Cardiac resynchronization therapy

Refinements in patient selection and technology

Odette A. E. Salden

Cardiac resynchronization therapy: Refinements in patient selection and device technology

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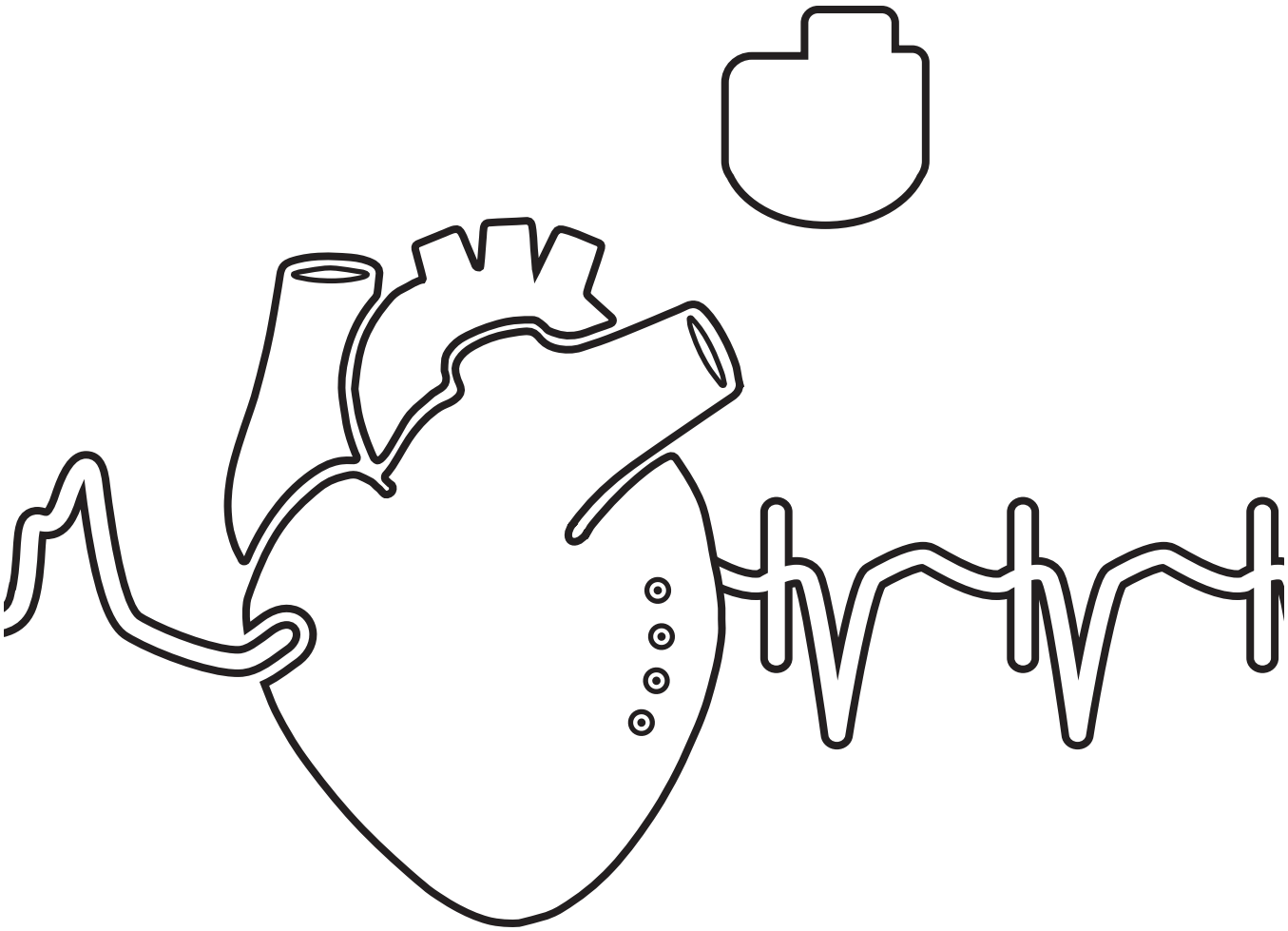
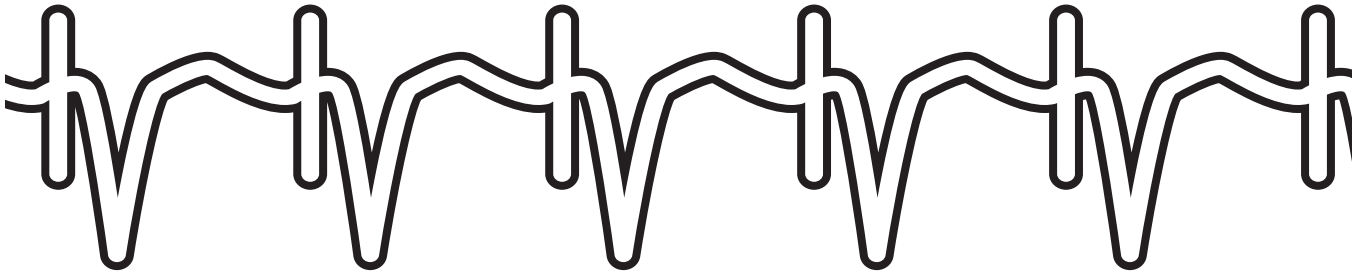


Chapter 1

Introduction and thesis outline



More than twenty years of research has established the role of cardiac resynchronization therapy (CRT) in patients with medically refractory systolic heart failure with abnormal QRS complex morphology and duration.[1] In this patient population, CRT bestows a mortality benefit, a reduction in heart failure hospitalizations and an improved functional status.[2–4] The first CRT implantation took place back in March 1993 in the University Medical Center of Utrecht.[5] Its introduction has been no less than revolutionary for patients with advanced heart failure whose only previous option was cardiac transplantation. Nowadays CRT is also a realistic and cost-effective treatment option for patients with mild heart failure. One could probably say that CRT has been one of the most exciting recent advancements in heart failure treatment. Moreover, besides radically transforming patient care, CRT has also united the fields of electrophysiology and heart failure, once distant cardiac subspecialties.[1,6] Despite that CRT has become one of the pillars of heart failure management, it continues to face a relatively high non-responder rate of 30-40%, depending on the definition for non-response used.[7] Accordingly, there is still room for improvement of the therapy. The desire to increase CRT response rates has led to refinements in technology and patient selection. By addressing several treatment-refinement strategies this thesis aims to gain more insight into the possibilities to better diagnose and treat patients with CRT.

HEART FAILURE AND DYSSYNCHRONY

Heart failure is a clinical syndrome caused by abnormalities in myocardial structure, which result in reduced cardiac performance. It is present in about 2-4% of the adult population, but its prevalence increases with age, affecting 6-10% of the population aged >65 years.[8,9] The prognosis of patients with heart failure is generally poor with 50% of patients surviving 5 years, and only 10% of patients surviving at 10 years after the primary diagnosis.[10] In over a third of patients with heart failure, electrical conduction disturbances, such as left bundle branch block (LBBB) or intraventricular conduction delay, are present.[11] Disturbances in the electrical conduction of the heart may develop due to heart failure and are independently associated with an unfavourable prognosis.[12] Yet, abnormalities in the electrical conduction system of the heart may by itself also be causative of heart failure.[13–15] New-onset LBBB, for example, has an immediate harmful effect on cardiac function and survival.[12,16] Due to electro-mechanical coupling -the process that converts the electrical excitation of cardiac cells into mechanical contraction - it is not surprising that abnormal electrical activation (electrical dyssynchrony) coincides with abnormal contraction patterns (mechanical dyssynchrony).[17] Via this mechanism, electrical dyssynchrony leads to mechanical inefficiency, a reduction in cardiac function and the triggering of cardiac remodeling.[18]

This process is characterized by a maladaptive change in cardiac geometry resulting in left ventricular (LV) dilatation, impairment in cardiac contractility and LV relaxation which altogether result in a deterioration of cardiac output. The recognition -already in 1925- that electrical conduction disturbances lead to mechanical inefficiency and cardiac dysfunction has provided the paradigm for CRT[13]

CARDIAC RESYNCHRONIZATION THERAPY

Electrical dyssynchrony is caused by timing differences and can be divided into dyssynchrony within the ventricles (intraventricular), between the left and right ventricle (interventricular), and between the atria and the ventricles (atrioventricular).[18,19] All these three kinds of dyssynchrony may be treated with a CRT. CRT is an advanced device-based electrical therapy which uses a pacemaker device (with or without defibrillator function) connected to the heart with three leads. CRT leads are implanted via the venous system with one lead positioned in the right atrium, one in the right ventricle and one lead overlaying the epicardial LV free wall. By coordinated pacing at these locations (biventricular pacing) a CRT device can improve electrical synchrony and, thereby, is able to improve cardiac performance and mechanical efficiency.[20] This may result in a direct improvement of cardiac function and ultimately may induce reverse remodeling, which is characterized as a reduction in LV dimensions and improvement in LV function.[21] Still, it is imperative to realize that cardiac pacing by itself induces a stage of dyssynchronous electrical activation. In patients who have only little underlying electrical dyssynchrony, biventricular pacing will induce electrical dyssynchrony.[22,23] This CRT-induced iatrogenic electrical dyssynchrony will subsequently lead to worsening of cardiac function and will have a deleterious effect on patient outcomes. The effect of CRT, thus, relies on its benefits exceeding any harm that it might do. Accordingly, being able to distinguish between patients that may or may not benefit from CRT depends, for an important part, on the establishment of sufficient baseline electrical dyssynchrony. Several electrical and mechanical parameters have been proposed for this purpose, and a few promising parameters are discussed in the first part of this thesis.

ONE PATIENT SELECTION

According to current international guidelines, CRT is indicated for patients with symptomatic heart failure with New York Heart Association class II-IV symptoms, who remain symptomatic despite stable optimal pharmacological therapy, and who have an LV ejection fraction (LVEF)

≤35%.[24,25] On top of these requirements, patients should have signs of significant underlying electrical dyssynchrony, for which the 12-lead electrocardiogram (ECG) is used in current international guideline recommendations for CRT. On the ECG, patients should have a prolonged QRS duration of at least 130ms but preferably ≥150ms with an LBBB QRS morphology,[24,25] because patients with an LBBB as a group have been shown to benefit more favorably from CRT than patients who do not display an LBBB (non-LBBB).[26–29] Yet, when the ECG is used to assess suitability for CRT, approximately 30-40% of patients do not respond to the therapy. A disadvantage of using parameters derived from the electrocardiogram is that they provide only a general overview of ventricular electrical activation abnormalities. Furthermore, the definition of true LBBB to date remains a topic of continuing debate and there are currently multiple criteria to define LBBB.[30,31] Due to these shortcomings, the ECG may not be the most optimal tool for determining the true electrical substrate for CRT. Alternatives for the establishment of an underlying substrate amendable by CRT may be found in the assessment of mechanical dyssynchrony with cardiac imaging modalities and in the evaluation of electrical dyssynchrony with vectorcardiography.[32–34]

Cardiac imaging for quantification of mechanical dyssynchrony

The mechanical consequences of electrical dyssynchrony -often referred to as mechanical dyssynchrony or mechanical discoordination- can be identified with various deformation imaging modalities. These imaging modalities include echocardiography and cardiac magnetic resonance imaging. Especially the analysis of mechanical dyssynchrony by echocardiography has been adopted into clinical practice due to its advantages of being easily available, relatively cheap and non-invasive. While using echocardiographic dyssynchrony markers for CRT patient selection has long been a topic of debate, there is accumulating evidence that the detection of specific wall motion patterns can serve as predictor for CRT response, and hence, may aid in the selection of patients.[20,33,35] These specific wall motion patterns can be i) identified by the visual assessment of dyssynchrony, and ii) quantified in detail with speckle tracking echocardiography (STE). An early systolic, short septal contraction pulling the septum leftwards (septal flash) followed by a delayed lateral wall contraction which causes a rightward motion of the septum and a left-to-right rocking motion of the apex (apical rocking) are specific patterns of contraction that can be assessed visually on conventional two-dimensional echocardiography. These visual patterns of mechanical dyssynchrony are both strongly associated with better survival and volumetric response after CRT.[32] Still, when using these more simple visual markers to determine the presence of dyssynchrony, a continuous mechanical process is translated to a binary yes/no phenomenon. STE, on the other hand, analyzes the motion of myocardial tissue during the cardiac cycle in detail by tracking specific greyscale speckle patterns of the myocardium.[36] The speckle pattern is caused by interference of natural acoustic backscatter and is unique for each myocardial region. During

the cardiac cycle this speckle pattern is relatively stable, therefore, it can be traced in time and place. The relative displacement of these speckle patterns can be evaluated with STE software algorithms by the generation of myocardial strain curves.[36] (**Figure 1**) With these strain curves the timing and amount of myocardial shortening (contraction) and stretching (relaxation) that takes place during the cardiac cycle can be quantified. Stretching of the myocardium during systole does not contribute to LV ejection and, therefore, systolic myocardial stretching represents a waste of energy.[17] Considering that CRT may convert systolic stretching into shortening, the amount of systolic stretching in the dyssynchonous heart may reflect the potential for recovery of LV function with CRT. Accordingly, by assessing the amount of systolic LV stretching at baseline (e.g. systolic rebound stretch of the septum or LV systolic stretch index) potential CRT responders may be identified.[20,33]

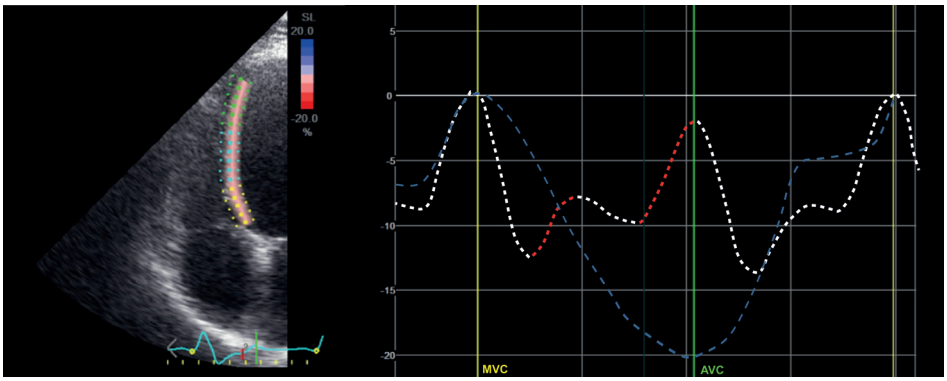


Figure 1. Myocardial speckle tracking strain curves of the interventricular septum. Echocardiographic image of the left ventricular septal wall (**left**) with tracing of the interventricular septum. Generated strain curves (**right**) derived with dedicated speckle tracking echocardiography software. Systole is occurring between MVC (mitral valve closing) and AVC (aortic value opening) and diastole after AVC. Myocardial contraction results in negative strain values (dotted lines going down), while stretching is reflected by positive strain (lines going up) Systolic rebound stretch of the septum (SRSsept) (in red) is defined as septal stretching after initial shortening during systole. CRT aims to convert systolic stretching into shortening and hence create predominant shortening during systole and stretching in diastole (dotted blue curve, representing a normal septal strain pattern).

Vectorcardiography for quantification of electrical dyssynchrony

CRT patient selection may also be improved by the evaluation of electrical dyssynchrony with vectorcardiography.[34,37] Vectorcardiography is a method for recording the magnitude and direction of the electrical forces generated by the heart in three-dimensional space. While vectorcardiography originates already from the 1950s, the demand for an easy, widely applicable and non-invasive robust parameter to assess the extent of electrical dyssynchrony has led to renewed interest in vectorcardiography. In particular, the vectorcardiography-derived parameter

'QRS area', which is the area under the 3-dimensional QRS complex, shows potential to overcome the previously mentioned shortcomings of contemporary ECG-based patient selection (by QRS duration and QRS morphology). Strong unopposed electrical forces generated within the heart are assumed to be the underlying mechanism of a large QRS area.[37] Moreover, QRS area is lower in patients with ICM.[38] A larger QRS area, thus, reflects both a greater degree of electrical dyssynchrony and a more favorable myocardial substrate (e.g. non-ischemic) which is amendable by CRT. Although vectorcardiography is not yet commercially available, it can be 'calculated' from the 12-lead ECG.[39] (**Figure 2**) Therefore, a major advantage of the vectorcardiogram is that it can be derived from commercially available ECG machines, allowing markers such as QRS area to be provided without additional recordings or leads.

