A wholehearted computational assessment of cardiac pacing

Appendix A

Summary

The pumping action of the healthy human heart ensures circulation of blood through our cardiovascular system. Normal cardiac pump function is by no means self-evident, but requires all four chambers to work together in a continuous and tightly coordinated effort. Cardiac muscle tissue and thereby the heart contracts when it is triggered with an electrical stimulus. Disturbances in conduction of this electrical stimulus can result in impaired cardiac function and thereby insufficient blood circulation.

When disturbances in electrical conduction lead to symptoms, artificial electrical stimulation of the heart using a pacemaker may (partially) restore a patients' electrical activation. One or more electrodes are placed in the atria and/or ventricles to provide an electrical stimulus. In this thesis, we aim to improve mechanistic understanding of how the variable aspects of the delivery of pacemaker therapy influence cardiac pump function. Where most studies primarily focus on left ventricular (LV) function we used a whole-heart approach to better understand how cardiac pacing therapy can be optimized and selection of patients receiving pacing can be improved. For this whole-heart assessment we used the CircAdapt computer model to study interactions between the heart chambers and between the heart and surrounding circulation. CircAdapt is a lumped parameter computer model of the heart and circulation that enables real-time beat-to-beat simulations of the mechanics and hemodynamics of the human cardiovascular system under physiological and pathophysiological circumstances.

In a healthy heart, the atrioventricular (AV) node is the only location where electrical signals can propagate from the atria to the ventricles. In the AV node the electrical wave front propagation is slower than in cardiac tissue, causing a delay between atrial and ventricular activation, which is essential for ventricular filling. Cardiac pacing can be employed to restore AV coupling in patients with a blockage in the AV node. In **Chapter 2** we used CircAdapt computer simulations to find the optimal AV delay at various inter-atrial delays, ventricular pacing sites and heart rates. The simulations showed that an increase in heart rate leads to a shift of optimal pump function to shorter AV delays. In contrast, the optimal AV delay increases with increasing interatrial activation delay and with decreasing interventricular activation delay (such as during

biventricular rather than right ventricular (RV) or LV pacing). The latter observations suggest that both LV and RV filling dynamics determine the optimal AV delay. Simulations suggested that the effective whole-heart AV delay as percentage of the cardiac cycle length, incorporating activation times of both the left and right heart, enabled a more consistent definition of AV coupling.

Blockage of parts of the ventricular rapid conduction system, such as the left and right bundle branch, can lead to dyssynchronous ventricular activation and a less efficient contraction. Cardiac resynchronization therapy (CRT) can be applied in patients with ventricular dyssynchrony to obtain a more synchronous activation by pacing both ventricles. In CRT, besides the AV delay, the timing between ventricular contractions can also be affected by the ventriculo-ventricular (VV) delay of the pacemaker. In **Chapter 3** we combined animal-experimental data and computer simulations, covering a wide range of AV and VV delay settings, and demonstrated that the LV and RV respond in an opposite manner to variations in LV or RV pacing delays, with RV contractility being optimal during RV pre-excitation and LV contractility being optimal during LV pre-excitation. On the other hand, simulated cardiac output data showed optimal values during (almost) simultaneous RV and LV pacing, suggesting that overall cardiac pump function depends on both left and right heart function. In **Chapter 4** we showed the importance of ventricular dyssynchrony during pacing for outcome after CRT in patients and computer simulations. We demonstrated that the presence of significant LV dyssynchrony during pacing is associated with lack of LV reverse remodeling in CRT patients.

The benefit of CRT not only depends on the settings of the pacemaker but also on the condition of the patient’s heart. Echocardiographic measurements of regional ventricular deformation and myocardial work may be used to improve the selection of CRT candidates.

In **Chapter 5** we demonstrated that the abnormal distributions of myocardial deformation and work that exist during dyssynchronous ventricular activation are amplified when the same electrical dyssynchrony coincides with a higher loading (afterload) of the LV. Afterload is thus an important additional variable that should be known for proper interpretation of ventricular deformation data.

A further study in this thesis extents animal experimental and clinical work of others, showing that prediction of CRT response can further be improved by not only measuring LV deformation but also RV deformation. As shown in **Chapter 6** a decrease in RV contractile reserve decreases the CRT response. Noninvasive measurement of RV deformation can help to identify patients with impaired RV function and thereby improve patient selection for CRT.

The work presented in this thesis demonstrates that CircAdapt can be a valuable tool to unravel the complex mechanical and hemodynamic interactions that play a role in the working mechanism of cardiac pacing therapy. The combination of computer simulations with animal experimental and clinical data showed that measurements providing insight in whole-heart activation are important for determining the patient’s potential for positive response to cardiac pacing. Measurement of LV deformation alone provides incomplete insight into ventricular electrical dyssynchrony, since right ventricular function and LV afterload also modulate the mechanical discoordination in dyssynchronous hearts. Therefore, an integrative whole-heart assessment is the key to achieve optimal response in patients receiving cardiac pacing therapy.