Multi-modality imaging in cardiac resynchronization therapy

Summary

Heart failure (HF) is a clinical condition characterized by symptoms of breathlessness, ankle swelling, and fatigue, often accompanied by reduced cardiac output and elevated intra-cardiac pressure. In the Western world, HF has been identified as an epidemic, affecting 1-2% of the adult population. In approximately 25% of HF patients, there is an irregular contraction of the ventricles due to delayed ventricular conduction, known as 'dyssynchronopathy', which can result from a malfunctioning left bundle branch (LBBB) or an unspecified intraventricular conduction defect (IVCD).

Cardiac resynchronization therapy (CRT) is a treatment that involves simultaneous pacing of the two ventricles to reduce dyssynchrony. CRT has been shown to be effective in reducing symptoms, morbidity, and improving survival, and has become an important guideline-recommended treatment for dyssynchronopathy in the last two decades. However, there is a broad range of patient outcomes with CRT, which has led to investigations into mechanisms that contribute to the variability in response.

This thesis aims to enhance the efficacy of CRT by improving patient selection and optimizing device implantation. To achieve this, the thesis will focus on two parallel aims:

1) To understand the electrocardiogram for better patient selection in CRT **(Part 1)**.
2) To develop an image-guided strategy for better LV lead positioning **(Part 2)**.

Knowledge about the pathobiology of dyssynchronopathy is a prerequisite for adequate therapy delivery. **Chapter 2** therefore provides a more in-depth background about the various processes involved in the development of dyssynchronopathy, and its correction by CRT. This review illustrates that conduction abnormalities lead to extensive immediate and long-term changes in the heart and reversal of functions by CRT. The long-term adaptations of the myocardium can be characterized as “maladaptive” because many functions continue to decrease over time. This also explains why CRT continues to increase its therapeutic effect over time.

The first part of this thesis examines the variations in electrocardiogram (ECG) and the factors that contribute to them.

The 12-lead ECG and vectorcardiogram (VCG) have provided extensive information on ventricular conduction abnormalities and the overall electrical activity of the heart, measured in two- and three-dimensional (3D) formats, respectively. The current European guidelines for CRT are based on specific morphological ECG criteria that define LBBB, intraventricular conduction defect (IVCD), and right bundle branch block (RBBB). However, theoretical considerations suggested that these morphological criteria could be influenced by geometric factors such as heart-torso geometry and ECG electrode positions. **Chapter 3** investigates the influence of these factors by utilizing tailored computational models of CRT recipients. The findings demonstrate that heart-torso geometry significantly affects LBBB morphological criteria on the ECG and voltage VCG parameters, while QRS duration (QRSd) remains relatively stable.

In addition to ECG morphology, the presence of myocardial scar has been proposed as a significant factor in determining patient benefit from CRT. Since CRT is a purely electrical

treatment, it may be assumed that it only addresses electrical disease and not structural disease such as myocardial scar. To investigate this relationship, **Chapter 4** explores the association between VCG parameters, including QRS_{area}, and myocardial scar as measured by cardiac magnetic resonance imaging (CMR) in clinical CRT patients. The results indicate that QRS_{area} is inversely associated with focal scar, but not with diffuse. The combination of CMR and QRS_{area} may improve the prediction of CRT outcomes.

Besides the presence of scar itself, placing the LV lead remote from scar during implantation is important as well to enhance CRT response, but also to avoid life threatening pacing-induced ventricular arrhythmias. Delayed enhancement CMR (DE-CMR) is currently the gold standard for delineation of myocardial scar in clinical patients. CRT implantation is an invasive procedure involving positioning of leads with electrodes in the heart. This invasive nature also allows one to measure intra-cardiac electrograms (EGM) at the position of the lead tips with little extra patient burden. Extracting information about myocardial scar from these intra-cardiac EGMs would be a two-for-one, as it could navigate the device cardiologist to a LV lead position remote from scar during implantation without an additional CMR investigation. **Chapter 5** therefore investigates whether voltage amplitudes from the unipolar EGM reflect myocardial scar on DE-CMR in patients with HF. The findings show that voltage amplitudes from the unipolar EGM are slightly lower in myocardial scar compared to non-scar. However, substantial inter-individual differences and large overlap between non-scar and scar (particularly at the epicardium) limits the reliability of accurate scar assessment by unipolar EGMs. **Chapter 6** subsequently investigates how the wavefront of electrical activation could affect these unipolar voltage amplitudes in HF patients and tailored in-silico models without myocardial scar. The findings indicate that in HF patients and computer models without myocardial scar, lower septal unipolar voltage amplitudes are associated with a LBBB activation sequence. Changing the wavefront of activation by ventricular pacing substantially affects voltage amplitudes, particularly at the epicardium. While in Part 1 signal analysis plays a dominant role, the majority of Part 2 deals with imaging by focusing on the development of an optimal multimodal-imaging-guided CRT implantation in our clinic.