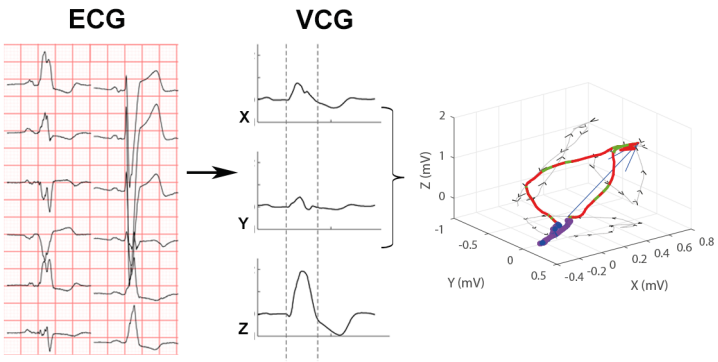


Figure 2. Vectorcardiography. The 12-lead ECG (**left**) can be transformed by the Kors regression matrix in a vectorcardiogram (**right**), which records the magnitude and direction of all electrical forces generated by the heart. The vectorcardiogram is constructed from three orthogonal leads containing all electric information. The three leads are represented by an X-axis (right-left), Y-axis (head-to-feet), and a Z-axis (front-back).

TWO IMAGE-GUIDED CRT DELIVERY

The effectiveness of CRT is, not only, influenced by a patients underlying electromechanical substrate at baseline, but also, by the position of the LV lead.[40] LV leads are placed in a tributary of the coronary sinus overlying the LV epicardium. Placing the LV lead at an optimal position is one of the most challenging technical aspects of a CRT device implantation. Improving and facilitating CRT delivery, therefore, is the next strategy evaluated for the refinement of CRT in this thesis. An LV lead position away from scar and in an area displaying delayed electromechanical activation, have been shown to markedly improve response and survival after CRT, whereas pacing in scar or an area without significant activation delay are associated with suboptimal response

and poor prognosis.[41–45] Unfortunately, the cardiac silhouette is radiolucent on fluoroscopy, therefore, neither myocardial scar, nor electromechanical activation delay is visible on the fluoroscopic projections made during CRT implantations. Intra-procedural visualization of so-called 'target areas' for LV pacing (e.g. out of scar and in an area with significant activation delay), therefore, might improve the LV lead position in patients undergoing CRT. Data derived from more sophisticated cardiac imaging modalities, such as cardiac magnetic resonance imaging (CMR), may be used to identify these LV lead target areas. CMR is the gold-standard technique for the identification of myocardial scar (using late gadolinium enhancement) and with CMR feature tracking (the CMR equivalent of speckle tracking echocardiography) mechanical activation delays may be evaluated.[46,47] By integration and fusion of three-dimensional CMR data sets with live-fluoroscopy, implanting cardiologist are enabled to directly interact with CMR data during the CRT implantation procedure (**Figure 3**). In this way, LV lead delivery may be guided away from scarred myocardium and towards an area with significant activation delay. The feasibility of this advanced CRT delivery strategy is explored in the second part of this thesis.

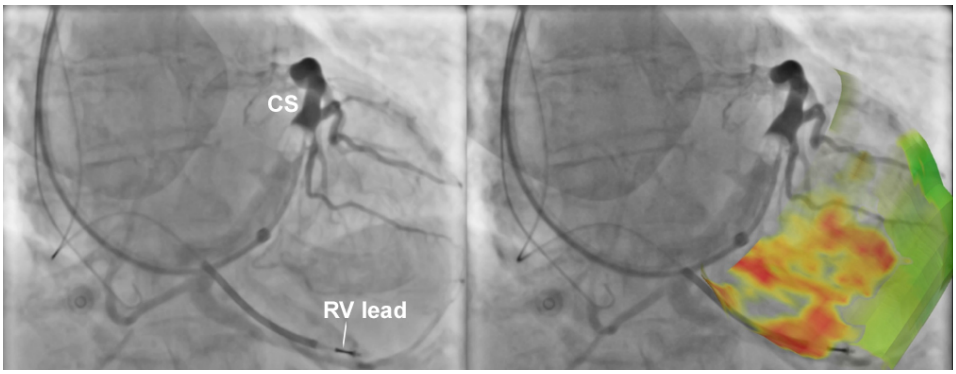


Figure 3. Fusion of 3D-cardiac magnetic resonance data with live-fluoroscopy. Fluoroscopic projections made during CRT implantation (**left**) with visualization of the coronary venous system/coronary sinus (CS) and the right ventricular (RV) lead. LV leads are placed in a tributary of the CS overlying the LV epicardium. Intraprocedural visualization (**right**) of scar transmurality (red-yellow) and delayed LV activation (green) derived from cardiac magnetic resonance imaging may help to guide the LV lead towards an optimal site for LV stimulation.

THREE OPTIMIZING DEVICE PROGRAMMING

A third strategy for ensuring the best possible outcome for patients undergoing CRT is the optimization of device programming. Several optimization strategies exist, these include individualized programming of the atrioventricular (AV) and interventricular (VV) delay, selection

of the most beneficial LV pacing electrode, or stimulation of the LV by multiple electrodes. AV delay optimization aims to acutely improve LV performance by allowing adequate LV diastolic filling, whereas VV delay optimization aims to improve cardiac function by synchronous LV contraction.[48,49] In addition, because current LV leads contain four electrodes on the distal end which are spaced several centimeters apart (quadripolar lead)(**Figure 4**), implanting cardiologist may choose to pace the LV with one of the four pacing electrodes (conventional biventricular pacing) or with multiple electrodes from a single quadripolar lead (multi-point pacing). Multipoint pacing (MPP) may lead to a more homogeneous electromechanical activation of the LV, and subsequently, may induce an additional improvement in cardiac function.[50] Optimizing device configurations can be performed with various tools (e.g. invasive measurements or echocardiography) and at different timings after implantation of a CRT device. One way to acutely assess the effect of different device configurations on cardiac performance is invasive hemodynamic testing.[51] Typically, the maximum rate of LV pressure rise (dP/dt_{max}) is used as an index of ventricular performance, for which a pressure guidewire is inserted in the LV cavity. Alternatively, pressure-volume (PV) loops can be obtained by the use of a conductance catheter inserted in the LV cavity. A major advantage of the PV loop approach is that they provide a more physiological insight in the total cardiac cycle with information on preload, afterload and contractility. Stroke work (which is the surface of the PV loop) incorporates all pressure and volume changes throughout the cardiac cycle and, therefore, provides a comprehensive appraisal of LV pump function.[51] In the third part of this thesis, we use PV-loop analyses to assess the effect of hemodynamic optimization of CRT device configurations.

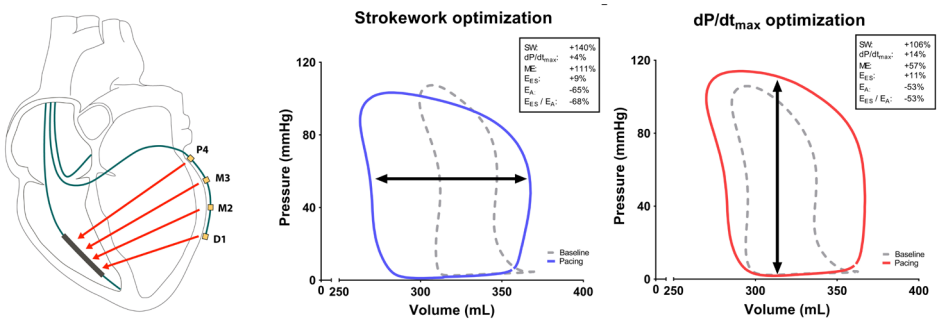


Figure 4. Acute hemodynamic testing of pacing configuration from a quadripolar lead. Quadripolar leads contain four electrodes (**left**) which can be used stimulated separately for stimulating the left ventricle or in combination (multi-point pacing, e.g. simultaneously from electrode D1 and P4). With pressure-volume (PV) loop analysis (**right**) the acute hemodynamic response of multiple pacing settings can be obtained. Dotted line represents the PV-loop during intrinsic rhythm, the blue and red curve display the effects of biventricular pacing at a pacing setting of interest on stoke work and $dPdt_{max}$. By calculating the differences in the dotted and colored curves, the effect of different device configurations on left ventricular function can be assessed. D1/M2/M3/P4 represent the four pacing electrodes of a quadripolar left ventricular lead.

THESIS OUTLINE

This thesis aims to provide more insight into the possibilities to better diagnose and treat patients with CRT by addressing several promising treatment-refinement strategies. The first part of this thesis focusses on the refinement of patient selection. In **Chapter 2** awareness is created for the shortcoming of electrocardiography-based patient selection that is currently proposed in international guideline recommendations. Furthermore, this chapter presents an overview of several existing and new strategies that may be used for the improvement of patient selection. In doing so, this chapter focusses primarily on the important patient subgroup displaying a non-LBBB QRS morphology, in whom CRT is becoming increasingly controversial. In **Chapter 3** we examine how the assessment of mechanical dyssynchrony may aid in the selection of patients for CRT. In a Dutch multicenter cohort, the added value of the STE-derived 'systolic rebound stretch of the septum' is investigated for its potential supplementary role over QRS morphology and 'visual dyssynchrony' in improvement of patient selection. Finally, based on the frequently observed better CRT response in women, especially in patients with intermediate QRS duration (120-150ms), previous work suggested more lenient CRT selection criteria in women.[52] To gain a deeper understanding of why women respond better to CRT **chapter 4** provides insight into sex-specific differences in the electrical substrate responsive to CRT and its contribution to the better CRT response in women. For this, the vectorcardiography-derived QRS area is used.

After selection of the right patient for CRT, a next key step for ensuring the best possible patient outcome is optimization of the LV lead position. In this respect, the second part of this thesis examines the role of image-guided LV lead delivery towards a pre-procedurally defined target site for LV pacing. In **Chapter 5**, we *retrospectively* assess the feasibility and potential benefit of a full CMR work-up for the pre-procedural identification of LV target sites (e.g. out of scar and in the area of latest contraction) in patients with an ischaemic cardiomyopathy. In **Chapter 6** we then demonstrate the feasibility of *intra-procedural visualization* of LV target sites to achieve real-time image-guided LV lead delivery. For this, multimodality imaging data from CMR scans (segmental scar distribution and mechanical activation delay) and computed tomography scans (course of the left phrenic nerve) is merged with live fluoroscopic projections made during CRT implantation.

After LV lead placement, multiple device settings are programmable to enhance the effect on CRT. The third and final part of this thesis focusses on the optimization of device settings by invasive hemodynamic testing. In **Chapter 7** we use pressure-volume loop analysis to make a direct comparison between dP/dt_{max} and stroke work-guided CRT optimization and relate acute

changes in hemodynamic parameters to long-term volumetric CRT response. The rationale behind this is that a standardized approach for invasive optimization is lacking and because previous work displayed that within an individual patient, changes in dP/dt_{max} and stroke work are often poorly correlated. In **Chapter 8** pressure-volume loop analysis is performed to assess the potential benefit of multipoint pacing (MPP) over biventricular pacing. In a patient cohort with strict LBBB we make a comparison between the optimal MPP setting versus the optimal biventricular pacing setting. To do so, all four electrodes during biventricular pacing are compared to multiple MPP settings, after optimization of the AV delay. Lastly, the effect of MPP is evaluated for specific subgroups to investigate which patient may benefit from MPP.

In the final chapter, **chapter 9**, the findings of this thesis are discussed and put in a broader perspective. Potential clinical implications and challenges still to overcome for refinement of CRT are discussed and suggestions for future research are proposed.

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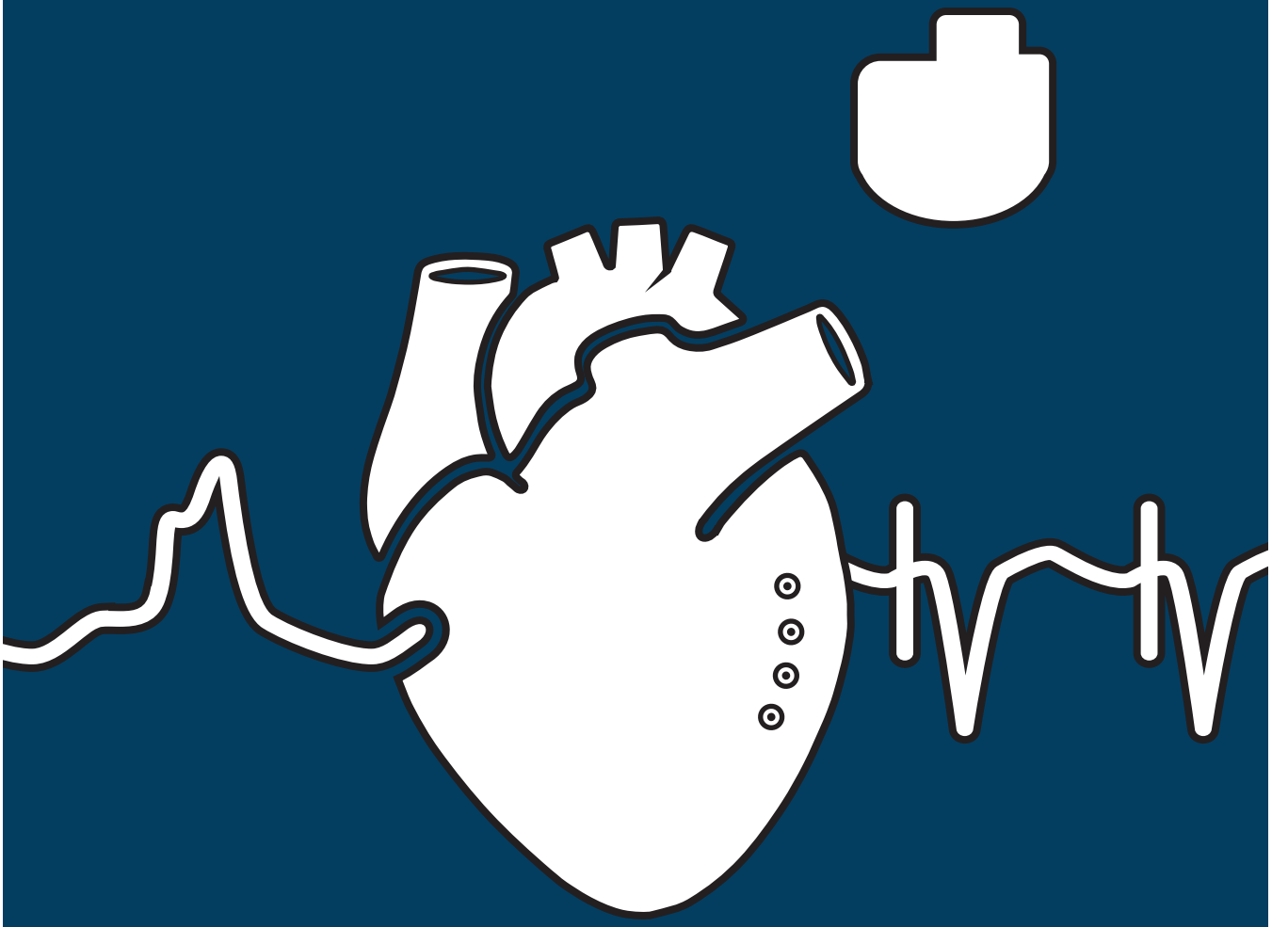
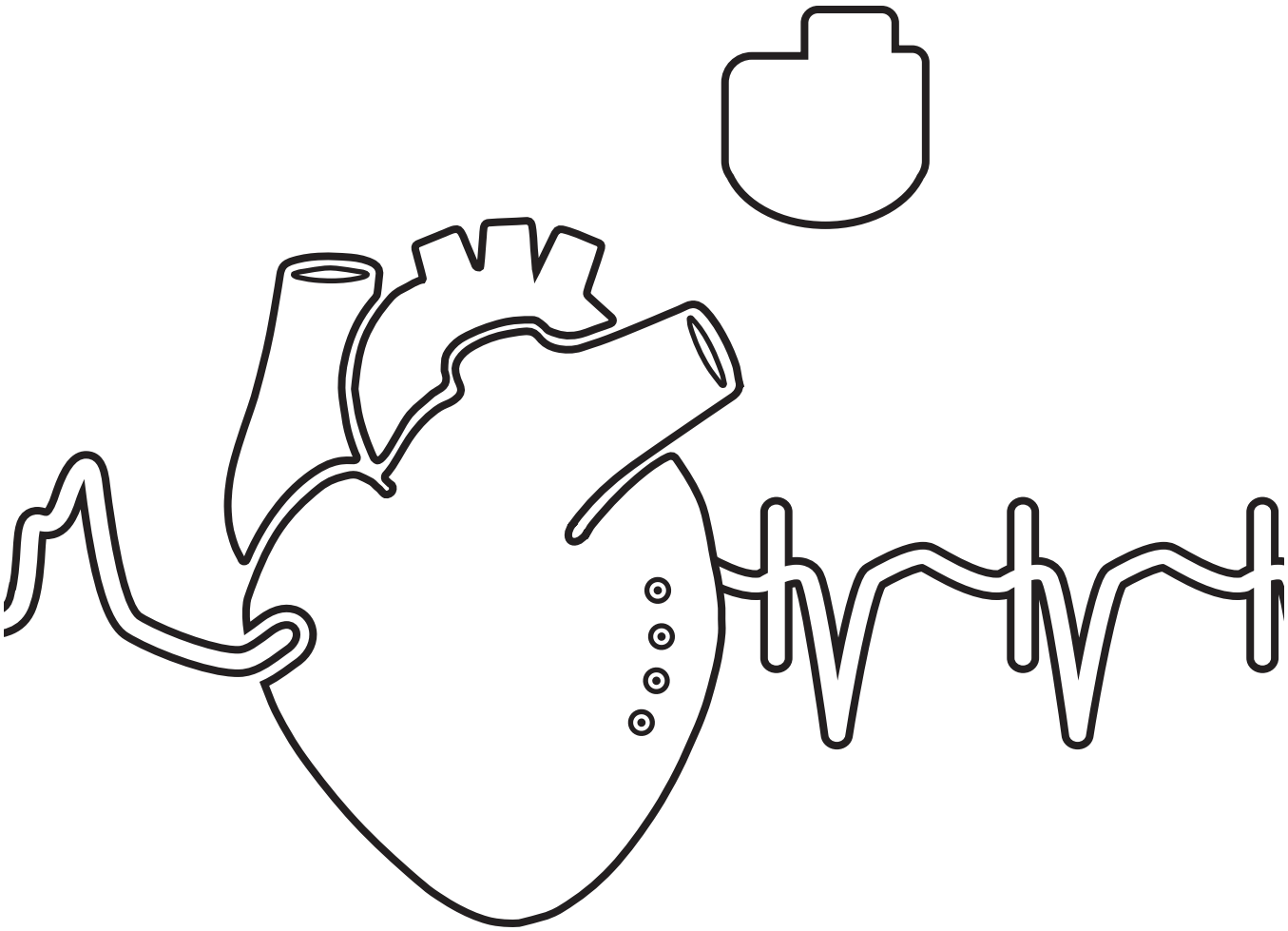
Part one

