Multimodality imaging in the characterization and risk-stratification of cardiac disease and CRT recipients

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Citation

Bijl, P. van der. (2020, September 3). *Multimodality imaging in the characterization and risk-stratification of cardiac disease and CRT recipients*. Retrieved from https://hdl.handle.net/1887/136092

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Issue date: 2020-09-03

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General introduction and outline of the thesis

GENERAL INTRODUCTION

Cardiac resynchronization therapy (CRT), the implantation of a dedicated device to resynchronize the ventricles in heart failure, is an established treatment for patients who remain symptomatic despite optimal medical therapy. It has a multitude of potentially beneficial effects, which include: improvement of symptoms, left ventricular reverse remodeling, improvement of left ventricular ejection fraction (LVEF), reduction of functional mitral regurgitation (FMR), decrease in the risk of ventricular arrhythmias and improvement in survival (Figure 1).[1-4] The probability of these favorable outcomes occurring after CRT implantation, is dependent on the appropriate patient characterization by echocardiography.

Risk-stratification of cardiac disease entails the scientific estimation of the probability for serious, disease-related events, e.g. heart failure and sudden cardiac death (SCD), either to inform prognosis or guide management. Multimodality cardiac imaging (echocardiography, magnetic resonance and radionuclide techniques) has assumed a central role in the risk-stratification of various cardiac diseases, encompassing multiple etiologies (Figure 2).[5]

Echocardiography for the prediction of outcome after CRT

Patients with a left bundle branch block (LBBB) morphology on the surface ECG, as well as a QRS duration of ≥150 ms, appear to derive most benefit from CRT in terms of symptom improvement and survival.[6-8] It is less clear if these baseline characteristics also translate into a greater degree of left ventricular reverse remodeling and improvement in LVEF, both of which are quantified by means of echocardiography.[9] Reverse remodeling is most commonly defined as a ≥15% reduction in the left ventricular end-systolic volume (LVESV) at 6 months after CRT implantation.[10] Long-term outcome after CRT is strongly linked to reverse remodeling, but also to improvement in global longitudinal strain (GLS), which can be measured with speckle tracking strain echocardiography.[11-13] These two measures, i.e. a reduction in LVESV and an improvement in GLS, reflect different mechanisms of CRT response – resynchronization and recruitment of contractile reserve, respectively. It is unknown whether an improvement in both, an improvement in only one or no improvement in either, has different prognostic implications.

Echocardiography may be useful for predicting outcome after CRT not only when performed before implantation, but also thereafter. CRT exerts its beneficial effects by resynchronization of the left ventricle.[1,2] Left ventricular dyssynchrony can be quantified with a novel, speckle tracking strain parameter, i.e. mechanical dispersion (MD).[14,15] It is calculated as the standard deviation of the time from the onset of the QRS complex on the triggered ECG to the peak longitudinal myocardial strain in a 17-segment model.[14,15] The degree to which left ventricular synchrony has been restored by CRT, quantified with MD, appears to predict outcome, i.e. a decrease in ventricular arrhythmias.[16] What remains unknown, is if MD (as a measure of residual dyssynchrony after CRT implantation) also leads to improved survival. CRT restores mechanical efficiency to the failing left ventricle by resynchronization of contraction. The less efficiently the left ventricle operates at baseline, the greater the potential is for recovery of efficient work after CRT. It is unknown whether a greater reserve of potentially recoverable left ventricular myocardial work efficiency before CRT occasions better outcome. Global, left ventricular work efficiency can now be quantified with a non-invasive technique, which involves speckle tracking strain echocardiography.[17,18]

FMR is common in heart failure patients, and a reduction in FMR is counted among the beneficial effects of CRT.[19-27] This is achieved by a variety of mechanisms, i.e. resynchronization of the atrioventricular, inter- and intraventricular contraction, preload reduction and an increase in mitral valve closing forces.[26,28-30] The impact of the evolution of FMR after CRT on mortality has not been adequately investigated in a large cohort. Furthermore, atrial fibrillation (AF) is a common occurrence in heart failure, and may contribute to the severity of FMR through left atrial and mitral annular dilatation.[31-33] The impact of AF on the extent of FMR improvement in CRT has never specifically been investigated.

Echocardiography therefore plays a central role in the characterization of heart failure recipients of CRT, as well as in the delineation of the factors which will determine outcome. Results of research which have been included in this thesis, focus on the intersection of echocardiography and the following determinants of outcome after CRT: reverse remodeling, resynchronization and FMR improvement.

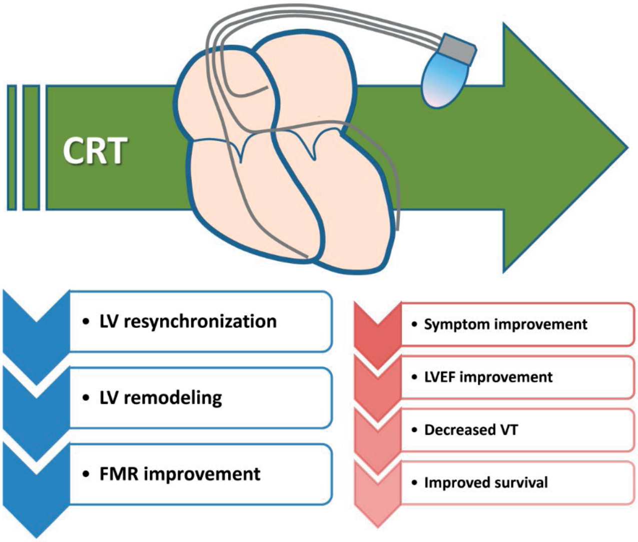

Figure 1: Summary of beneficial effects of cardiac resynchronization therapy (CRT), with highlighted (blue) determinants of outcome which are addressed in this thesis. FMR: functional mitral regurgitation, LV: left ventricular, LVEF: left ventricular ejection fraction, VT: ventricular tachycardia.

