Pacing the heart

Appendix

Valorization

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Introductory remarks

Approximately 230,000 people are suffering from heart failure (HF) in the Netherlands alone. Annually, 31,000 patients are hospitalized and 7,700 die due to HF[1]. The total costs of HF treatment equaled 937 million euros in 2017 in the Netherlands, representing a severe economic burden[2].

In those patients with dyssynchronous HF, i.e. reduced LV ejection fraction (<35%) and increased QRS duration (>120 ms), cardiac resynchronization therapy (CRT) has proven the most effective treatment[3-5]. In general, CRT aims to resynchronize atrial, right (RV) and left ventricular (LV) activation, resulting in improved pump function of the heart. Hence, CRT has been shown to reduce HF symptoms and mortality, and improve quality of life in dyssynchronous HF patients[3, 6]. Each year, approximately 3,100 CRT devices are implanted for treatment of dyssynchronous HF in the Netherlands, a number which is growing[7]. However, 30% to 50% of the patients treated with CRT according to the current guidelines do not benefit from this highly invasive and expensive pacemaker device[3, 6, 8], while potential responders who do not fulfill current guidelines may be withheld from receiving this therapy.

By combining cardiovascular computer modeling with animal experiments or patient data, the ultimate goal of this thesis was to increase the success rate of CRT. This chapter addresses the valorization potential of this work and presents how the combined computational, experimental and clinical research as presented in this thesis may impact society.

Innovation in cardiovascular computer modeling: who benefits how?

The first step of valorization is to transfer knowledge among academic and non-academic peers. In addition to transferring knowledge, it is important to consider how the research performed in this thesis can actually be used by the society. The latter valorization aspect of societal impact is presented in detail for each peer group below.

Innovation in patient care:

Each **patient** is different: a large variability in the underlying pathology is present among patients with dyssynchronous HF. As shown in this thesis, these inter-individual variations in pathology make treatment of dyssynchronous HF a complex puzzle. Therefore, it requires a personalized approach to solve the clinical problem of non-response to CRT which goes beyond the use of the 12-lead body surface electrocardiogram (ECG) as a sole diagnostic tool.

As an initial step towards personalized treatment of dyssynchronous HF, we showed in **Chapter 2** that interventricular dyssynchrony (activation delay between the RV and the LV) is the major driver of response to CRT. To translate this novel insight

into clinical application, we provided evidence that commercially available noninvasive electrocardiographic imaging (ECGi; CardioInsight™, Medtronic, Minneapolis, MN) can be used in a real world clinical setting to assess interventricular dyssynchrony in HF patients eligible for CRT (**Chapter 3**). Although this thesis provides important supportive data for the clinical introduction of interventricular dyssynchrony measures to improve patient selection for CRT, we foresee two major challenges that are essential to overcome to achieve clinical adoption and application on a larger scale.

First of all, ECGi may be too advanced and too expensive to be used to measure interventricular dyssynchrony in a routine clinical setting. It has to be investigated whether interventricular dyssynchrony can be accurately detected by simpler and cheaper techniques. As also noted in an editorial comment to our work by Waks *et al.*[9], insights obtained in **Chapter 2** and **Chapter 3** can be used to further improve relatively simple non-invasive measurements currently being developed to measure dyssynchronous ventricular activation. Two examples of these simple and non-invasive measurements are the ECG-belt (Medtronic, Minneapolis, MN)[10] and QRS_{AREA}, a 12-lead ECG derived measurement under development at Maastricht University[11]. In addition, revealing the mechanisms underlying abnormal septal motion in **Chapter 6** enables further development of ultrasound and magnetic resonance imaging techniques for characterizing ventricular activation in the individual patient.

Although the predictive value of interventricular dyssynchrony for acute hemodynamic response to CRT is larger than current conventional 12-lead ECG measurements (**Chapter 2**), we foresee a second challenge that has to be addressed to reach clinical application of interventricular dyssynchrony measures. In **Chapter 2** we were unable to predict acute hemodynamic response to CRT on an individual basis based on interventricular dyssynchrony *alone*. These results emphasize that electrical measurements alone give an incomplete picture of the underlying pathologies determining response to CRT in patients with dyssynchronous HF. Response to CRT cannot be predicted by "just" one number, but integration of multiple noninvasive imaging modalities and measurements is required to accurately predict response to CRT for each patient.

The open source CircAdapt cardiovascular model (www.circadapt.org) used in this thesis describes electro-mechanical and hemodynamic interactions based on physical and physiological principles. This makes the model the ideal platform to integrate multi-modality diagnostic data into a virtual patient simulation. This *in silico* approach has the potential to improve diagnostics and tailor treatment to the patient's electro-mechanical and hemodynamic characteristics (Figure 1). Insights derived in this thesis provide an essential step towards accurate integration of patient's measurements into the modeling platform to perform personalized medicine.

A key player in patient care is the **health care provider**. In the short term, computer modeling-enriched interpretation of non-invasive measurements and response to CRT will help the health care provider to improve patient selection and therapy delivery among dyssynchronous HF patients. In the future, integration of non-invasive imaging into a computer simulation platform may lead to a cheap decision support to optimize patient care.