Refining patient selection

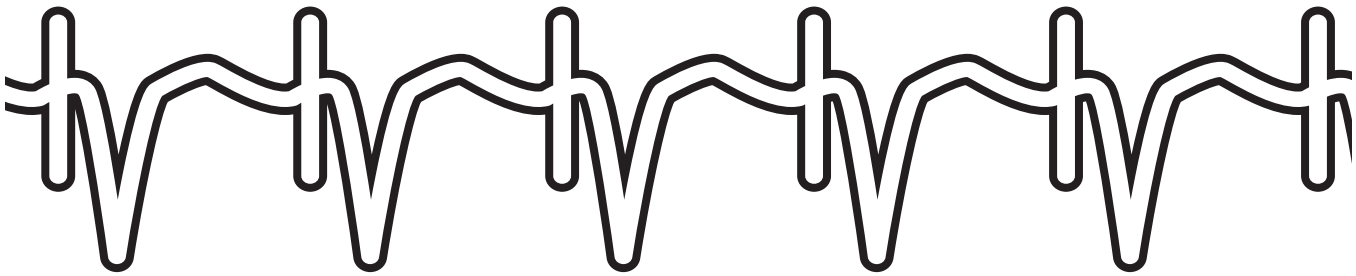




Chapter 2

Strategies to Improve Selection of Patients without Typical Left Bundle Branch Block for Cardiac Resynchronization Therapy

JACC: Clinical Electrophysiology 2020;6:129-142.



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ABSTRACT

Cardiac resynchronization therapy (CRT) is becoming increasingly controversial in patients without typical left bundle branch block (LBBB). Yet, several recent studies displayed that a distinct subpopulation of non-LBBB patients does benefit from CRT. Patients with non-LBBB should, therefore, not as a group be withheld a potentially very beneficial therapy. Unfortunately, current clinical practice lacks validated selection criteria that may identify possible CRT responders in the non-LBBB subgroup. Consequently, clinical decision making in these patients is often challenging. A few studies, strongly differing in design, have proposed additive selection criteria for improved response prediction in non-LBBB patients. There is accumulating evidence that more sophisticated echocardiographic dyssynchrony markers, taking into account the underlying electrical substrate responsive to CRT, can aid in the selection of patients with a non-LBBB who may benefit more favorably from CRT. Furthermore, it is important that cardiologists are aware of the shortcomings of current electrocardiographic selection criteria for CRT. While these provide an evidence-based approach for selecting patients for CRT, they do not necessarily guarantee the most optimal strategy for patient selection. Parameters obtained with vectorcardiography, such as QRS area, show potential to overcome the shortcomings of conventional electrocardiographic selection criteria and may improve response prediction regardless of QRS morphology.

INTRODUCTION

Cardiac resynchronization therapy (CRT) has shown major favorable effects on the treatment of patients with symptomatic heart failure, severe left ventricular (LV) dysfunction, and prolonged QRS duration. However, several sub-analyses of landmark trials and meta-analyses displayed that patients without a left bundle branch block (non-LBBB) QRS morphology benefit less from CRT than patients with an LBBB.[1–4] Non-LBBB is frequently encountered in the heart failure population, yet, only a fraction of CRT devices is implanted in patients with a non-LBBB. Approximately 12-18% of all CRTs are implanted in patients with non-LBBB and wide QRS complex (≥150ms), and only 9% of CRTs are implanted in non-LBBB patients with a relatively narrow QRS complex (130-149ms).[5] Response rates in these patients are poor with volumetric responders varying from 38-50% to 31-38% of patients, respectively.[5,6] Logically, the question arises whether to continue to implant CRT devices in heart failure patients with a non-LBBB. Yet, the group of patients with non-LBBB is very heterogeneous, consisting of patients with both right bundle branch block (RBBB) and interventricular conduction delay (IVCD) and with a considerable diversity of underlying myocardial substrates. Hence, it seems unreasonable to expect a consistent response to CRT in these patients. Indeed, recent trials displayed that a subgroup of patients with a non-LBBB QRS morphology does benefit from the therapy.[5,7,8] Striking is that current guideline recommendations are based on evidence that stems from subanalyses of studies which included limited patient numbers with RBBB and IVCD (**Figure 1**). The relevance of these subgroup analyses, therefore, should be questioned. Unfortunately, prospective randomized trials addressing the effect of CRT in patients with RBBB or IVCD are lacking. Consequently, deciding whether a patient with non-LBBB should be implanted with a CRT device often leads to clinical challenges.

This article reviews the current literature regarding the use of CRT in patients with non-LBBB QRS morphology and sets out to evaluate existing and new parameters that could be helpful for clinical decision making in this subgroup.

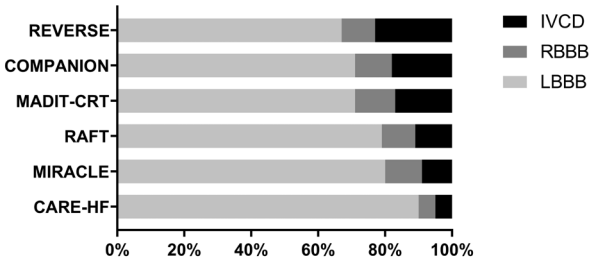

Figure 1. Percentage of patients included in CRT landmark trials based on QRS morphology. Current CRT guideline recommendations are based on evidence that stems from subanalyses from landmark trials which included only limited numbers of patients without LBBB. IVCD: intraventricular conduction delay, LBBB: left bundle branch block, and RBBB: right bundle branch block.

The pathophysiological mechanism for becoming a CRT responder

The assumed substrate for CRT is the existence of intrinsic left ventricular electrical dyssynchrony. Through a process called electrical-mechanical coupling, electrical dyssynchrony leads to mechanical inefficiency, a reduction in stroke work and the triggering of cardiac remodeling processes. Biventricular pacing, delivered by a CRT device, can improve electrical synchrony and, thereby, is able to improve mechanical efficiency and induce reverse remodeling[9]. Yet, it is imperative to realize that (bi)ventricular pacing by itself induces a stage of dyssynchronous electrical activation, especially at the level of the LV.[10] As a consequence, biventricular pacing can only be of benefit to patients with sufficient baseline electrical dyssynchrony. In patients with little or no electrical dyssynchrony, biventricular pacing will prolong total and LV activation times and hence cause iatrogenic electrical dyssynchrony, which will result in worsening of cardiac function and poor patient outcomes (**Figure 2**).[10] This has been highlighted by the results of the multicenter randomized LESSER-EARTH and ECHO-CRT trials, which included patients with narrow QRS duration and were both terminated prematurely due to safety concerns.[11,12] Being able to distinguish between patients that may or may not benefit from CRT, therefore, for a large part depends on establishing the existence of sufficient baseline electrical dyssynchrony. Currently, only parameters derived from the 12-lead electrocardiogram (ECG) are used for this purpose.

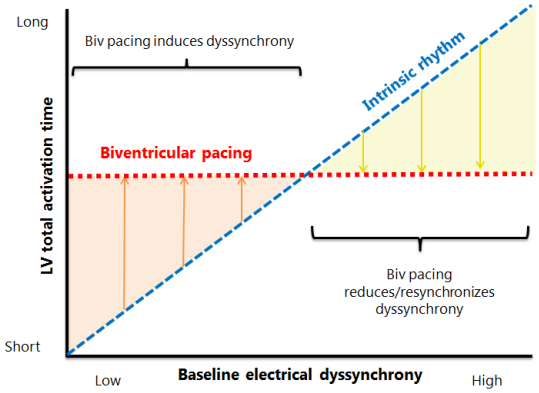

Figure 2. Effect of biventricular pacing on electrical dyssynchrony. Schematic illustration displaying the effect of biventricular pacing (dotted red line) on electrical dyssynchrony with regard to the level of intrinsic dyssynchrony during sinus rhythm (dotted blue line). In patients without or with little dyssynchrony (e.g. patients with narrow QRS complex morphology or RBBB) biventricular pacing induces dyssynchrony (orange arrows). In patients with high level of intrinsic dyssynchrony (e.g. patients with typical LBBB with QRS ≥150ms) biventricular pacing can revert or resynchronize dyssynchrony (yellow arrows). Based on the data from Ploux et at.[10] Biv: biventricular

Limitations of current electrocardiographic criteria for patient selection

When using current electrocardiographic guideline selection criteria to assess suitability for CRT, approximately one-third of all CRT-recipients do not respond to the therapy. A disadvantage of using parameters derived from the ECG is that they provide only a general overview of ventricular electrical activation abnormalities. The ECG, therefore, may not be the most optimal tool for determining the true electrical substrate for CRT.[6] Furthermore, it is noteworthy that multiple criteria exist to define LBBB on the ECG. These differ in their classification of patients and are not equally associated with clinical outcomes with regard to reverse remodeling, heart failure hospitalization, and survival rates. A recent retrospective multicenter study demonstrated that the frequency of LBBB in a CRT cohort of 316 patients, strongly depended on the ECG classification used, and varied from 29% for the AHA/ACC/HRS[13] criteria, to 47% for the ESC[14] criteria and 61% according to the Straus[15] criteria.[16] In addition, clinical outcomes after CRT varied greatly depending on the LBBB definition used. Among the LBBB definitions (AHA/ACCF/HRS, ESC[14], and Strauss), the association of LBBB definition and the combined study endpoint of heart failure and mortality was significant only for the ESC and the Straus definition (HR 0.61, 95% CI 0.43-0.87 and HR 0.57, 95% CI 0.40–0.80, respectively). The ESC definition also showed the strongest association with reverse remodeling (ECS 2013: OR 8.7, 95% CI 1.4–56.4). More striking perhaps is that defining LBBB, even when applying these specific criteria, seems subjective to personal interpretation. Furthermore, the interpretation of morphological criteria, such as notching and slurring, may be affected by the format and filtering of the ECG and the positioning of the lateral precordial leads.[17] A recent study revealed significant inter-observer (P range: 0.81-0.88, kappa range: 0.19-0.44), and to a lesser extent, intra-observer (P range: 0.87-0.95, kappa range: 0.47-0.74) variability in the classification of LBBB by the use of the various definitions (ESC, AHA/ACC/HRS, Strauss and MADIT).[17] Meaning that one in every five or six ECGs will be classified differently by different observers, and one in ten ECGs will be classified differently by the same observer, despite applying specific LBBB criteria.

With these results in mind, it should be appreciated that the exact LBBB definition used in a large proportion of the scientific publications on CRT is either not described or non-specific.[1,2] This is a problem since an important part of patients would have been classified differently when other LBBB criteria would have been applied, or when different observers would have scored the presence of LBBB in these trials.[16] This could explain why in a meta-analysis of 3782 individual patient data from five randomized key CRT trials (CARE-HF, RAFT, MIRACLE, MIRACLE-ICD, REVERSE) QRS morphology was not associated with response to CRT regards to morbidity and mortality.[18] Clearly, evidence regarding the relationship between LBBB and CRT response is somewhat clouded. Nevertheless, finding the patient that may have a most favorable response to CRT will possibly not depend on defining true LBBB on the ECG but on defining a dominant leftward

electrical delay. This dominant leftward electrical delay may be present or absent in patients classified as having an LBBB or non-LBBB.[10]

Visualising a dominant leftwards electrical delay

Comprehensive information regarding the underlying electrical activation patterns of the heart can be acquired with ventricular activation maps. Various techniques both invasive (e.g. three-dimensional electro-anatomical reconstruction contact or non-contact mapping) and non-invasive (electrocardiographic imaging or body surface mapping) allow for mapping of the electrical activation sequences.[19–21] Previous work that mapped the electrical activation of the ventricles exposed that in most patients with an LBBB there is a dominant leftward electrical delay.[20,22] This predominant leftwards electrical conduction delay is a fundamental component of the electrical substrate, which is amenable to CRT. Hence the greater benefit from CRT in LBBB patients. Still, some patients without a typical LBBB on the ECG may exhibit an electrical activation pattern that is very similar to that observed in typical LBBB patients. These patients have an underlying electrical substrate that may be responsive to CRT.[19–21]

Identifying the electrical substrate responsive to CRT in IVCD

Patients with IVCD generally exhibit more complex and heterogeneous ventricular activation patterns compared to patients with a typical bundle branch block on the ECG. These are often not primarily related to conduction system disease, but are predominantly caused by an underlying myocardial disease (e.g. ischemic).[22,23] Moreover, LV activation times in IVCD patients are generally shorter compared to LBBB patients and the location of the region of the latest electrical activation is highly variable. The absence of sufficient left ventricular electrical delay together with more extensive underlying myocardial disease likely results in the lower response rate observed in patients with IVCD.[19,20,22] Despite an overall poorer response to CRT in patients with IVCD, there appears to be great variability in CRT response in this subgroup. This seems only logical given the diversity of underlying substrates and pathophysiological mechanism involved in IVCD.[23] Several studies that mapped the ventricular activation sequences of heart failure patients displayed that conduction disturbance at a similar level of that observed in patients with LBBB may exist in 20-52% of patients that display an IVCD on the ECG.[19,20,23] Ploux et al demonstrated that visualizing these LBBB-alike ventricular activation sequences has the potential to be a useful tool for selecting IVCD patients who may benefit from biventricular pacing. The authors acquired both detailed ventricular activation maps (electrocardiographic mapping) and invasive LV pressure measurements (LV dP/dt) during baseline activation and biventricular pacing in patients with heart failure.[10] Baseline ventricular electrical uncoupling (defined as the difference between left and right ventricular mean activation time) was significantly correlated with acute

hemodynamic changes in both patients with LBBB and IVCD[10] and with clinical response to CRT (based on change in NHYA functional class and occurrence of major clinical events).[20]

Despite the positive results from studies that used ventricular activation maps for assessing the electrical substrate responsive to CRT, widespread clinical application of detailed electrical mapping is currently limited. This is because the existing techniques are time-consuming, and sometimes only possible during the CRT implant procedure. Unfortunately, identifying possible CRT responders using the 12-lead ECG is challenging in IVCD patients. A study that mapped the electrical activation sequences of hearts with IVCD showed that axis deviation, the presence of fascicular block and QRS duration did not differ between patients with and without delayed LV lateral wall activation.[19] Yet, a few studies suggested that specific ECG features might indicate an underlying electrical substrate responsive to CRT in IVCD patients.[1,23] In patients with a preexisting LBBB, a myocardial infarction might alter the typical LBBB morphology into an 'atypical' LBBB (e.g. with QS complex in the anterior leads and a QR wave in V5/V6). The electrical activation sequence of this patient can be assumed to be very close to that of a patients with a typical LBBB, and very different from a patient with a widened QRS complex but relatively unchanged QRS morphology. Consequently, an atypical LBBB might –despite the presence of myocardial scar- indicate an underlying substrate better amendable by CRT. In an analysis of the MADIT-CRT trial, Zareba et al observed that IVCD patients with LBBB features (defined as: predominantly negative QRS morphology in leads V1-V3/V4 and Q-waves in V5/V6 or without significant conduction delay in V5/V6) may obtain some benefit after CRT.[1] When the authors combined the LBBB patients with the IVCD patients displaying LBBB-like features, the hazard ratios for heart failure episode or death changed from 0.47 to 0.55 ($p<0.001$) which still is a very significant reduction in the risk for heart failure or death. In addition, recently published data of 11 505 non-LBBB CRT-eligible patients from the National Cardiovascular Data Registry ICD registry, displayed that CRT implantation appeared to be associated with better outcomes compared to ICD therapy alone in IVCD patients with a QRS duration of ≥150ms, but not in patients with QRS<150ms or an RBBB of any QRS duration.[24] Yet, the nonrandomized retrospective study design, unclear definition of LBBB and unclear reasons why certain CRT-eligible patients did not receive a CRT prevent the drawing of firm conclusions. An ongoing double-blind multi-center randomized controlled trial comparing a CRT ON versus CRT OFF in IVCD patients will add substantial knowledge to the modest amount of existing data on CRT in patients with IVCD and should reduce uncertainties for guidelines and clinical practice.[25]

Identifying the electrical substrate responsive to CRT in RBBB

In patients with RBBB, the earliest ventricular activation is located in the LV myocardium, while the electrical activation of the right ventricle occurs slowly.[26] The absence of significant LV conduction delay in RBBB may explain why conventional CRT in these patients induces, rather than resolves, electrical dyssynchrony. This has been exposed by preclinical research and computer simulations assessing the hemodynamic consequences of pure RBBB failing hearts.[26,27] Still, in some patients displaying a RBBB on the ECG, both right and left sided ventricular conduction systems can be affected.[21] This was demonstrated in a case report series by Fantoni et al, who in 2005 performed detailed three-dimensional invasive electro-anatomic mapping of the electrical activation patterns of six RBBB and 94 LBBB failing hearts.[21] Interestingly, total and regional LV endocardial activation times were not significantly different between RBBB and LBBB patients.[21] From this observation the authors hypothesized that some patients exhibiting an RBBB on the ECG might have an underlying substrate responsive to CRT. Computer simulations using the CircAdapt model later indeed established that in an RBBB model, stroke work only improves in the presence of sufficient co-existing LV conduction delay.[26] This data further fuels the concept that RBBB patients with a coexisting LV activation delay may respond to CRT.

