A wholehearted computational assessment of cardiac pacing

Impact

In the Netherlands a total of 12.176 pacemakers were implanted in 2018 [45]. The European average is a bit higher with 938 implants per million inhabitants in 2011 [46]. A better understanding of cardiac pacing and pacing therapy delivery can therefore impact a large amount of people and society as a whole. By combining cardiovascular computer modeling with animal experimental and patient data, we aimed to improve our understanding of the working mechanism(s) of cardiac pacing and thereby facilitate optimal pacing delivery and patient selection. Here, we summarize the clinical impact of the findings reported in this thesis and address the impact our findings have on future scientific and computational modeling work.

Clinical impact

The results presented in this thesis provide opportunities for the improvement of pacing therapy delivery through optimization and selection through measurement of deformation patterns. Our finding that both optimization of cardiac pacing and selection of candidates for CRT require a whole-heart approach may have major clinical impact. While the right heart is often not taken into account in current clinical practice, **Chapters 2, 3,** and **6** demonstrate that the right heart does have a significant role in cardiac performance during pacing therapy. A singular focus on improving LV function through optimization of pacemaker settings might not provide the largest improvement in global cardiac pump function (**Chapter 3)**. Taking into account both the right- and left atrial and ventricular activations can provide a universal AVd optimization target, applicable in all forms of cardiac pacing. Additional research, as suggested previously in this chapter and in **Chapter 2**, can provide insights in how to obtain this whole-heart activation data in clinical practice. In **Chapter 4** we found that measurements of conduction times between the left and right

ventricular pacing electrodes can predict LV reverse remodeling after 6 months. Performing these measurements at the time of implant is quick and easy, enabling rapid clinical implementation. Future research is required to check if VVd optimization (**Chapter 3**) can help to improve outcome in patients where non-response is predicted through measurement of PLVD.

As demonstrated in this thesis, echocardiographic measurement of myocardial deformation can be a powerful tool for selection of patients for CRT. Our simulations strongly suggest that LV afterload should be taken into account when interpreting deformation data in the context of ventricular dyssynchrony (**Chapter 5)**. At the same time, acute manipulation of afterload could potentially extend the applicability of deformation imaging for the identification of ventricular dyssynchrony. In addition, including data on RV deformation in the diagnostic assessment of CRT candidates is advised based on the results from **Chapter 6.** RV deformation is similar to septal deformation in patients with LV dyssynchrony without RV failure, since both the RV and septum are early activated in these patients. Our results suggest that RV failure changes this pattern and that RV failure itself makes patients less likely to respond to CRT. Taking into account LV afterload and also assessing RV deformation can help in improving the selection for CRT patients which will have significant clinical impact.

Computational assessment can make research more efficient, reducing animal burden

The work presented in this thesis demonstrates how animal experimental and/or clinical research studies can be enhanced through simulations. For example, the simulated cardiac output data in **Chapter 3** add an important level of detail that was not measurable in a sufficiently accurate manner in the animal experiments. Knowledge about the overall cardiac pump function, in terms of cardiac output, enabled conclusions which were not possible based on the

experimental pressure data alone. Additionally, in **Chapter 2** we demonstrated that computer simulations alone can be used in hypothesis generation which hopefully leads to a new and improved focus in future clinical/experimental research studies. Multidisciplinary collaboration between scientists from different but complementary fields, such as biomedical engineering, physiology and clinical cardiology, is key to harvest most potential from computational modeling and simulation. This includes indirect collaboration by building upon previous work, which is an essential part of checking validity of propositions and thereby the creation of scientific evidence. Striving for a more open scientific community, such as sharing the source code during publishing as in **Chapter 3**, can therefore speed up the scientific process. Data from animal experimental and clinical research is needed in order to develop and validate computer models. However, these same computer models requiring experimental data can help in reducing the amount of animal and clinical studies required by improving hypotheses and related research protocols. Furthermore, once a computer model is sufficiently validated, and thereby credible, parts of the research process can be performed through computer simulations in 'in silico trials'[47], potentially significantly reducing costs and time.