Making it personal

Summary

Arrhythmogenic cardiomyopathy is an inherited pathology of the heart. In 60% of probands, a (likely-)pathogenic mutation can be found. Even before disease expression, mutation carriers are already at risk of sudden cardiac death. To prevent sudden cardiac death in apparently healthy individuals, early detection of pro-arrhythmic tissue substrates is important. This thesis aims to get more insight in the myocardial disease substrate in patients with early-stage arrhythmogenic cardiomyopathy using a *Digital Twin approach*. In the *Digital Twin approach*, a biophysical model is personalized to clinical measurements. Unlimited features describing myocardial behavior can be extracted from this *Digital Twin*. Therefore, it may reveal myocardial (mal)function underlying the measurements.

In this thesis, the CircAdapt model of cardiovascular system is used as biophysical model. This model allows fast calculation of regional myocardial mechanics and global hemodynamics. To explore the ability of personalizing this model, a simple protocol was made which focused on optimizing the right ventricular model parameters (**Chapter 2**). This protocol confirmed that the CircAdapt model was able to reproduce clinically measured deformation. A more robust parameter optimization algorithm was needed to cope with the non-linear parameter space and to further personalize the model.

Keeping the high complexity of the problem in mind, an extensive sensitivity and identifiability analysis was performed (**Chapter 3**). The most important model parameters needed to model left and right ventricular deformation were identified using the Morris Screening method and using Monte Carlo simulations. By reducing the number of model parameters, reproducibility of the estimation was improved. The final subset includes regional tissue contractility, passive stiffness, activation delay, and wall size. Subsequently, a parameter optimization protocol based on Particle Swarm Optimization was designed. We demonstrated that the CircAdapt model was still able to accurately simulate deformation in subjects with genetic mutations related to arrhythmogenic cardiomyopathy.

The parameter optimization protocol was applied to a cohort of 68 patients with arrhythmogenic cardiomyopathy and 20 control subjects who were evaluated at the UMC Utrecht in the Netherlands between 2006 and 2015 (**Chapter 4**). Simulations revealed that in subjects with clinically advanced disease compared to mutation carriers without clinically established disease, regional RVfw heterogeneity of both contractile function (17±13% vs. 8±4%, p=0.01) and compliance (18±11% vs. 10±7%, p<0.01) was increased and. No significant difference in activation delay was found.

The estimations obtained in Chapter 3 and 4 contain noise. Among others, measurement uncertainty propagates through the optimization adding noise. This is

negligible on a population level, but will affect the individual result. Therefore, in **Chapter 5**, a Bayesian optimization approach was applied to include measurement uncertainty. Hereby, a posterior distribution was estimated rather than a single point. This allows to predict whether disease substrate deteriorates over time, or not. To do so, the Adaptive Multiple Importance Sampling algorithm was used, which iteratively updates the proposal distribution of the model parameters. This algorithm was shown to be accurate as virtual estimations were precise and real-world estimations were highly reproducible. This algorithm was applied to a case study of two subjects and revealed the evolution of early-stage AC disease over time using longitudinal follow-up datasets.

In **Chapter 6,** the Bayesian optimization approach as shown in Chapter 5 was applied to a cohort of 82 early stage patients with arrhythmogenic cardiomyopathy from a consecutive cohort evaluated at Oslo University Hospital, Rikshospitalet, Norway. A total of 313 baseline and follow-up echocardiographic assessments were included with a mean follow-up of 6.7 ± 3.3 years. Patients were divided into three groups based on age at baseline: early presenters (<30 years), mid-life presenters (30-50 years) and late presenters (>50 years). In all three age-groups, both global and segmental deformation characteristics deteriorated. The development of local tissue substrates in the RV free wall was expressed in increased heterogeneity in estimated RV tissue properties. This chapter showed that deformation imaging and patient-specific computer simulations can be used to follow-up disease substrate progression in patients with early arrhythmogenic cardiomyopathy.

With this thesis, we aimed to get more insight in the myocardial disease substrates observed in early-stage arrhythmogenic cardiomyopathy. By doing so, we developed a modelling framework for patient-specific estimation for model parameters representing regional myocardial tissue properties. With this framework, the tissue properties were estimated. This revealed the patient-specific tissue substrate underlying abnormal tissue deformation. **Chapter 7** discusses the results and main findings of the different chapters in a broader perspective. It addresses the limitations of this optimization framework, but also the possibilities within the context of arrhythmogenic cardiomyopathy and cardiovascular diseases in general as this framework can be easily adapted for other purposes. With this optimization framework, we are one step closer to use patient-specific computational simulations in precision medicine, *Making it Personal*.