A few studies over time suggested that a specific ECG pattern resembling RBBB can be used to identify RBBB patients with a coexisting LV activation delay. This pattern has first been introduced by Rosenbaum et al in the 1960s as "RBBB masking LBBB", characterized by a broad slurred R wave in leads I and aVL, together with a left axis deviation.[28] A few decades later, Tzogias et al reported on the electrocardiographic consequences of transient RBBB occurring during right heart catheterization in patients with LBBB compared to patients with either normal QRS complexes or left fascicular block.[29] While patients with a normal baseline QRS complex or left fascicular block developed a typical RBBB after catheter trauma to the right bundle, patients with baseline LBBB developed an atypical RBBB pattern (with RBBB pattern in lead V1 and absent significant S wave in the lateral leads I and aVL) (**Figure 3).** The authors hypothesized that an atypical RBBB may be an indication of a coexisting left bundle branch *delay*. An atypical RBBB could, therefore, be an electrocardiographic pattern that identifies possible CRT responders within a group of patients with RBBB. A retrospective multicenter study recently tested whether this atypical RBBB pattern could identify possible CRT responders within a group of 66 patients exhibiting a RBBB morphology.[8] Patients with an atypical RBBB at baseline (absent S wave in leads I, aVL) indeed showed significantly longer LV electrical delay measured as the QLV-interval (the interval from the onset of the intrinsic QRS on the surface ECG to the first large peak of the LV electrogram) (QLV 111.9±17.6ms and 73.2±15.4ms, p=0.001). At follow up, these patients also had significantly improved echocardiographic (71.4% vs 19.4%, p=0.001) and clinical outcome at 2 years follow

up after CRT implantation compared to patients with typical RBBB (**Table 1**).

Another characteristic on the RBBB-ECG that has been suggested as possible indicator for the presence of a leftward conduction delay is co-existence of a left hemiblock. Two previous studies that assessed the effect of a coexisting left hemiblock on CRT volumetric response in patients with an RBBB showed conflicting results.[30,31] Moreover, according to a MADIT-CRT substudy, there was no difference in the 3-year crude event rates for death or heart failure among RBBB patients with baseline left anterior hemiblock (22%), non-left anterior hemiblock (21%) who received a CRT, or patients who received ICD-only therapy (20%) (p=0.24) (**Table 1**). The heterogeneity on outcomes with CRT in RBBB with left anterior hemiblock probably can be explained by the fact that this ECG pattern can be caused either by primary conduction system disease, with associated mechanical dyssynchrony, or by an infarction of the proximal left anterior descending coronary artery, in which a classical mechanical dyssynchrony pattern of opposing wall motion is often absent.[32]

Despite the limited amount of studies performed on this subject, it is clear that pure RBBB without significant electrical delay of the LV is not a substrate that should be treated with CRT. RBBB with a significant leftwards electrical delay can be established with ventricular activation maps. Unfortunately, it remains uncertain how these patients can best be identified using the ECG. An atypical RBBB pattern, with absent significant S wave in the lateral leads I and aVL, may be useful as additive selection criteria in this subgroup, yet this parameter warrants further investigation in prospective trials.[29]

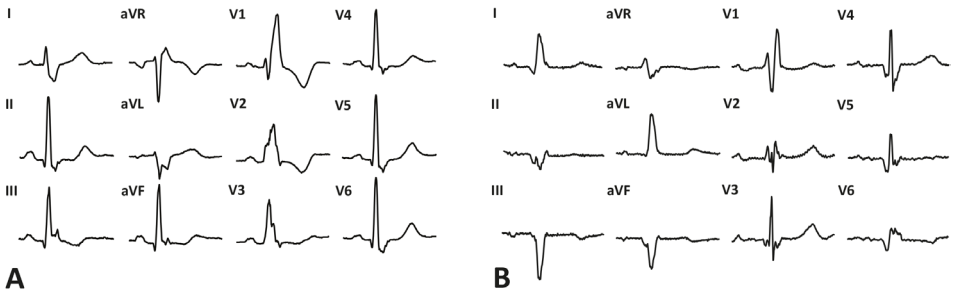

Figure 3. Right bundle branch block variants. A: Typical right bundle branch block (RBBB): RBBB pattern in precordial leads with characteristic wide S in lateral lead I and aVL. **B:** Atypical RBBB: RBBB pattern in precordial leads with absent S wave in lead I and aVL and co-existing left axis deviation. Note the co-existing PR prolongation due to delayed activation over the left bundle.

Table 1. Prognostic value of ECG-derived characteristics in RBBB

Study	Chandra et al. 2010[30]	Tompkins et al. 2013[26]	Pastore et al. 2017[8]
Design	Single-center, retrospective	Multicenter, post-hoc analysis (MADIT-CRT)	Multicenter retrospective
Inclusion period	Not described	2004-2008	2011-2017
No of patients **Typical RBBB** **Atypical RBBB**	44 18 26	219 52 80	66 31 35
Definition for atypical RBBB	Presence of co-existing left anterior or posterior fascicular block	Presence of left anterior fascicular block	Absence of characteristic S waves in I, AVL.
Long term outcome data	Not collected	**HR of association between (atypical) RBBB and heart failure or death** - Atypical RBBB: * HR 1.76 (95% CI 0.71-4.35) - Typical RBBB: * HR 1.94 (95% CI 0.71-5.31)	**Number of patients with reduction in NYHA class, no heart failure hospitalization or death** - Atypical RBBB: 71.4% - Typical RBBB: 29.0% *p*-value=0.001
Volumetric response	**Mean LVEF change per group** - Atypical RBBB: Δ LVEF +5,4% - Typical RBBB: Δ LVEF -1% *p*=0.0031	**Between group differences in LVEF change and LVESV change** CRT in typical RBBB vs CRT in atypical RBBB: Δ LVEF : +3%, *p*=0.008 ΔLVESV = -7%, *p*= 0.019 CRT in typical RBBB vs ICD only: ΔLVEF = +6%, *p*<0.001 ΔLVESV = -17%, *p*<0.001	**Number of patients with LVESV change≥15%** - Atypical RBBB: 71.4% - Typical RBBB : 19.4% *p*=0.002
Follow-up	6 months	36 months	24 months

*Adjusted HR for relevant covariates (not specified). HR reported for patients treated with a CRT-defibrillator compared to patients treated with ICD-only.
CRT: cardiac resynchronization therapy, HR: hazard ratio, ICD: implantable cardioverter defibrillator, LVEF: left ventricular ejection fraction, LVESV: left ventricular end systolic volume, RBBB: right bundle branch block.

Atrioventricular dyssynchrony as electrical substrate for CRT?

The beneficial effect of CRT is often thought to be attributed to ventricular resynchronization. Interestingly, recent work suggested that the existence of atrioventricular dyssynchrony, represented by prolongation of the PR interval on the ECG, is a potential target for CRT.[33] Proper atrioventricular coupling is of major importance for efficient pump function. Loss of atrioventricular coupling leads to elevated LV end-diastolic pressure, diastolic mitral regurgitation and reduced stroke work. Heart failure is often accompanied by atrioventricular conduction disturbances, which, in a heart failure population, are associated with an increased risk for adverse outcomes (e.g. atrial fibrillation, heart failure hospitalization and death).[34] It is therefore not surprising that several non-randomized trials exhibited worsened outcomes after CRT in patients with prolonged PR compared to patients with normal PR.[35,36] In a large medical registry of CRT-eligible patients that were implanted with a CRT defibrillator or an ICD, the beneficial effect of CRT was confined to patients with a normal PR interval and was absent in patients with prolonged PR, even when these patients had an LBBB.[35] Unfortunately the reasons why CRT-eligible patients were implanted with a CRT or ICD in this registry are unknown. Interestingly, on the other hand, are the results of several subanalyses of the COMPANION and MADIT-CRT trial, which showed a reduction of the risk of all-cause mortality and heart failure hospitalization in CRT patients with prolonged PR interval.[7,37,38] Two sub-analyses of the MADIT-CRT trial, that focused exclusively on non-LBBB patients, displayed that CRT reduced the risk of all-cause mortality and heart failure hospitalization in non-LBBB patients with prolonged PR interval (HR, 0.27 95% CI 0.13–0.57, p<0.001) Contrastingly, in non-LBBB patients with normal PR interval CRT therapy was associated with a trend towards an increased risk compared to ICD only therapy (HR 1.45 95% CI 0.96–2.19, p=0.078), and a significantly 2-fold higher mortality (HR 2.14 95% CI 1.12-4.09, *p*=0.022), which was sustained at long-term follow-up.[7,39] These results suggests that the potential unfavorable effects of biventricular pacing in non-LBBB patients could be overruled by the restoration of atrioventricular coupling in a subgroup of patients with prolonged PR interval.

The small number of studies, critically differing in design and outcome measures currently prevents the drawing of firm conclusions regarding atrioventricular dyssynchrony as electrical substrate responsive to CRT. Further clinical studies are needed to assess whether atrioventricular dyssynchrony is an electrical substrate that can be corrected with CRT especially in patients without a typical LBBB.

Prognostic value of mechanical dyssynchrony markers in non-LBBB

Due to electro-mechanical coupling it seems plausible that abnormal electrical activation coincides with abnormal contraction patterns. However, several multicenter studies, like PROSPECT and ECHO-CRT, were not able to show additive benefit of the use of echocardiographic

markers for predicting the outcome of CRT.[11,40] It is, therefore, interesting that recent data has presented a few emerging echocardiographic dyssynchrony parameters that show promising results for improving CRT response prediction.[41,42] These new indices consist of (relatively complicated) strain-based speckle tracking echocardiography (STE) derived dyssynchrony parameters, and of the (simple) visual assessment of dyssynchrony (eyeballing) (**Figure 4**).

Two recent subanalyses of large international multicenter studies revealed that the presence of mechanical dyssynchrony can improve the prognostic value of guideline-based patient selection for CRT.[5,42] One of these studies analyzed patient data of the PREDICT-CRT database and evaluated the potential additive prognostic value of echocardiographic septal flash and apical rocking for the different CRT guideline recommendation classes.[5] The presence of apical rocking and/or septal flash at baseline was associated with lower all-cause mortality (HR 0.30, 95% CI 0.24–0.39; $p<0.0001$) for the entire cohort, but, interestingly also for patients with intermediate ECG criteria according to the American and European guideline recommendations[43,44] (American: HR 0.52 95%-CI 0.35-0.77 for Class II, Level of Evidence: A patients [LBBB 120-149ms or non-LBBB≥150ms]. European: HR 0.47 95%-CI 0.27–0.82 for Class II, Level of Evidence: A patients [non-LBBB QRS≥150ms], and HR 0.35, 95%-CI 0.14–0.87 in Class II, Level of Evidence: B patients [non-LBBB QRS<150ms]). Additionally, adding mechanical dyssynchrony as selection criterion coincided with a significantly higher percentage of volumetric responders (≥15% reduction in LVESV) compared to patient selection based on QRS duration and morphology alone (77% versus 65%

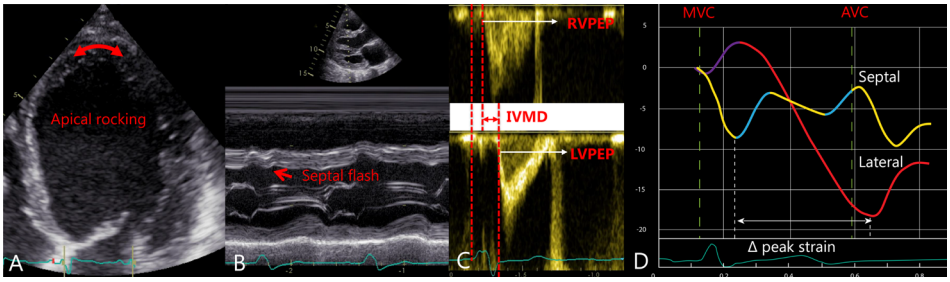

Figure 4. Echocardiographic mechanical dyssynchrony indices. A: Apical Rocking: apical transverse motion (apical four-chamber view), occurs due to an early septal contraction which moves the apex towards the septum, while delayed lateral wall contraction subsequently 'rocks' the apex towards the lateral wall. **B:** Septal flash: Short inward motion of the septum caused by early septal contraction and interrupted by the delayed activation of the lateral free wall. **C:** Interventricular Mechanical Delay: Difference in onset of outflow of pulsed-wave Doppler signal of left ventricular (LVPEP) and right ventricular outflow tract (RVPEP). **D:** strain curves of the LV septal and lateral wall displaying the difference between timing based dyssynchrony measures (Δpeak strain delay which is the timing difference of peak strain values of the left ventricular septal and lateral or posterior wall) and strain patterns that are specific to the electrical substrate responsive to CRT. These strain patterns consist of the systolic pre-stretch of the lateral wall (purple), systolic rebound stretch of the septum (blue) or the combination of both, which, covers all LV stretching during systole (systolic stretch index: purple + blue). AVC: aortic valve closing, IVMD: interventricular mechanical delay, LVPEP: left ventricular pre-ejection time, MVC: mitral valve closing, RVPEP: right ventricular pre-ejection time.

in LBBB, 75% versus 50% in non-LBBB with QRS 130-149ms and 62% versus 38% in non-LBBB patients with QRS≥150ms).[5] (**Table 2**)

Complementary to this work are data from a recently published substudy of the multicenter Adaptive-CRT trial.[42] When assessing the STE-derived dyssynchrony parameter '*systolic stretch index*' (SSI), the authors found a strong association between baseline dyssynchrony and clinical outcome after CRT in patients with a QRS duration of 120-149ms or non-LBBB (Class II indication according to American guideline recommendations[43]). This was observed for SSI derived from both longitudinal and circumferential strain curves (HR 2.08 95% CI 1.27-3.42, and HR 2.13 95% CI 1.24-3.67, respectively)(**Table 2**). In Kaplan-Meier survival analysis, patients with a QRS 120-149 or non-LBBB (Class II American guidelines) and high SSI even had nearly identical outcomes compared to patients with LBBB and QRS≥150ms (Class I American guidelines).[42] In line with the aforementioned analyses, a prospective single-center study reported similar positive effects of mechanical dyssynchrony at baseline on volumetric and clinical CRT response in patients with non-LBBB.[45] Mechanical dyssynchrony (defined as interventricular mechanical delay of ≥40ms and a septal-to-posterior radial peak strain delay of ≥130ms assessed with STE-strain curves) was present in 28-52% of non-LBBB patients. Yet, despite these promising results, not all studies focusing on the association of mechanical dyssynchrony parameters with CRT response found that non-LBBB patients with mechanical dyssynchrony have improved outcomes. A retrospective multicenter study with 137 non-LBBB patients did not show a lower incidence of death, transplant or LV assist device (adjusted HR 0.66 [0.32-1.36], p=n/s) when mechanical dyssychrony was present.[46] (**Table 2**) It should, however, be noted that the authors used exclusively timing based STE dyssynchrony parameters (Δ Time to peak septal to posterior wall strain ≥130ms) for CRT response prediction. Time-to-peak indexes of dyssynchrony have been shown to be inferior to the assessment of a specific strain-based contraction pattern (e.g. early systolic shortening of the septum and pre-stretch of the lateral wall) by Risum et in a prospective multicenter study of 208 CRT patients.[47] The reason for lack of predictive ability of timing-based dyssynchrony parameters, such as, time to peak strain, has been further exposed by computer simulations.[48] Via these stimulations, Lumens et al displayed that different myocardial substrates exist that may lead to some degree of LV mechanical dyssynchrony. These substrates include electrical substrates, which are generally responsive to CRT, and non-electrical substrates, such as hypocontractility and myocardial scar, which do not respond to CRT. All three substrates are likely to exist in patients with heart failure. Interestingly, computer simulations showed that both electrical and non-electrical substrates cause time-to-peak mechanical delay, yet, the strain pattern of mechanical dyssynchrony differs considerable between electrical and non-electrical substrates. These findings nicely illustrate that time-to-peak dyssynchrony measures are not specific to the electrical substrates responsive to CRT, and therefore, they are not likely to be effective for selecting patients