A more in-depth introduction about imaging modalities in CRT is provided in **Chapter 7.** We conclude that the future of image-guided LV lead placement may be integration of multiple modalities, combining the strengths of multiple techniques. Key components in this process, and relevant for LV lead guidance, include coronary venous anatomy, electrical or mechanical activation, and delineation of scar.

Placing the LV lead in a position in late activated myocardium remote from scar is thus important for response to CRT. The rationale behind this, is that pacing the latest activated region, advances its activation and contraction to an earlier phase thus leading to a more synchronous electrical activation and thereby more coordinated contraction. The device cardiologist can only reach a pre-defined target segment for LV lead implantation if this part of the heart is covered by an appropriate coronary vein. Fluoroscopic angiography is most commonly used for visualization of the coronary veins but prohibits pre-procedural anticipation of patient-specific anatomy. **Chapter 8** therefore illustrates the additive

value of computed tomography (CT) angiography for visualization of the coronary veins prior CRT implantation. We found that in about one-fourth of our patients, pre-procedural coronary venous CT angiography impacted the CRT implantation approach due to various reasons including unfavorable coronary venous anatomy, persistent left-sided superior caval vein with no innominate vein, and presence of LV thrombus.

As previously mentioned, positioning the LV lead remote from scar in late activated myocardium is important. The gold standard for measuring intra-cardiac electrical activation is electro-anatomic mapping (EAM). EAM is an invasive procedure involving positioning catheters in the heart that measures local EGMs and simultaneously reconstructs an anatomy of the mapped structure by 3D navigation. In **Chapter 9** we develop a roadmap for CRT implantation by integration of coronary venous EAM with DE-CMR to guide LV lead placement to the latest electrical activated region in a coronary vein remote from scar intra-procedurally in CRT recipients in our center. A more patient friendly approach that generates similar information as invasive EAM is ECG imaging (ECGI). ECGI reconstructs the electro-anatomic activation of the epicardium based on body surface potential measurements using ~200 body-surface electrodes and a patient-specific heart-torso geometry. In the final research chapter, **Chapter 10**, we developed an alternative non-invasive CRT implantation roadmap that can be used pre-procedurally by 3D integration of epicardial activation maps from ECGI, with myocardial scar from DE-CMR, and information on coronary venous anatomy from CT. In both **Chapter 9 and 10** an optimal LV lead position remote from scar in electrical late activated myocardium could be accomplished in about two-third of the patients but was not present due to extensive scarring or limited coronary venous anatomy in about one-third of the patients. In the last chapter, **Chapter 11**, the findings of this thesis are discussed in broader perspective. In this chapter we review current literature on the assessment of electrical dyssynchrony for patient selection in CRT and the use of these techniques in guided LV lead implantation. The literature overview revealed that VCG QRS_{area} displayed superior performance in patient selection for CRT and is the closest parameter to clinical implantation, a tailored LV lead implantation guided by (multi-modal) imaging or mapping in randomized clinical trials was not consequently associated with improved clinical outcome, and that detecting baseline dyssynchrony has huger impact on outcome than optimizing synchrony within a patient. We end our thesis by proposing future projects including: comparing QRS_{area} with electrophysiological findings to gain more mechanistically insight in this parameter, comparing ECGI or EAM with strain CMR or echocardiography to unravel the electro-mechanical interplay and understand why a guided LV lead approach did not always lead to improved outcomes. Finally, we will investigate the effect of biventricular pacing on dispersion of repolarization and its potential relation to ventricular arrhythmias. The latter project has been awarded with a Dekker Clinical Scientist grant (appendix).