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Personalized multi-scale model of cardiac function in patients with dilated cardiomyopathy

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Heart failure is a chronic disease associated with high hospitalization rates, costs and mortality. Dilated cardiomyopathy is one of the common causes of non-ischemic heart failure and the leading cause of heart transplantation in the young. The diversity of this disease, in its etiologies and clinical presentations, calls for new strategies in risk stratification, medical management and therapy. Computational modelling of cardiac function promises to improve our understanding of the disease pathomechanisms, identify new prognostic cardiac biomarkers and simulate therapies. This project investigates the ability and precision of the personalized multi-scale cardiac models in capturing systolic and diastolic function in patients with dilated cardiomyopathy. Furthermore, the possibility of deriving new cardiac parameters from the cardiac model is investigated.

After the generation of the computational models, the precision of the model in capturing the systolic function was assessed. Upon completion, the ability of the model in capturing the diastolic function was subsequently investigated. This project was performed in cooperation with Siemens AG. A total of 58 patients with primary dilated cardiomyopathy were recruited in this project. Probable secondary causes of dilated cardiomyopathy were excluded through comprehensive clinical phenotyping including

performing coronary angiography, echocardiography and cardiac MRI. Validated mathematical models were integrated into the anatomical model to create a personalized multi-scale mutli-physics cardiac model capturing patient specific cardiac anatomy, electrophysiology, biomechanics and hemodynamics.

Parameters representing the systolic function, namely left ventricular ejection fraction and stroke volume, from real measurements and from the simulated model were compared together. The mean model error in the left ventricular ejection fraction was 3±1% (R=0.99, p<10-10). At the same time, the very high accuracy of the computed model was seen in the mean model error of only 9±6mL (R=0.96, p<10-10) with respect to stroke volume.

Unlike systolic function, the assessment of diastolic function presents a challenge to treating physicians. Tau, the time constant of isovolumetric relaxation is a widely accepted surrogate for cardiac relaxation and was chosen as a parameter representing diastolic function. The diastolic parameter from the personalized model, global stiffness factor, showed moderate correlations with Tau (τ). Patients with elevated NT-proBNP had a higher correlation between HO and Tau. This accentuates the possible benefit of integrating cardiac molecular biomarkers with simulated parameters in search of new prognostic markers.

The potential use of computational modelling in patient risk stratification was evaluated through the correlation of the functional systolic parameter of the cardiac model, left ventricular active force, with a validated prognostic score, the Seattle Heart Failure Score. The left ventricular active force, computed from the patient-specific cardiac model, significantly correlated with the Seattle Heart Failure Score (R=0.77, p=2.7x10-5). Although the presented correlations were not perfect and the results need to be validated in larger patient cohorts, it presents the possibility of the identification

of novel parameters, that cannot directly be derived from conventional clinical procedures.

This project could show that the creation of a multi-scale multi-physics cardiac model is feasible in a clinical setting. The cardiac model was able to capture the systolic function of the heart accurately. Furthermore, the model was also able to capture the patient-specific diastolic function and proved to be promising in identifying novel parameters of cardiac function.