Table 2. Additive prognostic effect of echocardiographic dyssynchrony markers on CRT respons in non-LBBB

Study	Hara et al. 201245	Bank et al. 201546	Beela et al. 20185	Gorcsan III et al. 201942
Design	Prospective, single-center	Retrospective, multicenter	Substudy of multicenter PREDICT-CRT database	Substudy of multicenter Adaptive CRT
Inclusion period	Not described	Not described	1999-2012	2009-2010
No of patients **LBBB** **Non-LBBB**	278 128 126	318 181 137	1060 687 87	428 321 107
(non) LBBB definition	According to definition used in the MADIT-CRT trial (ref)	From automated computer analysis of ECGs and review of electrophysiologist notes prior to CRT implantation	Not described	Not described
Dyssynchrony parameter	1: IVMD≥40ms 2: ΔTime to peak Septal to posterior wall ≥130ms	1: Δtime to peak septal to posterior wall strain ≥130ms	1: Presence of apical rocking and/or septal flash	Systolic Stretch Index (SSI) 1. Longitudinal SSI ≥2.6 2. Circumferential SSI ≥3.2 3. Radial SSI ≥7.3
Long term outcome data	**Dyssynchrony and survival free of heart transplant and LVAD**	**Dyssynchrony and occurrence of death, heart transplant or LVAD**	**Dyssynchrony and occurrence of all-cause mortality**	**Dyssynchrony and survival free of HF hospitalization**
HR [95%-confidence interval] reported on the presence of dyssynchrony with long-term outcome*	Unadjusted HR 1: 4.88 [2.60-9.16], *p*=0.0007 2: 2.58 [1.47-4.53], *p*=0.0008 in non-LBBB cohort Adjusted HR (for QRSd and ICM) 1: HR 2.5, *p*=0.002 2: HR 5.34, *p*=0.002 in non-LBBB cohort	Adjusted** HR 1: 0.66 [0.32-1.36] in non-LBBB cohort Adjusted** HR 1: 0.52 [0.28-0.99], *p*=0.047 in Class II° cohort	Unadjusted HR 1: 0.21 [0.15-0.30] p<0.0001 in Class I† cohort 1: 0.47 [0.27-0.82], *p*=0.007 in Class IIa† cohort 1: 0.35 [0.14-0.87], *p*=0.020 in Class IIb† cohort	Unadjusted HR 1: 2.08 [1.27-3.42], *p*=0.004 2: 2.13 [1.24-3.67], *p*=0.006 3: 1.36 [0.81-2.29], *p*=0.25 in Class II° cohort **Dyssynchrony and survival** Unadjusted HR 1: 5.08 [1.94-13.31]. p<0.001 2: 3.00 [1.26-7.13], *p*=0.013 3: 1.90 [0.85-4.27], *p*=0.12 in Class II° cohort

Volumetric response:	**Pre- versus post implantation LVEF**	**Change in LVEF and LVESV at follow-up**	**Percentage of patients with ≥15% reduction in LVESV at follow-up**	No echocardiographic follow-up data analyzed
	- *Dyssynchrony present*: 23+6% vs 31+10%, p< 0.001 - Dyssynchrony absent : 25+6% vs 27+8%, *p*=0.151 (in non-LBBB cohort)	*Dyssynchrony present vs absent* - LVEF: 8.8±9.4% vs 6.1±9.7%, *p*=0.04 - LVESV: -30±41ml vs -10±30ml, p<0.01	*Dyssynchrony present*: Class I†: 77% Class IIa†: 75% Class IIb†: 62 *Dyssynchrony absent*: Class I†: 15% Class IIa†: 8% Class IIb†: 17%	
Follow-up	48 months	n/a	59 months [37-86]	2 years

CRT: cardiac resynchronization therapy, HF: heart failure, ICM: ischemic cardiomyopathy, IVMD: intraventricular mechanical delay, LBBB: left bundle branch block, LVAD: left ventricular assist device, LVEF: left ventricular ejection fraction, LVESV: left ventricular end systolic volume, QRSd: QRS duration

* Hazard ratios are reported for the association of mechanical dyssynchrony with either the occurrence of survival (with corresponding HR>1) or the occurrence of all-cause mortality (with corresponding HR<1)

**Adjusted for age, gender, HF aetiology, systolic blood pressure, diabetic status, serum creatinine, β-blocker usage, ACE inhibitor or ARB usage, aldosterone antagonist usage and EF

° According to American AHA/ACCF/HRS guideline recommendations[43] (Class II: QRS 120-149 or non-LBBB QRS>150ms)

† According to European Society for Cardiology guideline recommendations Classes[14] (Class I: LBBB, Class IIa: nonLBBB QRS≥150, Class IIb: nonLBBB QRS 130-149)

that may benefit from CRT. This could explain why several multicenter studies that primarily used timing-based dyssynchrony measures, such as PROSPECT and ECHO-CRT, found that (timing-based) measures of dyssynchrony were not able to improve patients selection for CRT.[11,40] Implementation of specific strain patterns, on the other hand, may improve patient selection because they are specific to the electrical substrate responsive to CRT. These strain patterns consist of the systolic pre-stretch of the lateral wall (caused by an early septal contraction), systolic rebound stretch of the septum (caused by delayed lateral wall contraction) or the combination of both, which, covers all LV stretching during systole (systolic stretch index: SSI).[41,48] (**Figure 4**)

To conclude, there is increasing evidence showing that more sophisticated mechanical dyssynchrony measurements, taking into account the underlying electrical substrate responsive to CRT, can aid in the selection of patients who may benefit more favorably from CRT. Nonetheless, since current evidence stems primarily from retrospective studies, randomized trials with sufficient power are still needed to determine whether mechanical dyssynchrony parameters can indeed improve response prediction, and which parameter is most robust and feasible.

Future directions in patient selection

The demand for an easy, widely applicable and non-invasive robust parameter to assess suitability for CRT has led to renewed interest in vectorcardiography (VCG). VCG is a method for recording 3-dimensional information regarding the magnitude and direction of the electrical forces generated by the heart **(Figure 5)**. The area under the 3-dimensional QRS-complex (QRS area) and 3-dimensional T-wave (T area) are assumed to reflect unopposed electrical forces during ventricular depolarization and repolarization respectively. In particular, the QRS area, but also T area and sum of QRS- and T-area (QRST area), have been shown to be strong predictors of volumetric response and survival after CRT.[49,50] Both retrospective analyses and prospective studies have recently evaluated QRS area as a predictor for CRT response. All of these trials demonstrated QRS area to be strong predictor of CRT response, superior even to QRS duration and morphology.[6,49,51,52] (**Table 3**) One retrospective multicenter study displayed that this was not only true for a whole cohort of patients that received CRT but, interestingly, also for patients without a class I indication for CRT according to American guideline recommendations[43] (QRS 120-149ms or non-LBBB).[6] In these patients, only the QRS area was significantly associated with all-cause mortality(adjusted HR 0.49 95% CI 0.34-0.71). With regard to volumetric CRT response, both QRS area and LBBB morphology were associated with an LVESV reduction of ≥15% (adjusted OR, 1.70 95% CI 1.05–2.76, and adjusted OR 2.02 95% CI 1.12–3.62, respectively).[6] Yet, some caution should be taken when interpreting these results since patient data was retrospectively analyzed.

It is noteworthy that the combination of vectorcardiographic QRS area, and echocardiographic

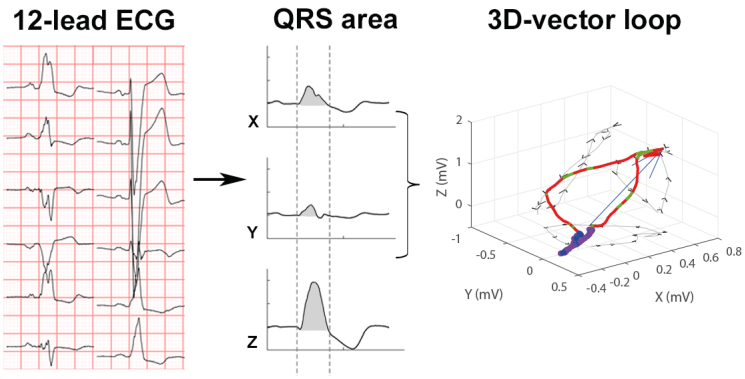

Figure 5. Vectorcardiography derived from the ECG displaying the 3-dimensional vector loop of electrical activation. Vectorcardiography recording 3-dimensional information regarding the magnitude and direction of the electrical forces generated by the heart. The 3-dimensional vector loop is created by conversion of the 12-lead ECG by the Kors method.

dyssynchrony indices may improve CRT response prediction even further. This was demonstrated in a multicenter prospective trial, in which QRS area and echocardiographic dyssynchrony markers (apical rocking and intraventricular mechanical delay) were associated to volumetric CRT response in multivariable analysis -whereas QRS duration or QRS morphology were not- and also predicted clinical outcomes assessed by heart failure hospitalizations and all-cause mortality[52]

Although not yet commercially available in clinical practice, QRS area seems to be a promising alternative selection criterion for identifying possible CRT responders. QRS area could possibly also be of use in a subgroup of patients with non-LBBB. The VCG can be derived from commercially available ECG machines, allowing markers such as QRS area to be provided without additional recordings or leads.[53] The advantage of QRS area is that it is an observer-independent parameter whereas the definition for LBBB is operator-dependent. Like QRS duration, QRS area is a continuous variable, but variability in its measurement is likely to be less since it is largely determined by QRS complex amplitude and not the beginning and end of the QRS complex.[6]

CONCLUSIONS

Current electrocardiographic selection criteria for CRT have shortcomings since various definitions for LBBB exist, which are subjective to personal interpretation and are all differently associated with outcomes. In daily practice, this presumably leads to a suboptimal patient selection. There is accumulating evidence that the presence of baseline dyssynchrony on echocardiography (apical

Table 3. Prognostic value of VCG derived QRS area versus conventional guideline selection criteria in overall CRT population

Study	Deursen et al 2015[51]	Emerek et al 2018[49]	Stipdonk et al 2018[6]
Design	Prospective, single center	Retrospective, single center	Retrospective, multicenter
Inclusion period	Not described	2006-2015	2001-2015
No. patients	81	705	1462
Dyssynchrony parameters tested	1.QRS area ≥98 µVs 2. QRSduration>156 3. LBBB AHA/ACCF/HRS 4. LBBB Straus 5. LBBB MADIT-CRT	1.QRSarea ≤95 µVs 2. QRSduration<150ms 3. LBBB (nonstrict)	1: QRS area (quartiles) 2:LBBB ESC + QRS duration
Long term outcome data HR [95%-confidence interval] of electrical dyssynchrony with long-term outcome	Not collected	**All-cause mortality, Htx, LVAD** Unadjusted HR 1: 2.11 [1.68-2.65], *p*=0.02 2: 1.44 [1.14-1.81], *p*=0.002 3: 1.66 [1.22-2.27], *p*=0.001 Adjusted* HR 1:1.65 [1.25-2.18], p<0.001 2: 1.27 [0.91-1.77], p=0.15 3: 0.87 [0.58-1.31], p=0.51	**Survival free from Htx or LVAD** Adjusted HR† 1: 0.75 [0.69-0.83], p<0.001 2: 0.93 [0.69-1.02], p= 0.134 **HF hospitalization <1 year after implantation** Adjusted HR† 1: 0.76 [0.60-0.96], p=0.019 2: 0.96 [0.76-1.21], p=0.711
Volumetric response OR [95%-confidence interval] of electrical dyssynchrony on volumumetric response	**LVESV reduction ≥15%** Unadjusted OR: 1: 10.2 [3.4-31.1] 2: 2.5; [0.9-6.6] 3: 4.5; [1.6-12.6] 4: 10.0 [3.2-31.1] 5: 5.5 [0.9-32.4]	Not collected	**LVESV reduction ≥15%** Adjusted OR† 1: 1.65 [1.43-1.90], p<0.001 2: 1.29 [1.09-1.52], p=0.002
Follow up	± 6 months	3.1 (1.8-5.4) years	3.4±2.4 years

LBBBB left bundle branch block according to: AHA/ACCF/HRS: American Heart Association/American College of Cardiology/Heart Rhythm Society[13], ESC: European Society of Cardiology[14], Straus criteria [15] and criteria used in MADIT-CRT[1]. HR: Hazard ratio, Htx: heart transplant, LVAD: Left ventricular assist device, OR: odds radio
*HR adjusted for QRS duration and morphology, age, sex, ischemic heart disease, and atrial fibrillation/flutter
† HR adjusted for sex, age, cardiomyopathy, atrial fibrillation, device type, LV lead, position, baseline New York Heart Association, baseline ejection fraction, and medication.

rocking, septal flash, systolic stretch index) can identify volumetric and clinical responders. A promising and observer-independent new electrocardiographic marker, which could improve response prediction irrespective of QRS morphology is the VCG-derived 'QRS area'. In current clinical practice, these tools could especially be useful for selecting patients without a typical LBBB on the ECG, but with a possible underlying substrate responsive to CRT.

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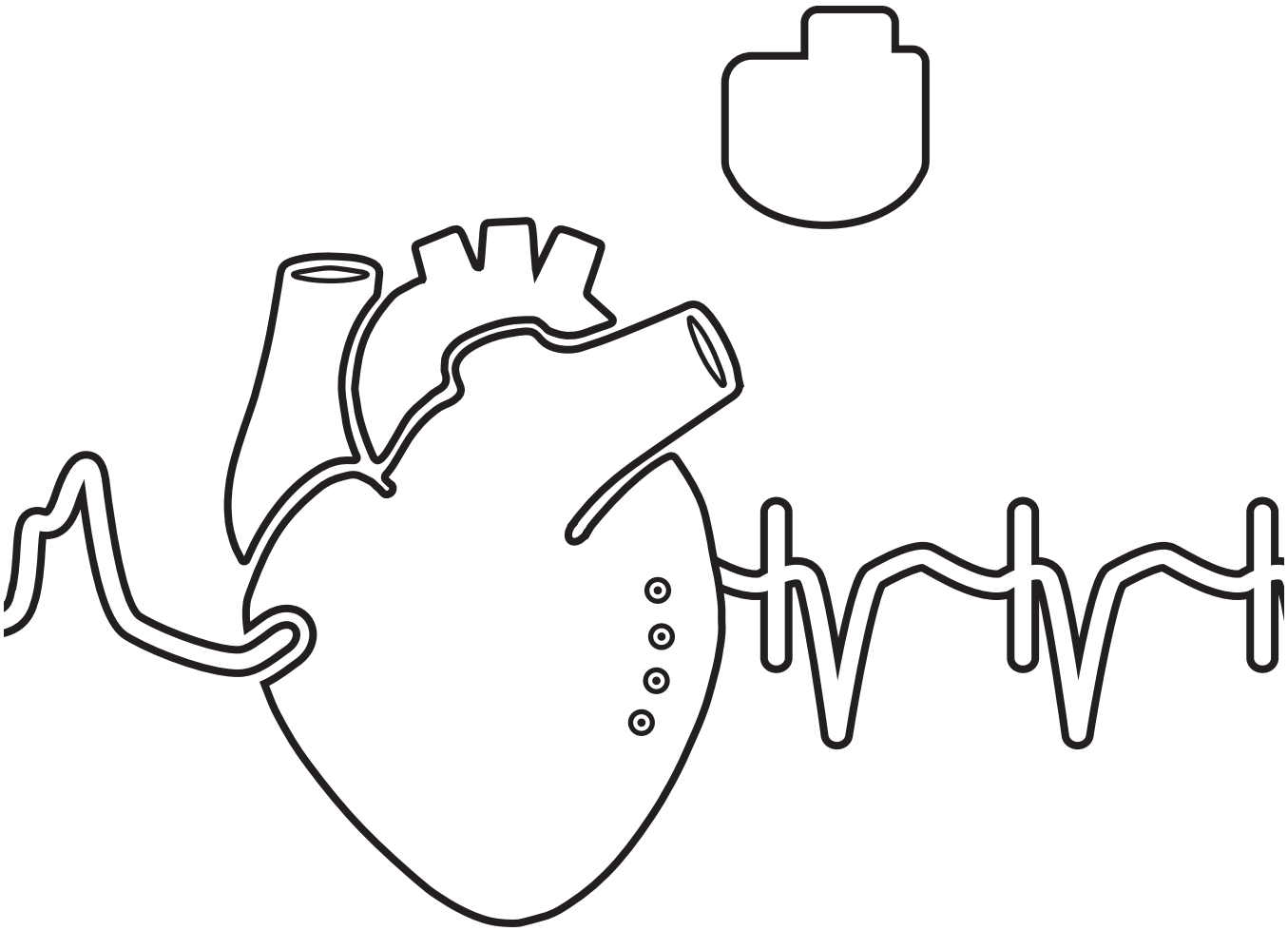
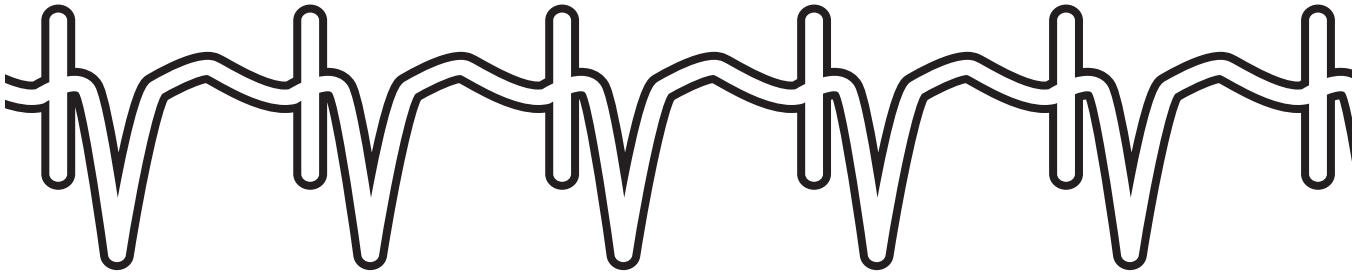


Chapter 3

The value of septal rebound stretch analysis for the prediction of volumetric response to cardiac resynchronization therapy

European Heart Journal - cardiovascular imaging (in print)



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ABSTRACT

Aims

Patient selection for cardiac resynchronization therapy (CRT) may be enhanced by evaluation of systolic myocardial stretching. We evaluate whether systolic septal rebound stretch (SRSsept) derived from speckle-tracking echocardiography is a predictor of reverse remodeling after CRT and whether it holds additive predictive value over the simpler visual dyssynchrony assessment by apical rocking (ApRock).

