Making it personal

Impact

The estimated prevalence of AC is 1 in 1000 to 5000 [51,52]. Family screening of first-degree relatives of probands is an important for identifying those at risk for sudden cardiac death [11,12]. Currently, only 40% of family members are screened [12] due to a lack of adequate screening infrastructure and due to anxiety and distress associated with the personal experience of a life-threatening arrhythmia or a recent family bereavement from an inheritable cardiac condition [53,54]. For those who are screened and monitored, accurate risk stratification is essential to not burden the patient more than needed.

In this impact section, we hypothesize on the potential added value of the Digital Twin approach presented in this Thesis for early recognition of AC and for arrhythmic risk stratification.

Digital Twin as a tool to get more insight in physiology

Computational models are used to get insight in the working mechanisms of the heart, its diseases and their treatments. As demonstrated in this Thesis, they can be used to reveal functional information that can't be measured without injuring the patient, e.g. pressures, or can't be measured at all, e.g. myofibre stress [43]. Over the years, various types of models have been developed to investigate cardiac pathologies. In the recent decade, the Digital Twin approach is becoming more popular [48,55] and models are now personalized to reveal the (patho)physiology of one single patient rather than the cohort.

Although work in this thesis is limited to the development of a modelling framework to create a Digital Twin of early-stage AC patients, this platform can easily be extended to other pathologies. It has been shown that the CircAdapt model is able to reproduce clinical data for different pathologies, including pulmonary hypertension [56], valvulopathies [57], left bundle branch block [58], and heart failure [59]. These simulation studies aimed at getting more insight in the physiology of the population or predict responses in the population, and thereby shows the model could be personalized to these pathologies (Model Challenge). Creating the Digital Twin of patients in the population might reveal new insights in the variety of disease expression.

Digital Twin as a tool for teaching

To extend the application range of the comprehensive CircAdapt model from research to education, the interactive user-friendly CircAdapt Simulator has been developed as an environment that can be used by medical students with the aim to improve their understanding of cardiovascular haemodynamics and related physiology [60]. This tool is available as a free download from *www.circadapt.org*. It is implemented in the medical curriculum at Maastricht university to teach haemodynamics and cardiac mechanics in healthy physiology, in valvopathies, and in congenital heart diseases, and it has been adapted by other universities. The CircAdapt Simulator in the current version does not use the full potential of the model, as it is limited to global pressures, volumes, and flows limiting the tool to teach general pump function in (patho)physiology.

The computational framework developed in this Thesis could add opportunities to the CircAdapt Simulator tool. As the Digital Twin reveals more details on the complex physiology and pathophysiology of the individual patient and the differences between patients, cardiac pathologies can be simulated more accurately and realistically. When (regional) myocardial data are added to the visualizations in the CircAdapt Simulator, the tool could be used to teach the pathophysiology in many more pathologies.

Digital Twin as a tool for precision medicine and aid clinical decision

Precision medicine is becoming more popular and big steps have been made to improve disease diagnosis and management [61]. Precision medicine is data-science driven and often includes genomics to create subgroups to better prescribe treatment strategies [62]. Also in AC, genomics is included in the 2010 TFC and geno-positive subjects are likely to develop AC [13]. In the two cohorts studied in **Chapters 4** and **6**, the pathogenic plakophilin-2 mutation is dominant. Although these subjects are at high risk of developing AC, **Chapter 6** shows that early stage disease can be found in all age groups. In the future, the Digital Twin could aid precision medicine by better characterizing and quantifying the myocardial tissue substrate.

As computational models are maturing, the step to add value to the process of clinical decision taking becomes smaller. As shown in this Thesis, Digital Twins can reveal information currently not measurable. This information can be used in randomized clinical trials to quantify its predictive and differential value. Reduction of computational cost is essential to implement a computational framework as presented in this Thesis into clinical workflow. Different protocols have been proposed to do so, including machine learning approaches and model emulator approaches [51]. These approaches can be used to increase the speed of parameter inference or as a direct inverse of the computational model.

Digital Twin as a tool for in silico trials to partially guide and reduce animal experiments

The CircAdapt model has been used to generate hypotheses which can guide further trials [63,64]. These studies predicted the effect of a clinical device on a population level. By using Digital Twins rather than a generic simulations, a more realistic cohort could be created to improve the predictive value of these in silico trials. Outcome of these trials can generate hypotheses and thereby guide the design of real clinical trials and animal studies. The chance of a positive result from these will increase, reducing the amount of trials and animal studies needed.

The work presented in this thesis demonstrates how the Digital Twin can be used to get more insight in the myocardial tissue substrate without the direct use of animal experiments. Without this in silico approach, biopsy could give insight in the tissue substrate but is limited to endocardial tissue. It is highly invasive, has a risk on complications, and is likely to produce false negatives [65,66]. Autopsy generally only gives insight in later stage AC. Alternatively, animal studies can be used to get insight in the tissue substrate. Necropsy on sacrificed animals could reveal insight in the substrate which is not possible to get with non-invasive measurements [67]. The Digital Twin could be used to estimate tissue properties without the need to sacrifice animals, reducing animal burden.

Digital Twin as a tool for virtual diagnostics

Cardiac stress testing is a test used in the diagnosis of various pathologies [68]. Potentially diseased subjects are stressed to increase the loading of the heart to better reveal the substrate. Cardiac stress tests are not included in the diagnosis of AC [10,13], but it has been shown that present deformation abnormalities increase during stress-test [69]. As exercise is associated with disease progression [70,71], performing a cardiac stress test could be considered unethical. As alternative, an in silico cardiac stress test could be performed with the Digital Twin. This could be used to better estimate arrhythmic risk or disease progression as result of exercise.

The Digital Twin could also be used as a tool to guide the diagnosis path. For established pathologies, guidelines aid professionals to diagnose and develop treatment strategies according to the best available evidence [10]. However, for less established pathologies, the best diagnosis and treatment strategies are unknown. Using the model framework developed in **Chapter 5**, not only insight in the myocardial tissue substrates is obtained, also regular clinical measurements can be obtained. Given the available evidence at that time, the Digital Twin can provide information on possible diagnosis and which measurements should be considered to improve differential diagnosis. This may reduce time spent in the hospital by the patient, which increases quality of life of the patient and reduces healthcare cost.