamten (Fig. 4).

The predicted P-V diagram for HCM at basic condition shows lower volumes and higher ventricular pressures than normal, with LVEF (LVEF=59.33%). The principal effects of drugs on HCM after simulations are decrease in peak pressures and shift of P-V loops toward higher volumes, which is in accordance with previous studies and clinical observations [11, 12].

The results provide a quantitative assessment of the effects of different on the cardiac output, including both systolic and diastolic LV pressures and volumes, as well as the LVEF. This approach can give better insight in estimated effects of drug therapy, leading to improved patient monitoring and treatment.

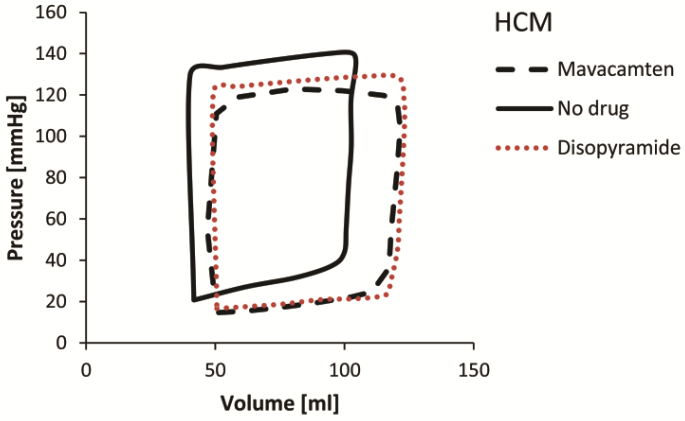

Fig. 4. P-V diagrams for HCM at basic condition (without administered drug) and with using drugs Disopyramide and Mavacamten.

4 Conclusions

In order to achieve more personalized medical treatments and better estimate the patient's condition, this study is devoted to modelling of HCM using coupled macro and micro simulation through FE, FSI and molecular drug interaction with the cardiac cells. FSI is used for modelling the HCM with nonlinear material model for heart wall.

Analysis of myocardial work and changes of pressure and volume within the LV parametric model of HCM are presented at basic condition and after simulated effects of administered drugs. The obtained results provide better insight into the myocardial work of HCM patients as well as in estimated effects of drug therapy, leading to improved patient monitoring and treatment.

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References

1. Elliott, P., Anastasakis, A., Borger, M. A., Borggrefe, M., Cecchi, F., Charron, P., Hagege, A. A., Lafont, A., Limongelli, G., Mahrholdt, H., McKenna, W. J., Mogensen, J., Nihoyannopoulos, P., Nistri, S., Pieper, P. G., Pieske, B., Claudio Rapezzi, Rutten, F.H., Tillmanns, C., Watkins, H.: 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy. European Heart Journal, 35(39), 2733–2779 (2014). Doi: https://doi.org/10.1093/eurheartj/ehu284
2. Nishimura, R.A., Ommen, S.R., Tajik, A.J.: Hypertrophic Cardiomyopathy, A Patient Perspective. Circulation, 108(19), 133–e135 (2003). Doi: https://doi.org/10.1161/01.CIR.0000097621.97566.96
3. SILICOFCM H2020 project: In Silico trials for drug tracing the effects of sarcomeric protein mutations leading to familial cardiomyopathy. (2022). 777204, 2018-2022. www.silicofcm.eu
4. Filipovic, N., Saveljic, I., Sustersic, T., Milosevic, M., Milicevic, B., Simic, V., Ivanovic, M., Kojic, M.: In Silico Clinical Trials for Cardiovascular Disease. Journal of Visualized Experiments, 183 (2022). Doi: https://doi.org/10.3791/63573
5. Filipovic, N., Sustersic, T., Milosevic, M., Milicevic, B., Simic, V., Prodanovic, M., Mijailovic, S., & Kojic, M.: SILICOFCM platform, multiscale modeling of left ventricle from echocardiographic images and drug influence for cardiomyopathy disease. Computer Methods and Programs in Biomedicine, 227, 107194 (2022). Doi: https://doi.org/10.1016/j.cmpb.2022.107194

6. Mijailovich, Srboljub M., Prodanovic, M., Poggesi, C., Geeves, M. A., & Regnier, M.: Multiscale modeling of twitch contractions in cardiac trabeculae. Journal of General Physiology, 153(3), e202012604 (2021). Doi: https://doi.org/10.1085/jgp.202012604
7. Prodanovic, M., Stojanovic, B., Prodanovic, D., Filipovic, N., Mijailovich, S.M.: Computational Modeling of Sarcomere Protein Mutations and Drug Effects on Cardiac Muscle Behavior. 2021 IEEE 21st International Conference on Bioinformatics and Bioengineering (BIBE), 1–6 (2021). Doi: https://doi.org/10.1109/BIBE52308.2021.9635428
8. Cheng, Y., Oertel, H., Schenkel, T.: Fluid-Structure Coupled CFD Simulation of the Left Ventricular Flow During Filling Phase. Annals of Biomedical Engineering, 33(5), 567–576 (2005). Doi: https://doi.org/10.1007/s10439-005-4388-9
9. Djorovic, S.: Myocardial work and aorta stenosis simulation. In Cardiovascular and Respiratory Bioengineering, pp. 135–147 (2022). Elsevier. Doi: https://doi.org/10.1016/B978-0-12-823956-8.00010-9
10. BIOIRC Kragujevac Serbia 2022, PAK Finite Element Software
11. Tomasevic, S., Milosevic, M., Milicevic, B., Simic, V., Prodanovic, M., Mijailovich S.M., Filipovic, N.: Computational Modeling on Drugs Effects for Left Ventricle in Cardiomyopathy Disease. Pharmaceutics, 15(3):793 (2023). Doi: doi.org/10.3390/pharmaceutics15030793
12. Warriner, D.R., Brown, A.G., Varma, S., Sheridan, P.J., Lawford, P., Hose, D.R., Al-Mohammad, A., Shi, Y.: Closing the Loop: Modelling of Heart Failure Progression from Health to End-Stage Using a Meta-Analysis of Left Ventricular Pressure-Volume Loops. PLoS ONE, 9(12), e114153 (2014). Doi: https://doi.org/10.1371/journal.pone.0114153