Methods and results

The association between SRSsept and change in left ventricular end-systolic volume (ΔLVESV) at six months follow-up was assessed in 200 patients. Subsequently, the additive predictive value of SRSsept over the assessment of ApRock was evaluated in patients with and without left bundle branch block (LBBB) according to strict criteria. SRSsept was independently associated with ΔLVESV (β 0.221, p=0.002) after correction for sex, age, ischemic cardiomyopathy, QRS morphology and duration, and ApRock. A high SRSsept (≥optimal cut-off value 2.4) also coincided with more volumetric responders (ΔLVESV≥-15%) than low SRSsept in the entire cohort (70.0% and 56.4%), in patients with strict LBBB (83.3% vs 56.7%, p=0.024), and non-LBBB (70.7% vs 46.3%, p=0.004). Moreover, in non-LBBB patients, SRSsept held additional predictive information over the assessment of ApRock alone since patients that showed ApRock and *high SRSsept* were more often volumetric responder than those with ApRock but *low SRSsept* (82.8% vs 47.4%, p=0.001).

Conclusion

SRSsept is strongly associated with CRT induced reduction in LVESV and holds additive prognostic information over QRS morphology and ApRock. Our data suggest that CRT patient selection may be improved by assessment of SRSsept, especially in the important subgroup without strict LBBB.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is an effective treatment for patients with advanced systolic heart failure and a prolonged QRS duration. In current CRT guideline recommendations, patient selection is primarily guided by QRS morphology and duration.[1,2] Yet, due to an overall reported non-responders rate of 30-40%, there is room for improvement of patient selection.[3] Whether echocardiographic dyssynchrony parameters can enhance the selection of patients has been an area of debate since the multicenter PROSPECT trial was not able to show additive benefit of the use of (timing-based) echocardiographic dyssynchrony markers for predicting CRT outcomes.[4] In the meantime, the field of echocardiography has moved from using timing-based dyssynchrony measures towards the detection of specific wall motion patterns to serve as markers for CRT response.[5–8] These specific wall motion patterns can be identified by the visual assessment of dyssynchrony and quantified by myocardial strain imaging techniques.[5,9–11] A pre-ejection, short septal contraction pulling the apex septally followed by a delayed lateral wall contraction, which causes a lateral motion of the apex -known as apical rocking (ApRock)- is a specific pattern of contraction that has been shown to be strongly associated with better survival and volumetric CRT response.[12–15] Still, when using ApRock to determine the presence of dyssynchrony, a continuous mechanical process is translated to a binary yes/no phenomenon. Speckle tracking echocardiography, on the other hand, allows for a detailed quantification of left ventricular (LV) dyssynchrony -often called discoordination-. Previous work revealed that the interplay between early septal contraction and delayed lateral wall activation results in myocardial stretching of the opposing wall during systole.[6,8,16,17] This paradoxical systolic LV stretching does not contribute to LV ejection and, hence, causes a waste of energy. Biventricular pacing may convert systolic stretching into shortening and, therefore, may, reduce myocardial wasted work.[5,18,19] Previous work suggested that the amount of systolic stretching of the septum after initial systolic shortening ['systolic rebound stretch of the septum'(SRSsept)] reflects the potential for recovery of LV function with CRT, and may be used to identify potential CRT responders.[5,20,21] Yet, this parameter has not been validated in a multicenter setting. Therefore, the primary objective of the present study was to investigate whether SRSsept is a robust predictor of LV reverse remodeling defined as reduction in LV end-systolic volume (ΔLVESV) in a multicenter setting.[14] The secondary objective was to test the additive prognostic power of SRSsept when evaluated in addition to the simpler visual assessment of dyssynchrony by ApRock for the prediction of volumetric response after CRT (ΔLVESV ≥15%). Lastly, we assessed the value of mechanical dyssynchrony in patients with and without strict left bundle branch block (LBBB).

METHODS

Patient population

This is a subanalysis of the prospective multicentre Markers of Response to Cardiac Resynchronization Therapy (MARC) study.[14] The MARC study included 240 patients with a CRT device with defibrillator function and was designed to investigate which clinical, electrical and echocardiographic parameters can improve CRT response prediction. All electrocardiograms (ECG) were assessed by a blinded ECG core lab (university medical center of Utrecht), and all echocardiograms were handled by a blinded echocardiography core lab (university medical center of Utrecht). The study was initiated and coordinated by the six centers within the framework of the Center for Translational Molecular Medicine (CTMM), project COHFAR. Details of the original MARC study were published previously.[14] In short, inclusion criteria were sinus rhythm, LBBB with QRS duration ≥130ms or ≥150ms in non-specific interventricular conduction delay (IVCD) for patients with NYHA class II, LBBB with QRS duration ≥120ms, or QRS duration ≥150ms in non-specific IVCD patients with NYHA class III. Exclusion criteria were severe renal insufficiency (<30 mL/min/1.73m^2), previous pacemaker implantation, right bundle branch block, and permanent atrial fibrillation. Of the 240 patients included in the MARC study 213 patients had pre- and postimplant echocardiography data with paired left ventricular end-systolic volume (LVESV) measurements available (two failed implants, five implants not attempted, four deaths, four withdrawn consents, one missed visit and eleven unperformed of unreadable echocardiogram studies). The study was performed according to the Declaration of Helsinki. All patients provided written informed consent and all local medical ethics committees approved data collection and management.

Echocardiographic analysis

Echocardiograms of baseline and six months follow-up after CRT implantation were digitally stored and sent to the echocardiography core lab for detailed analysis, which has been described in detail before.[14] Standard echocardiographic images were obtained, accompanied with a zoomed and trimmed image of the LV and the interventricular septum, in apical four-chamber view. Frame rate of images obtained for STE was optimized to range between 50 and 120Hz. All echocardiograms were analysed with a dedicated vendor-independent software platform (TomTec Cardiac Performance Analysis, TomTec Imaging Systems GmbH, Unterschleissheim, Germany). The LV end-diastolic (EDV) and end-systolic volume (ESV) and ejection fraction (EF), were measured on three separate beats, using the biplane Simpson's method. Volumetric response to CRT was determined as a ≥15% decrease in LVESV between baseline and 6 months follow up. Systole was defined by the onset of the QRS complex and aortic valve closure time obtained from PW Doppler of the LV outflow tract.

Mechanical dyssynchrony parameters

ApRock was prospectively assessed on baseline conventional echocardiographic views as described before.[14] ApRock was defined as a short systolic rocking motion of the apex, observed in the apical four-chamber view.[9,22] Systolic rebound stretch of the septum (SRSsept) was defined as the total amount of systolic stretch after initial shortening of the septum.[5] (**Figure 1**) The amount of SRSsept was obtained by analysis of septal longitudinal strain, which was performed by an observer blinded for volumetric response. The region of interest (ROI) was set along the endocardial border from base to apex, excluding the apical cap, and adapted to match the wall thickness. The quality of speckle tracking performed by the software was visually checked and adjusted if necessary. SRSsept was determined on septal single wall echocardiographic views when possible (in 61% of patients) or when a septal single wall view was missing on zoomed four-chamber view (39% of patients). Images were deemed 'not analysable' if tracking of more than one segment per wall was not feasible. Images with frame rate between 50 and 120Hz were amenable for analysis.

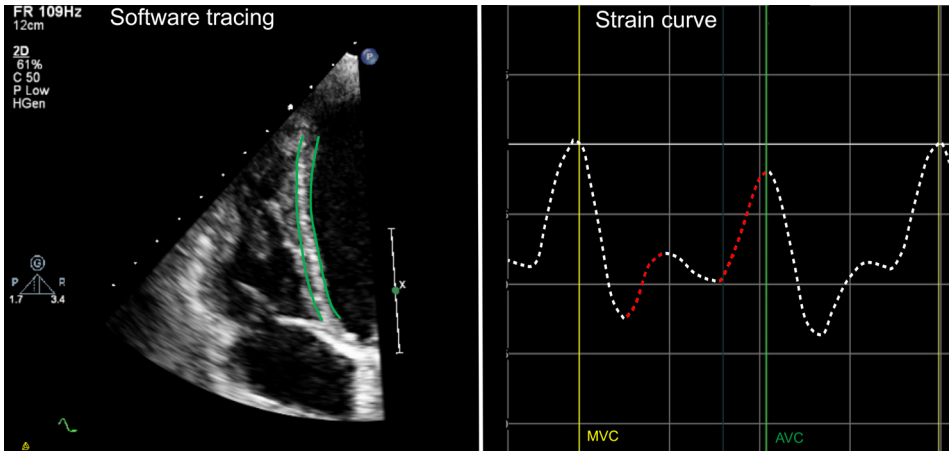

Figure 1. Acquisition of systolic rebound stretch of the septum on septal single wall image. Strain curves of the focused LV septal wall image derived with dedicated speckle tracking echocardiography software. SRSsept (in red) is defined as septal stretching after initial shortening. The apical cap is excluded from speckle tracking analysis. AVC: aortic valve closing, MVC: mitral valve closing

Electrocardiography

12-lead ECG's were recorded at baseline and analysed by the ECG core lab. The presence of LBBB was determined retrospectively by one experienced reader based on morphological features. This was done for the more strict AHA/ACC/HRS definition for LBBB (**Table 1**).[23] In order to qualify

as LBBB, an ECG had to comply with all the required criteria for that definition. Patients who did not comply with the LBBB definition were labelled as non-LBBB. QRS duration was determined by the automated ECG algorithm.

Table 1. American criteria to define left bundle branch block

AHA/ACC/HRS[23]	Criteria
	•QRS ≥120
	•Notch-, slurred R in I, aVL, V5 and V6
	•Occasional RS pattern in V5-6
	•Absent q in I, V5-V6 and aVL
	•R peak time >60ms in V5 and V6
	•Normal R peak time in V1-V3
	•No negative concordance
	•Usually discordant ST-T segments

Statistical analysis

Statistical tests were performed in SPSS version 25 (IBM, Armonk, New York, USA). Continuous data were expressed using mean ± standard deviation (normally distributed variables) or as median, interquartile range (non-normally distributed variables). Categorical data were described by an absolute number of occurrences and associated frequency (%). Data of subgroups were compared using a t-test or Mann-Whitney U test, dependent on normality of the data. Fischer Chi-Square test was used for categorical data. The c-statistic and cut-off value of SRSsept were calculated with volumetric response as a dichotomous parameter. Furthermore, intra-observer variability of SRSsept was determined by comparing the first and second analysis (interval of twelve weeks) of the observer, for which interclass correlation coefficient (ICC) were reported. To test the association between baseline SRSsept and reverse remodeling at follow up, univariable and multivariable adjusted linear regression analyses were performed with correction for potential confounders. Confounders were selected based on baseline differences between patients with high and low SRSsept, and parameters that showed an association with ΔLVESV in univariable analysis with $p<0.1$. Variables that were added to the final model were: sex, age, ischemic cardiomyopathy, LBBB morphology, QRS duration, ApRock, and high SRSsept. Assumptions of multivariable linear regression were checked for the existence of nonlinearity, heteroskedasticity and multicollinearity by graphical analyses and correlations tests. Normality of residuals was tested by a Q-Q plot. Furthermore, because visual dyssynchrony assessment by ApRock can be assessed relatively easily on standard 2D-echocardiography, the additive prognostic power of

the -relatively difficult- SRSsept over ApRock was evaluated. This was done for i) the total study population and ii) separately for patients with and without a strict LBBB. Finally, at 6 months follow up differences in ΔLVESV were compared for patients who kept their mechanical dyssynchrony and patients in whom mechanical dyssynchrony was corrected, for which a cut-off was arbitrarily chosen at 50% change in SRSsept. A two-sided *p*-value of <0.05 was considered significant.

RESULTS

Of the 213 patients with paired LVESV measurements, a total of seven patients had missing strain data due to irregular heart rhythm (n=1), a frame rate below 35Hz (n =3) or an overall low image quality (n=3). Furthermore, six patients had missing baseline electrocardiograms. As a result, 200 patients were included representing a typical CRT cohort, predominantly men (62%) with a mean age of 67±10 years, reduced ejection fraction of 26±7%, 42% with an ischemic cardiomyopathy and 30% with an LBBB and QRS duration of 179±23ms (**Table 2**). Median SRSsept was 2.0% [IQR 0.7-4.5] and the overall intra-observer agreement for SRSsept was high (ICC 0.89 [0.69-0.88], *p*<0.001). A c-statistic of 0.65 (0.58-0.72), p<0.001 was found with a best-fit cut-off value of 2.4% SRSsept (sensitivity of 0.541%, specificity of 0.728%). The c-statistics of SRSsept derived from the septal single wall (0.69, p<0.001) and the apical four-chamber image (0.60, *p*=0.08) are displayed in **Supplemental Figure 1**.

Mechanical dyssynchrony and volumetric CRT response

The baseline characteristics for patients with high (≥2.4%) and low (<2.4%) SRSsept are displayed in **Table 2.** Based on significant baseline differences, eight variables were identified as possible confounders in the association between baseline SRSsept and reverse remodeling at follow up being sex, age, origin of heart failure, renal dysfunction, LBBB morphology, QRS duration, and ApRock. After correction for univariable predictors of ΔLVESV with a multivariable linear regression model, SRSsept was significantly associated with ΔLVESV (β 0.221, *p*=0.002) **(Table 3**).

Additive prognostic value of septal rebound stretch to visual dyssynchrony assessment by apical rocking

When assessing volumetric response to CRT, one hundred and twenty-one patients (60.5%) showed volumetric response at six months follow-up with a mean ΔLVESV of -21.8±24.1%. Patients with *high SRSsept* more often were volumetric responder than patients with *low SRSsept* (75.0% vs 49.1%, *p*<0.001). Furthermore, because ApRock can be assessed relatively easily on standard 2D-echocardiography, the additive prognostic power of the -relatively difficult- SRSsept over

Table 2. Baseline characteristics

	All patients	SRSsept ≥2.4%, n=88	SRSsept <2.4%, n=112	*p*-value
Demographics				
Male sex - n (%)	124 (62.0)	42 (47.7)	82 (73.2)	<0.001
Age - yr	67±10	66±10	68±9	0.054
NYHA functional class - n (%)				
Class II/IV	125 (62.5)	54 (61.4)	70 (62.5)	
Class III/IV	75 (37.5)	34 (38.6)	41 (36.6)	0.654
Ischemic cardiomyopathy - n (%)	84 (42.0)	29 (33.0)	55 (49.1)	0.022
History of atrial fibrillation - n (%)	25 (12.5)	9 (10.2)	16 (14.3)	0.389
Diabetes - n (%)	51 (25.5)	19 (21.6)	32 (28.6)	0.261
Kidney dysfunction - n (%)	9 (4.5)	8 (9.1)	1 (0.9)	0.006
Echocardiography				
LV ejection fraction -%	25.8±7.4	25.8±6.8	25.7±8.2	0.936
LV ESV - ml	133 [96-182]	132 [99-179]	134 [92-186]	0.416
LV EDV - ml	178 [145-234]	179 [146-237]	178 [137-232]	0.465
Electrocardiography				
LBBB - n (%)	60 (30.0)	30 (34.1)	30 (26.8)	0.263
QRS duration - ms	179±23	182±25	174±21	0.023
PR interval - ms	185 [168-212]	184 [167-205]	187 [168-240]	0.220
Plain dyssynchrony				
Apical rocking - n (%)	128 (64.0)	73 (83.0)	55 (49.1)	<0.001

EDV: end diastolic volume ESV: end systolic volume, LBBB left bundle branch block, LV: left ventricular

ApRock was evaluated and displayed in **Figure 2**. Similarly to patients with *high SRSsept*, patients with ApRock showed more response to CRT compared to patient that did not display ApRock (71.1% vs 41.7%, $p<0.001$). Still, of all the patients that showed ApRock, 43% displayed *low SRSsept* (n=55). In these patients, the response rate was only 54.5%, while patients with both ApRock and a *high SRSsept* (n=73) had the highest response rate of 83.% ($p<0.001$).(**Figure 2**) Of note, in patients that did not show ApRock (n=72), response rates were similar between patients with high (n=15) or low (n=55) SRSsept (33.3% vs 43.9%, $p=0.462$ respectively). In **Figure 3** four representative septal strain curves are displayed for patients with or without ApRock and high or low SRSsept.

