Multi-modality imaging in cardiac resynchronization therapy

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Heart failure

Heart failure (HF) is a serious clinical condition that has been identified as an epidemic in the Western world, affecting around 1-2% of the adult population and increasing to ≥10% among individuals aged 70 years and above.(1) The prevalence of HF has significant consequences on society as it places a considerable burden on both patients and their caregivers, while also requiring a substantial amount of healthcare resources.(2) The overall count of individuals who have HF is on the rise, which can be attributed to the chronic nature of the condition as well as the growth and aging of the population.(3) The case mix of HF is evolving as well in terms of etiology but also in diversity. A growing number of patients presenting with symptomatic HF now have a preserved ejection fraction. Myocardial infarction is slightly losing its prominence in HF etiology, while obesity is expected to play an increasingly important part.(3)

Cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT) had revolutionary impact on disease modification of patients with HF with reduced ejection fraction and wide QRS and is associated with improved pump function, reduced hospitality and mortality. CRT studies have notable gender and racial disparities, with men and white individuals comprising the majority of study participants.(4) Intriguingly, emerging evidence indicates that females and Asians exhibit a higher likelihood of deriving benefits from CRT. This phenomenon could potentially be attributed to the impact of height on the efficacy of CRT, with diminishing advantages observed as height increases.(5)

The greatest number of CRT devices are implanted in the age group of 65 to 84 years old, though there was a notable rise over the years in the number of CRT implants in patients aged 85 years and above.(4) Interestingly, the ongoing AdaptResponse trial (NCT02205359) has examined the potential superiority of preferential left ventricular (LV) only pacing using the AdaptivCRT algorithm over conventional CRT in terms of mortality and HF hospitalization.(6) The trial included approximately 4,000 patients, with a near equal distribution of women and men. The study did not achieve its primary endpoint (p=0.77) which could be partially attributed to the remarkably high number of responders, indicating advancements in medical treatment compared to CRT randomized controlled trials conducted over a decade ago, as well as a higher percentage of women in the study cohort.

Scientific and clinical impact

The long-term goal of this thesis was to further enhance patient benefit from CRT by studying variants of the electrocardiogram (ECG) to aid patient selection and by developing an image-guided strategy for LV lead implantation. The scientific and clinical impact of this thesis are closely linked, as the research in this thesis were largely motivated by clinical problems.

Electrocardiography (ECG) is the hallmark technique of clinical cardiology. In part one of this thesis we investigate factors affecting the surface ECG, reconstructed vectorcardiogram (VCG), and intra-cardiac electrograms in patients and computer models with dyssynchronopathy. The findings of this thesis demonstrate that heart and chest geometry, as well as electrode positioning, can influence the morphological criteria of left bundle branch block (LBBB) on the ECG. From a scientific perspective, these findings highlight that external measurements do not always reflect internal conditions and emphasize the value of high-end mapping techniques for evaluating the electrophysiological substrate. From a clinical standpoint, these results underscore the limitations of relying on morphological criteria from surface ECGs to diagnose patient eligibility for CRT, as heart-torso geometry may influence the class of recommendation for CRT.(7)
The utilization of VCG presents a promising partial solution to address the aforementioned issue. Among the VCG parameters, QRS_{area} demonstrates considerable potential as a marker for dyssynchrony, offering valuable insights for patient selection and optimization of CRT. It is a strong predictor for CRT outcome, outperforming the conventional QRS duration (QRSd) and morphology from the 12-lead ECG. However, little is known about what QRS_{area} truly reflects. In **Chapter 4**, we discovered that QRS_{area} is inversely associated with focal scar, but not with diffuse fibrosis on cardiac magnetic resonance imaging (CMR). These findings may explain why QRS_{area} outperforms QRSd, as it incorporates myocardial viability, while QRSd reflects only the total prolongation of ventricular activation and cannot distinguish between purely electrical or tissue substrate. Currently, VCG parameters are not included in the European pacing guidelines. However, an ongoing study will investigate the potential for QRS_{area} for patient selection prospectively.(NCT04120909) Therefore, this work does not directly change clinical practice, but may assist future clinicians in interpreting low QRS_{area}.
In clinical electrophysiology, intra-cardiac voltage amplitudes are measured to create an activation map and to delineate myocardial scar. Typically, low voltage amplitudes are associated with myocardial scar. However, CMR remains the gold standard for clinical scar evaluation. In **Chapters 5 and 6**, we demonstrate that unipolar voltage amplitudes have only a moderate (endocardium) to poor (epicardium) association with scar, and that there is high inter-individual variability between non-scar voltage amplitudes. Changing the wavefront of activation, for example, through pacing, can also affect voltage amplitudes. Notably, a left bundle branch block (LBBB) activation, in the absence of myocardial scar, is consistently associated with low septal voltages. **Chapter 5's** message was difficult to publish due to its deviation from established literature. However, detailed analysis of papers advocating low voltage amplitudes as indicative of scar revealed that their correlation coefficients for the endocardium were comparable to our findings and did not present inter-individual voltage analyses. From a clinical perspective, **Chapters 5 and 6** could have substantial impact, as electrophysiologists often rely on voltage mapping. In patients with LBBB, low

voltages in the septum may be inaccurately interpreted as scars. In these patients, structural imaging with CMR and intra-procedural integration of CMR with electro-anatomical mapping (EAM) could be useful.

Chapters 9 and 10 from part II of this thesis aimed to enhance CRT implantation efficacy by integrating CMR-based myocardial scar data with coronary venous anatomy and respectively invasive and noninvasive EAM. To the best of our knowledge, these papers are still the sole CRT roadmap studies utilizing a 3D approach that offers comprehensive information on coronary venous anatomy with respect to myocardial scar localization and electrical activation. This technological innovation marks a milestone from a scientific standpoint. From a clinical viewpoint, one can contend that the majority of the prior randomized controlled trials investigating guided LV lead placement failed due to the absence of such modalities in a 3D roadmap. The clinical value of these roadmaps lies in their potential to affect the pre-implantation phase. For instance, when the pre-procedural CRT roadmap indicates insufficient coronary venous anatomy in the target region, alternative resynchronization methods such as LV septal pacing may be considered. Similarly, in cases of septal scar, traditional biventricular pacing could be deemed more appropriate.

Societal impact

Enhancing benefit to CRT can have significant societal implications. Dyssynchronous HF is a prevalent condition, and when not treated effectively can lead to substantial burdens on both patients and caregivers. Moreover, the associated healthcare costs arising from frequent hospitalizations place an additional strain on healthcare providers and society as a whole by the associated healthcare costs.

Optimizing CRT can improve patients' quality of life and functional capacity, enabling them to actively participate in daily activities and potentially return to work. By restoring individuals' ability to engage in productive activities, CRT contributes to a more economically active population and reduces the economic burden associated with disability and loss of productivity.

In summary, optimizing CRT can leads to improved patient well-being and generates societal advantages, including reduced healthcare burden, increased economic productivity, and enhanced patient quality of life.

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