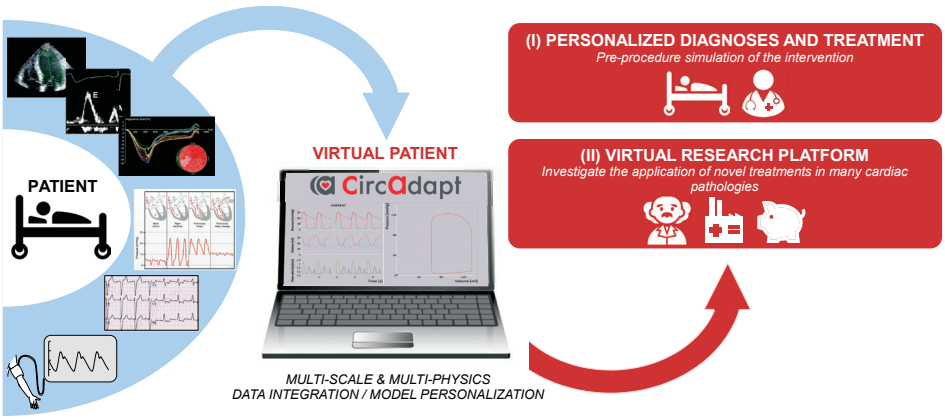

Figure 1. By integrating multi-modality diagnostic data of the patient, the CircAdapt model is an ideal platform for (I) modeling-guided decision making in patient care and (II) to investigate novel treatment options in a safe and cheap cohort of virtual patients with multiple cardiac pathologies.

Innovation in scientific research:

The work performed in this thesis is not limited to solely patient care, but also has a beneficial impact on **scientific research** (Figure 1). By sharing the CircAdapt source code in addition to publishing methods and interpretation of results, transfer of knowledge is guaranteed. In addition, this thesis provides several examples of 1) *enhancing mechanistic understanding* of clinical observations (**Chapter 6**); 2) *generating* new hypotheses through simulation studies (**Chapter 7**); and 3) *translating* animal experimental (**Chapter 4**) or computer simulation-derived insights (**Chapter 2**) into clinical applications. This way of performing *in silico* research is not limited to CRT, but is applicable to many other cardiovascular diseases.

On the one hand, computer models provide an integrative platform linking all the factors that affect cardiovascular function based on physical and physiological principles, while on the other hand they can isolate specific factors and their effect on cardiac

performance in a controlled manner. Although well-controlled **animal experiments** have been developed based on the same physical and physiological principles, practical and ethical issues limit the interventions that can be performed[12]. The usage of computer modeling in this thesis is therefore in line with new policies to reduce and refine animal experiments[13]. As shown in **Chapter 4**, computer simulations can complement, enhance and refine animal experiments, hence we were able to reduce the number of animals used in this study. The potential effect of discrepancies between animals and humans, such as heart rate and ventricular dyssynchrony, were investigated with the computer model to allow accurate translation of animal experiments towards the clinical setting. It is important to note that results derived from animal experiments were used to validate and confirm simulation-derived hypotheses, showing a true synergy between animal experiments and computer simulations.

The costs of the development of a drug or medical device are extremely high and the route from initial idea to an approved product on the market is very long. The **health care industry** plays a major role in the development of new products, especially when it comes to clinical testing in large multicenter trials. Similar to animal experiments, simulations of specific cardiovascular pathologies can complement, enhance and refine clinical trials. As specified in the AVICENNA roadmap project[14], performing these so called *in silico* clinical trials can increase the efficiency of clinical trials and therefore reduce their costs and risk for patients. In **Chapter 4** we closed the gap between our animal experiments and a currently ongoing clinical trial. In addition to animal experiments, CircAdapt simulations provided more insight in the effects of heart rate and ventricular dyssynchrony in a virtual cohort of prolonged PR interval patients, allowing us to develop a more efficient clinical trial protocol. Using computer simulations to improve clinical trial efficiency is currently gaining more attention from diagnostic imaging companies (e.g. Philips and GE) and device manufacturers (e.g. Medtronic and Abbott) resulting in collaboration between the health care industry and our research group at Maastricht University.

Computer modeling-guided treatment of patients has the potential to become efficient and cheap, reducing the economic burden of health care for the **society**. Reliable and cheap alternatives for both animal experiments and clinical trials allow reallocation and more efficient use of research budgets. In addition, investments will more quickly result in products as time from initial development to clinical application of new diagnostic and therapeutic innovations shortens.

Innovation in medical education:

Both a Matlab (MathWorks, Natick, NA) version of the open source CircAdapt cardiovascular computer model intended for research and a user-friendly interface of the CircAdapt simulator tool are available for free and disseminated through the CircAdapt web-portal: www.circadapt.org. The user-friendly CircAdapt simulator not only enables education of relatively simple physical and physiological principles to **medical students**, but also allows more advanced education for **cardiology fellows in training** through simulation of complex virtual clinical cases.

Concluding remarks

Non-response to CRT has a major societal impact as many patients do not respond to this invasive and expensive therapy. This thesis sheds more light on the role of computer modeling, both to improve diagnosis and treatment of individual patients with different cardiac pathologies as well as to enhance the efficiency, safety and costs of cardiovascular (pre-)clinical research. For the near future, the usage of computer modeling-enriched imaging technologies as presented in this thesis will improve patient selection and treatment of CRT candidates. These developments are not only important to improve patient care on the short term, but are also required to move forward towards personalized medicine in which computer modeling is a safe, reliable and cheap platform to guide both health care providers and (pre-)clinical scientists.

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