Mechanical dyssynchrony in patients with a strict LBBB

Overall response in patients with a strict LBBB (n=60) was 70%. High SRSsept values were observed in 50% of patients, whereas ApRock was observed in 77% of patients. LBBB patients with either

Table 3. Univariable and multivariable analysis of association with change in LVESV

	Univariable		Multivariable	
	β (standardized)	***p*-value**	**β (standardized)**	***p*-value**
Female sex - n (%)	0.180	0.011	-0.018	0.790
Age - years	-0.190	0.007	-0.121	0.069
Ischemic cardiomyopathy - n (%)	-0.319	<0.001	-0.182	0.013
Kidney dysfunction - n (%)	-0.052	0.468		
LBBB morphology - n (%)	0.215	0.002	0.150	0.022
QRS duration - ms	0.155	0.030	0.050	0.459
Apical rocking - n (%)	0.324	<0.001	0.149	0.041
SRSsept - %	0.354	<0.001	0.221	0.002

β: standardized regression coefficient (represents the number of standard deviations that the outcome will change as a result of one standard deviation change in the predictor) LBBB: left bundle branch block, SRSsept: systolic rebound stretch of the septum

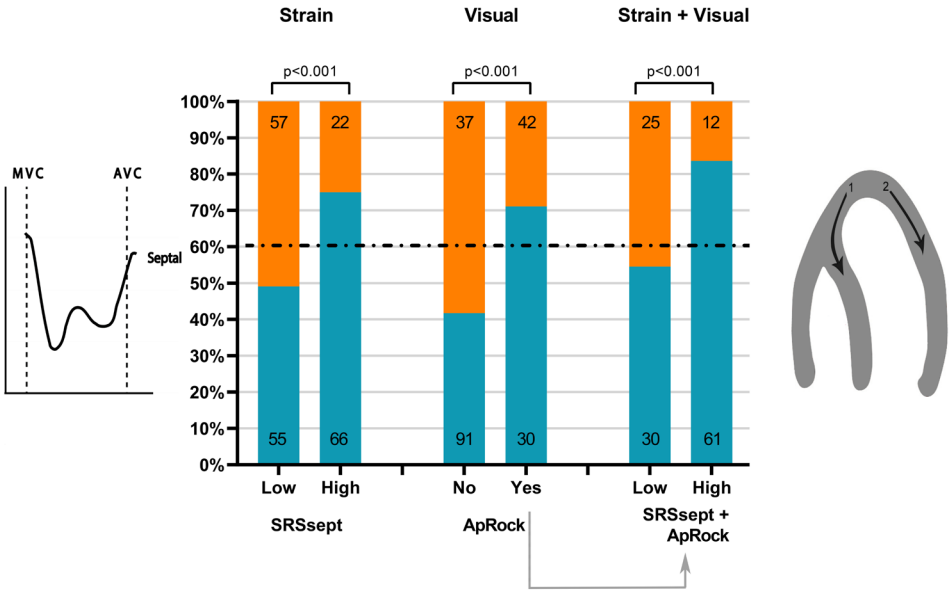

Figure 2. Discriminative ability of SRSsept for the prediction of volumetric CRT response. The percentage of responders (blue) and non-responders (orange) are displayed for patients with high versus low SRSsept (**left**), patients with and without apical rocking (**middle**) and patients with apical rocking and high or low SRSsept (**right**). Dotted line represents overall response to CRT in the study population. Numbers represent total amount of patients. ApRock: apical rocking, AVC: aortic valve closing, MVC: mitral valve closing, SRSsept: systolic rebound stretch of the septum

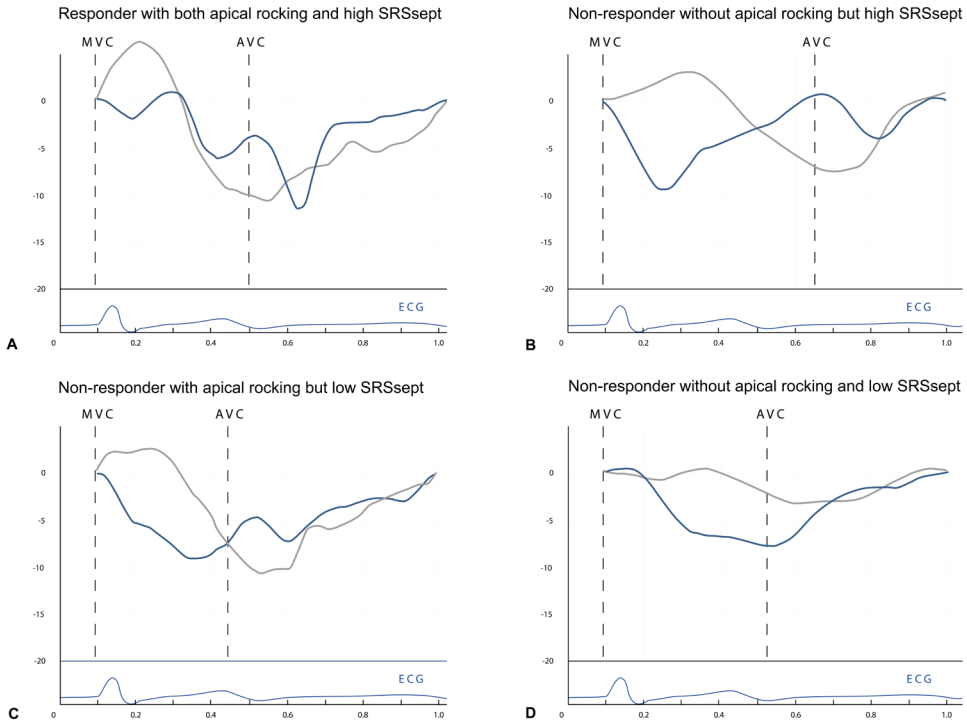

Figure 3. Strain based deformation patterns of patients with and without apical rocking.
Strain curves (blue=septal, gray=lateral wall) of representative CRT recipients with and without apical rocking at baseline. **A**: 50 year old women with non-ICM, LVEF 30%, LBBB, QRSd 186ms, *ApRock and high SRSsept (4.0%)* with a double peak pattern according to Leenders et al.[17] LVESV change at 6 months follow-up: -40.7%. **B**: 78 year old man with ICM, LVEF 15%, non-LBBB, QRSd 187ms, *no ApRock but high SRSsept values (10%)*. At follow-up LVESV change was -1%. **C**: 62 year old man with ICM, LVEF 28%, nonLBBB and a QRSd of 189ms. Echocardiography relieved *ApRock, but low SRSsept (1.6%)* and LVESV change at follow up was -3%. D: 69 year old man with ICM, LVEF 12%, LBBB, QRSd 188ms, *no ApRock and low SRSsept (0%)*. LVESV change at follow up was +1%. ApRock: apical rocking, ICM; ischemic cardiomyopathy, LBBB: left bundle branch block, LVEF: left ventricular ejection fraction, LVESV: LV end-systolic volume

high SRSsept or ApRock displayed more volumetric response compared to patients with low SRSsept or without ApRock (SRSsept: 83.3% vs 56.7%, p=0.024 and ApRock 78.3% vs 42.9, p=0.011). When SRSsept was evaluated on top of ApRock, there was a non-significant trend towards more responders in patients with ApRock and *high SRSsept* compared to patients with ApRock but *low SRSsept* (82.8% vs 70.6%, p=0.334)(**Figure 4**).

Mechanical dyssynchrony in patients without a strict LBBB

In patients without strict LBBB (n=140) only 56.4% displayed volumetric response. 41.4% of non-LBBB patients had high SRSsept values, 58.6% displayed ApRock, and 31.4% displayed both

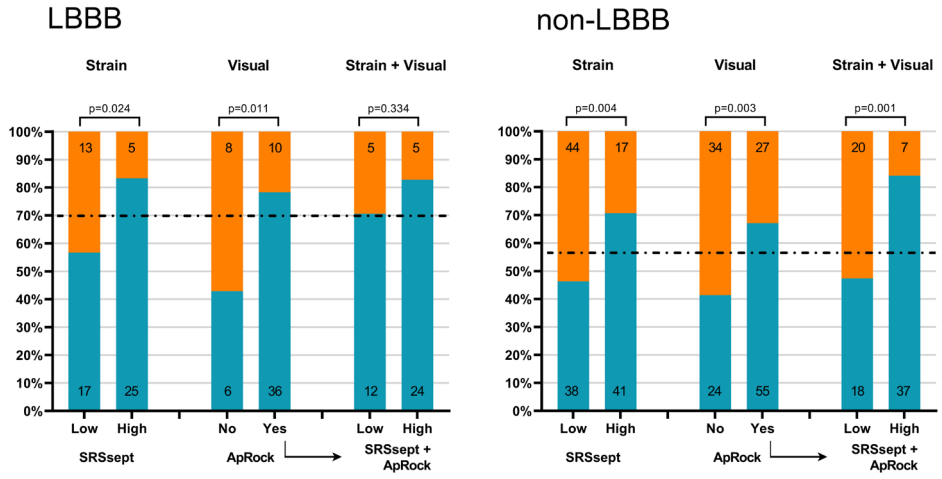

Figure 4. Discriminative ability of mechanical dyssynchrony in patients with and without a strict LBBB. The percentage of responders (blue) and non-responders (orange) are displayed for patients with high versus low SRSsept (**left**), patients with and without apical rocking (**middle**) and patients *with apical rocking* and high or low SRSsept (**right**). Dotted line represents overall response to CRT in the subgroups. Numbers represent total amount of patients. ApRock: apical rocking, LBBB: left bundle branch block, SRSsept: systolic rebound stretch of the septum

ApRock and *high SRSsept*. Assessment of SRSsept led to a better discrimination between responders and non-responders, since response rates were higher among patients with *high SRSsept* compared to patients with *low SRSsept* (70.7% vs 46.3%, *p*=0.004). Moreover, assessment of SRSsept held additional predictive value over assessment of ApRock alone, given that patients that displayed both ApRock and *high SRSsept* more frequently were responder compared to patients with *ApRock and low (* 84.1% vs 47.4%, *p*=0.001)(**Figure 4**).

Correction of mechanical dyssynchrony at follow up

Six months after CRT implantation, larger ΔLVESV was observed in patients that displayed a ≥50% reduction in SRSsept (n=60) compared to patients with a <50% reduction (n=140)(ΔLVESV:-26±23% vs -13±24%, *p*=0.001). Larger reductions in SRSsept tended to result in more reverse remodeling in both subgroup of patients with either baseline *low SRSsept* (ΔLVESV -19±22% vs -10±23%, *p*=0.052), and baseline *high SRSsept (*ΔLVESV: -32±26% vs -23±25%, *p*=0.201), yet, in these subgroups differences did not reach statistical significance.

DISCUSSION

This is the first multi-center study that investigated the association of baseline echocardiographic SRSsept with volumetric response after CRT. Our main findings were i) SRSsept is independently associated with favorable changes in LVESV after CRT, ii) assessment of SRSsept holds additional predictive information over the assessment of the more simple visual assessment of ApRock alone for the prediction of volumetric response, iii) particularly in patients without a strict LBBB, in whom response to CRT is less certain, SRSsept is able to identify patients who benefit more favorably from CRT. Consequently, assessment of mechanical dyssynchrony has additive predictive value, and may especially be useful to select patients without a strict LBBB but with an underlying substrate responsive to CRT.

Strain parameters for prediction of CRT response

Myocardial deformation analysis by speckle-tracking echocardiography has become an established echocardiographic modality for assessing the mechanical consequences of dyssynchonous hearts failure. Dyssynchronous electrical activation affects LV pump function in a negative way due to opposing shortening and stretching within the LV.[16] Systolic stretching of the myocardium does not contribute to LV ejection and, therefore, represents a waste of energy (wasted work).[24] Previous work suggested that the septum is particularly subject to wasted work caused by an LV activation delay and that the amount of septal wasted work is strongly correlated to CRT response.[25] In 21 CRT patients Vecara et al. displayed an average of 100% wasted work in the septum, whereas wasted work in the LV free wall was approximately 20%, meaning that in their study population the septum essentially made no contribution to LV ejection.[25] Although myocardial wasted work can be elegantly determined by the combination of speckle tracking-derived strain with LV pressure in LV pressure-strain loop analysis, specialized software is currently needed for its' assessment.[24] Strain analyses with speckle tracking echocardiography, on the other hand, is more readily available because it is already implemented into echocardiography machines. A few clinical studies and work from computer modeling suggested that the amount of systolic stretching, by itself, may serve as marker for CRT response.[5,8,17,26] A recent subanalysis of the multicenter Adaptive-CRT study displayed that the total amount of LV stretching (the systolic stretch index [SSI] which combines SRSsept with the prestretch of the LV lateral wall) was associated with better survival after CRT.[8] This was not only true for the whole cohort, but interestingly also for patients with intermediate ECG criteria (QRS 120-149ms or non-LBBB)(HR high SSI: 5.08, 95% CI: 1.94-13.31, p<0,001). In the present study, we choose to evaluate SRSsept instead of SSI because de Boeck et al. displayed that SRSsept is markedly more reduced by CRT than the systolic prestretch of the lateral wall.[5] In addition, acquiring high-quality images of the

septum is easier as compared to high-quality image acquisition of the LV lateral wall. The association between SRSsept and CRT response has been evaluated previously by multiple single center studies that displayed SRSsept to be independently associated with long-term prognosis and improvements in LV remodeling.[5,6,20,21] This may, for an important part, be attributed to the fact that SRSsept is not only affected by the underlying electrical substrate (increasing SRSsept) but is also influenced by myocardial stiffness and scarring (generally reducing SRSsept), given that early septal shortening happens in viable, early activated septal segments and rebound stretch is affected by the contractility of the late activated lateral wall.[5,20] Of particular interest is that septal hypocontractility increases rebound stretch and leads to a predominant stretching pattern of the septum described by Leenders et al. and displayed in our **Figure 3B**.[17,27] This might explain why in the present study some patients, despite high SRSsept values, demonstrated non-response to CRT. Lateral hypocontractility or scar, on the other hand, reduces rebound stretch and creates a pseudonormal septal strain pattern according to Leenders et al. (**Figure 3 C and D**), which is associated with an overall poor response to CRT.[17,27]

Finally, previous work displayed that not only the amount of mechanical dyssynchrony at baseline, but also its correction by CRT are associated to greater reductions in LVESV.[13] Moreover, a recent study displayed that not only do CRT-recipients with mechanical dyssynchrony have better survival over those without mechanical dyssynchrony, but also, that these patients have better long-term outcomes compared to patients with mechanical dyssynchrony who do not receive CRT.[28] These findings further fuel the notion that mechanical dyssynchrony parameters can be used to assess a patients underlying substrate which can be corrected by CRT. Still, in the present study, the greater ΔLVESV in patients with larger reductions of SRSsept at follow up seem to be driven in part by the amount of baseline mechanical dyssynchrony, since larger reductions in SRSsept did not result in significantly more reverse remodeling in the individual subgroups of patients with baseline *low or high SRSsept*.