The role of multimodality imaging in the risk-stratification of cardiac disease

SCD is the cause of >4 million global deaths per year (one-fifth of all recorded deaths).[34] Since it often occurs in individuals who were not previously known with cardiac disease, its prevention remains challenging.[34] Insertion of an implantable, cardioverter-defibrillator (ICD) is the most effective approach to primary prevention (persons at high risk of SCD) and secondary prevention (patients with a previous, aborted episode of SCD).[5] Currently, ICD candidates are selected on the basis of an LVEF <35%.[34] This criterion, however, is neither sensitive, nor specific, and new approaches are required to improve upon this strategy.[5] Various cardiac imaging techniques, e.g. speckle tracking strain echocardiography, late gadolinium contrast enhanced (LGE) cardiac magnetic resonance (CMR), as well as nuclear techniques, have shown promise for more accurate SCD risk-stratification than LVEF in isolation.[5]

Genetic, dilated cardiomyopathy (DCM) is associated with more than 50 pathogenic genes (sarcomeric and lamin A/C mutations being the most common), as well as neuromuscular disorders.[35-37] Mutation carriers often remain asymptomatic until heart failure, arrhythmias or SCD supervenes.[35,38] Preventive strategies have not been adequately defined, partly because early disease is challenging to detect.[35] Advanced cardiac imaging techniques (e.g. echocardiographic tissue Doppler imaging, speckle tracking strain echocardiography, CMR and nuclear scans) can identify both structural and functional abnormalities early during the course of genetic DCM.[35] Furthermore, multimodality cardiac imaging can provide incremental benefit to LVEF for the risk-stratification of individuals with established, genetic DCM.[35]

Multimodality imaging is very promising as a risk-stratification tool for cardiac disease, and it has been reviewed, as well as further researched, in the context of genetic DCM, in this thesis.

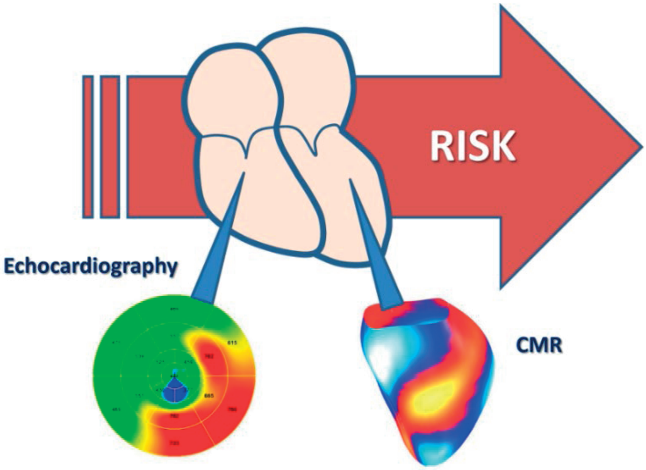

Figure 2: Examples of multimodality imaging in risk-stratification of cardiac disease. CMR: cardiac magnetic resonance.

OUTLINE OF THE THESIS

The objective of this thesis was twofold: i) to investigate the role of echocardiography in predicting outcome after CRT, and ii) to review and investigate multimodality imaging in the risk-stratification of cardiac disease.

In **Part I**, the role of echocardiography in predicting outcome after CRT is discussed. **Chapter 2** investigates the relation between baseline QRS duration and the presence of an LBBB on the one hand, and the degree of left ventricular reverse remodeling and improvement of LVEF, on the other, in CRT recipients. In **chapter 3**, results are presented on the interaction of two important determinants of outcome in CRT, i.e. left ventricular GLS and left ventricular reverse remodeling, as well as their impact on survival. The benefits of restoration of mechanical dyssynchrony (measured by MD) in CRT patients (decrease in ventricular arrhythmias, as well as survival) are discussed in **chapter 4**. A novel, non-invasive technique for assessing cardiac mechanical efficiency is applied to CRT prognostication in **chapter 5**. **Chapter 6** focuses on the prognostic influence of FMR in CRT recipients, with particular emphasis on the evolution thereof, i.e. what the impact on survival is when FMR is improved (or not improved) by CRT. In **chapter 7**, the impact of AF on the improvement in FMR in the CRT context is analyzed.

Part II provides a perspective on the use of multimodality imaging in the risk-stratification of various cardiac diseases. In **chapter 8** a brief overview of multimodality imaging in the prediction of SCD is given. **Chapter 9** reviews the role of cardiac imaging in the risk-stratification of genetic DCM, especially when associated with neuromuscular disorders. The use of speckle tracking strain echocardiography in risk-stratification of genetic DCM, is explored in **chapter 10**.

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