Novel indication and optimization strategies for cardiac pacing

IMPACT

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In 2019 nearly 250.000 people suffered from heart failure in the Netherlands, leading to almost 30.000 cases of hospitalization [1]. All-cause-mortality in patients with heart failure is 7% and even increases to 17% in case of hospitalization [2]. The total health care costs of heart failure in the Netherlands were 817 million euros in 2017 [1]. Besides trying to take away the underlying cause of heart failure, treatment consists of lifestyle changes and pharmacotherapy to reduce cardiac stress and filling pressures. Approximately a quarter of all patients with heart failure also have electrical conduction disorders, mainly left bundle branch block (LBBB). These patients may benefit from cardiac resynchronization therapy (CRT) as adjunct therapy [3]. CRT synchronizes the electrical activation and thereby contraction of the left and right ventricle (RV) using biventricular (BiV) pacing and thereby improve the overall cardiac output. In the Netherlands about 12.500 pacemakers were implanted in 2019 of which 2.500 were CRT devices [4]. Although CRT provides great reductions in heart failure burden on the population level, individual response varies significantly. The main objectives of this thesis were: 1) to study whether BiV pacing could also improve cardiac function in patients with first-degree AV-block and 2) to examine how the optimal benefit of CRT could be achieved by optimizing the delay between atrial and ventricular activation (AV-delay). In this chapter we summarize the clinical and societal impact of the main findings of this thesis.

Clinical impact

In **chapter 3** we showed that restoring physiological AV-delays using BiV pacing increased cardiac pump function in heart failure patients with first-degree AV-block who did not have clear intraventricular conduction disorders. Therefore, this acute hemodynamic study suggests that indications for CRT may be extended to patients who have heart failure and a first-degree AV-block. Obviously, larger and long-term studies are required to support this idea before it can be added to the CRT-guidelines. Additionally, the results in **chapter 3** implicated that the benefits that were achieved by restoring AV-coupling were reduced by cardiac dyssynchrony as induced by RV pacing, indicating that restoration of AV coupling by pacing therapy should be performed while maintaining as much as possible the normal ventricular conduction.

In **chapter 3** we also showed that optimizing the AV-delay in a porcine healthy heart resulted in greater cardiac output. This implicates that patients with first-degree AV-block but without heart failure might benefit from cardiac pacing as well. We hypothesize that pacing therapy in these patients does not necessarily treat symptoms, but may prevent the development of heart failure, and thereby decreases morbidity and mortality. Again, before this therapy can be broadly introduced in the clinic, additional research and preferably randomized controlled trials need to be done. These studies should not only focus on which patients are most eligible for the therapy but also which pacing modality shows the optimal result. As mentioned before maintaining ventricular synchrony is a must, something which can, besides BiV pacing, also be achieved by His-bundle, left bundle branch area, or LV septum pacing as well.

Scientific impact

In **chapter 3** and **chapter 4** the hemodynamic changes that occurred due to AV-delay optimization were thoroughly studied. As known from basic physiology, better filling of the ventricles leads to pre-stretching of the cardiac myocytes which in response leads to improved contraction, conform the Frank-Starling mechanism [5]. Our studies in **chapter 3** showed that in case of first-degree AV-block LV filling was improved due to a combination of increased forward flow over the mitral valve and a reduction in the amount of diastolic mitral regurgitation (MR). Therefore, also in future studies both these processes require attention.

Chapter 4 expanded these findings, by investigating the AV-coupling for both the right and left heart. In this regard it should be noticed that conventionally the AV-delay is defined by the time between stimulating (or sensing activity) the RA and stimulation of one or two of the ventricles. We showed that there are considerable differences in “effective” AV-delay between the right and left side of the heart (RA-RV vs. LA-LV delays) and that these delays also strongly depend on the site of ventricular pacing. The mean effective AV-delay takes into account the right and left side of the heart, and was able to more accurately predict the optimal AV-delay. Implication for future research is that both atrial (interatrial delay) and ventricular (interventricular dyssynchrony) activation sequences should be taken into account when searching for new algorithms for optimization of AV- and VV-delays.

In **chapter 5** we studied the SonR signal which is derived from intracardiac accelerations and gives mechanical information of cardiac contractility. We proved that the amplitude of this signal is not only sensitive for ventricular contraction, but also changes with alterations in ventricular filling at various AV-delays. On the contrary, we proved that the influence of interventricular dyssynchrony on the amplitude of the signal is small. **Chapter 6** shows that LV pre-excitation improves LV function but impairs RV function, while RV pre-excitation causes an improvement in RV function and a reduction of LV function. This indicates again that both ventricles should be taken into account while optimizing the AV-delay.

Societal impact

Part of the potential societal impact of this work relates to the ideas about improving pacemaker therapies. Doing so we believe that health care costs may be reduced due to less symptoms and decreased hospitalization rate. However, as mentioned above, there are several steps to be taken before this benefit can be proven.

This thesis also demonstrates how clinical and animal experiments can be enhanced through computer simulations. In **chapter 3** computer simulations aided in better understanding the hemodynamic improvements caused by AV-coupling restoration. In

chapter 6 animal data were the base for computer simulations showing that RV function is important for overall cardiac function. And the results from the animal study in **chapter 4** have already been replicated using the CircAdapt software, as well. This shows that computer models have a future in pacemaker research. They can be used in hypothesis generation or help in simulating experiments that are not possible in humans or animals. Multidisciplinary collaboration between cardiologists, physiologists and biomedical engineers, is key to gain the optimal result from computer modeling and simulation.

Currently, data from animal and experimental work is still necessary for the development, validation and improvement of models, like the CircAdapt model. On the other hand, these computer models can help to reduce the number of animal and clinical studies by improving hypotheses and gaining more accurate inside in hemodynamics. It is to be expected that in this field the number of animal experiments can decrease over time, while the contribution of computer models will increase.

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