Visual detection of dyssynchrony versus quantitative strain analysis

A known limitation of speckle tracking strain analysis is that technically adequate echocardiographic image quality is required. ApRock, on the other hand, can be easily visually assessed on conventional two-dimensional echocardiographic images, surpassing the need for expensive software and sophisticated strain analysis. Several studies, both single and multicenter, displayed that ApRock is associated with superior outcomes and more reverse remodeling after CRT and has added value over patient selection based solely on the 12-lead ECG.[12–15] In a subanalysis of the PREDICT-CRT database, presence of ApRock and/or septal flash at baseline was associated with lower all-cause mortality in both patients with an LBBB and non-LBBB morphology (HR 0.21, 95% CI 0.15–0.30, $p<0.0001$ in LBBB, HR 0.47, 95% CI 0.27–0.82, $p=0.007$ in non-LBBB

QRS≥150ms, and HR 0.35, 95% CI 0.14–0.87, p=0.02 in non-LBBB QRS<150ms).[15] Interestingly, this study also revealed that adding mechanical dyssynchrony as selection criterion coincided with a significantly more volumetric responders compared to patient selection based on QRS duration and morphology alone (77% versus 65% in LBBB patients, 75% versus 50% in non-LBBB QRS ≥150ms, and 62% versus 38% in non-LBBB QRS<150ms, respectively).[15] Although the PREDICT study did not report on the definition used to determine LBBB on the ECG, we believe that our results are in line with the aforementioned findings. Still, when using ApRock or septal flash to determine the presence of dyssynchrony, a continuous mechanical process is translated to an binary yes/no phenomenon. In the present study, approximately a quarter of patients with strict LBBB did not demonstrate ApRock. In these patients CRT response was limited (43%), and evaluation of SRSsept did not lead to a better response discrimination, suggesting that the absence of ApRock may be an important marker for predicting CRT non-response. Yet, 37% of patients with LBBB and ApRock had low SRSsept values. These patients were significantly less often CRT responder. Previous work suggested that other nonelectrical factors (e.g. scar) may mimic visual dyssynchrony (e.g. ApRock or septal flash), which are unresponsive to CRT.[27] This could explain why in the present study assessment of SRSsept held additional predictive power over the more simple assessment of ApRock.

Clinical implications

In the present study, presence of mechanical dyssynchrony markedly improved CRT response rates. This was not only true for patients with intermedicate ECG criteria (non-LBBB) but even for patients with a strict LBBB, in whom overall response to CRT is already fairly high. These present results should encourage cardiologists to look further than QRS morphology to determine a patient's eligibility for CRT. The assessment of SRSsept may be of special interest in patient showing ApRock, because nonelectrical factors might lead to ApRock which are unresponsive to CRT. Finally, in the current study the association between SRSsept and volumetric response to CRT was strongest for SRSsept derived from the focused septal single wall image, suggesting that high quality focused images of the septum may especially be suited for improvement of echocardiography-based patient selection.

Limitations

Although the MARC study was a prospective multicenter study, the non-randomized and observational study design precludes a formal analysis of the interaction between baseline predictors and the prognostic benefit rendered by CRT. In addition, only patients with an LBBB or wide IVCD (≥150ms) were included in the MARC study. Application of mechanical dyssynchrony in patients with RBBB or those with ICVD 130-149ms may, therefore, be of interest for future

research. Also, a known limitation of speckle tracking is that it cannot be applied to all patients. Yet in our study of six centers, only in seven out of 213 patients (3%) SRSsept assessment was not feasible, which is low compared to previously published work.[6,8] Acquiring high-quality images of the septum is easier as compared to high-quality image acquisition of the LV lateral wall. As a consequence, we believe that SRSsept is a robust and relatively easy to use predictor of CRT response. Importantly, besides being dependent on image quality, SRSsept is also dependent on the specific image chosen (i.e. focussed septal single wall vs. four-chamber view), the echocardiographic image system and speckle tracking vendor used.[29] The cut-off value of 2.4% can therefore not be extrapolated to other vendors. Accordingly, specific cut-off values for SRSsept should be investigated in prospective trials in order to make an impact on CRT patient selection.

CONCLUSION

Our findings indicate that current electrocardiographic guideline criteria for CRT leave a substantial place for improvement in patient selection by incorporating echocardiographic assessment of the mechanical consequences of electrical LV dyssynchrony. Moreover, measuring 'septal rebound stretch' by speckle tracking strain analysis provides additional prognostic information on top of visual detection of mechanical dysysnchrony (i.e. apical rocking) for prediction of volumetric CRT response. Especially in patients with non-strict LBBB in whom benefit of CRT is doubted, septal rebound stretch is a promising marker of benefit from CRT and should be considered for validation in prospective clinical trials.

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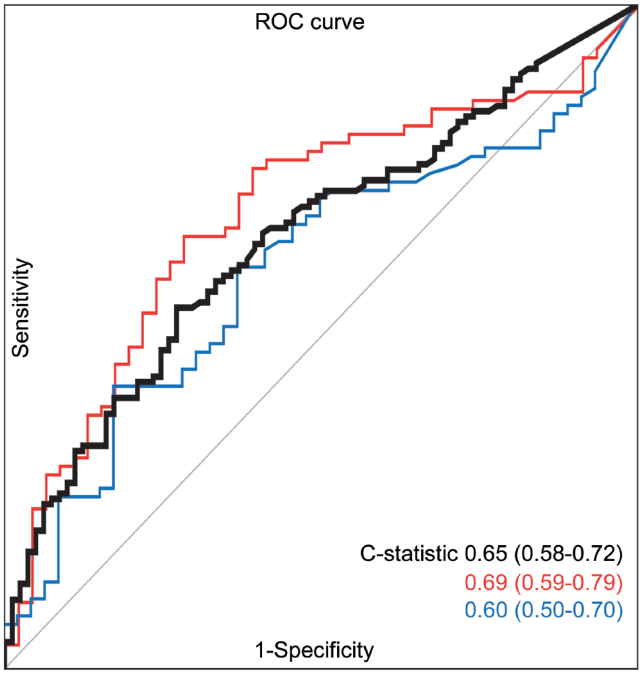
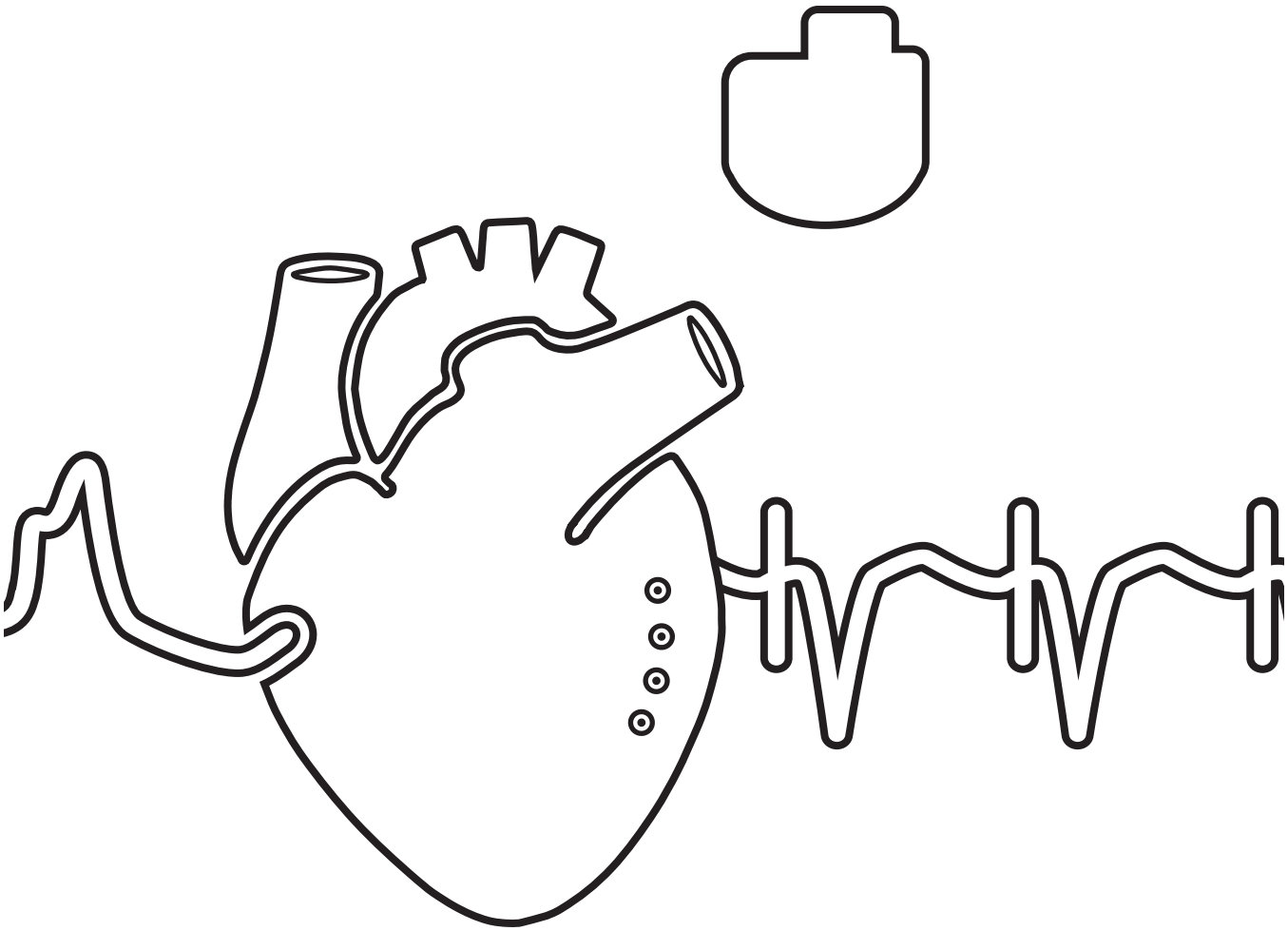
SUPPLEMENTAL MATERIAL



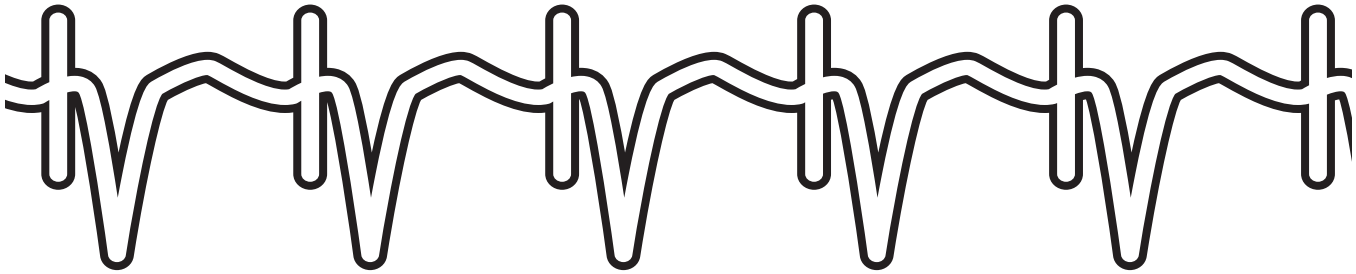
Supplemental figure 1. Area under the ROC curve of the association of SRSsept with volumetric CRT response
ROC curves are displayed i) for all patients (black) and ii) for patients with a focused image of the septal wall (red and blue). In patients with a focused image of the septal wall, the c-statistics of SRSsept derived from the septal single wall image (red) was comparatively better than the c-statistics of SRSsept derived from the apical four-chamber image (blue). Accordingly, we believe that for optimal speckle tracking analysis, efforts should be made to acquire high quality focused images of the LV septal wall.



Chapter 4

Heart size corrected electrical dyssynchrony and its impact on sex-specific response to cardiac resynchronization therapy

Under review



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ABSTRACT

Background

Women are less likely to receive cardiac resynchronization therapy (CRT), yet, they are more responsive to the therapy and respond at shorter QRS duration. In the present study, we hypothesized that a larger left ventricular (LV) electrical dyssynchrony in smaller hearts contributes to the better CRT response in women. For this we use the vectorcardiogaphy-derived QRS area, since it allows for a more detailed quantification of electrical dyssynchrony compared to conventional electrocardiographic markers.

Methods

Data from a multicenter registry of 725 CRT patients (median follow-up: 4.2 years [IQR: 2.7-6.1]) were analyzed. Baseline electrical dyssynchrony was evaluated using the QRS area, and the corrected QRS area for heart size using the LV end-diastolic volume (QRSarea/LVEDV). Impact of the QRSarea/LVEDV-ratio on the association between sex and volumetric response (≥15% reduction in end-systolic volume) and the composite outcome of all-cause mortality, LV assist device implantation or heart transplantation was subsequently assessed.

Results

At baseline, women (n=228) displayed larger electrical dyssynchrony than men (QRS area: 132±55μVs vs 123±58μVs, p=0.043) which was, even more pronounced for the QRSarea/LVEDV-ratio (0.76±0.46μVs/ml vs 0.57±0.34μVs/ml, p<0.001). Female sex was associated with greater volumetric response (unadjusted OR 2.05 (1.47-2.86), p<0.001) and a lower occurrence the composite outcome (unadjusted HR 0.56 (0.41-0.76), p<0.001). A part of the female advantage regarding volumetric response was attributed to a larger QRSarea/LVEDV ratio in women (adjusted OR female sex: 1.38 (0.95-2.02, p=0.093). The larger QRSarea/LVEDV did not contribute to the better survival observed in women. In both volumetric responders and non-responders, female sex remained strongly associated with a lower risk of the composite outcome (adjusted HR 0.59 (0.36-0.97), p=0.036 and 0.55 (0.33-0.90), p=0.018, respectively).

Conclusions

Greater electrical dyssynchrony in smaller hearts contributes in part to the greater volumetric response observed in women after CRT, but this does not explain their better long-term outcomes.

INTRODUCTION

In the past decade it has become increasingly clear that sex differences play an important role in cardiac disease susceptibility, related symptoms, disease progression and the effect of treatment.[1–3] Various clinical trials assessing the effect of sex-specific response to cardiac resynchronization therapy (CRT) showed that women more often demonstrate reverse remodeling and experience improved survival after CRT.[4–8] Unfortunately, the underlying mechanisms for the improved outcomes in women remain largely unknown. Because women have a survival advantage over men,[9,10] it is possible that improved survival trends observed in women after CRT are related to an intrinsic survival advantage in women who on average reach an older age.[5,11] Yet, some studies ascribed the better outcome in women to more favorable clinical characteristics.[4,12,13] Women more frequently have a non-ischemic etiology of heart failure and a typical left bundle branch block (LBBB).[1] Such factors may account for a better response to CRT, but also for differences in survival irrespective of CRT. Interesting is the notion that women generally have a shorter QRS duration (QRSd) than men and show response to CRT at shorter QRSd.[15,16] It has been suggested that because female hearts are smaller, they may experience -on a relative basis- greater LV dyssynchrony compared to male hearts at identical QRSd, hence the greater CRT benefit.[17,18] While, the extent of electrical dyssynchrony is in part reflected by the QRSd, recent work displayed that quantification of electrical dyssynchrony may better be achieved with the vectorcardiographic QRS area.[19–22] By normalizing the QRS area for LV dimensions using the LV end-diastolic volume (LVEDV) the impact of a relatively larger electrical dyssynchrony in women can be assessed for the involvement in their better CRT outcomes. Accordingly, in the present study we aimed to investigate whether sex-specific differences in volumetric response and long term outcome after CRT can be attributed to normalization of QRS area for heart size using the LVEDV (QRS/LVEDV-ratio).

METHODS

We analyzed data from the MUG (Maastricht-Utrecht-Groningen) database, consisting of a total of 1946 patients (1394men and 552 women) implanted with a CRT device in three university hospitals in the Netherlands between 2001 and 2015.[21] Seven hundred and twenty-five patients from this cohort were included in the present study of whom 228 were women and 497 were men. Inclusion criteria were as follows: i) all patients with a de-novo CRT implantation, ii) all patients with an intrinsic QRS duration of ≥120ms and an ejection fraction ≤35%, and iii) patients with available digital 12-lead ECG and echocardiogram at baseline and during follow up. Finally, patients with atrial fibrillation at baseline were excluded from the analysis due to its confounding

nature in CRT. The patient selection process is shown in detail in **Figure 1**. Optimization of CRT settings was led to the discretion of the patients' physician. The Dutch Central Committee on Human-Related Research (Centrale Commissie Mensgebonden Onderzoek, [CCMO]) allows the use of anonymous data without prior approval of an institutional review board provided that the data are acquired for routine patient care. All data used were handled anonymously.

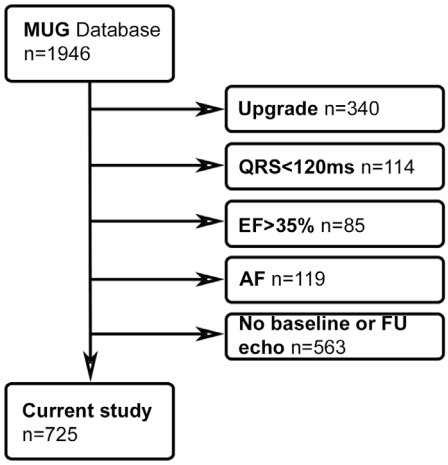

Figure 1. Patient data collection and availability for analyses. The entire MUG (Maastricht-Utrecht-Groningen) cohort consist of all patients implanted with a cardiac resynchronization therapy device from January 2001 to January 2015 in three university hospitals in the Netherlands. The figure displays the selection process of patient included in the present analyses. AF: atrial fibrillation, EF: ejection fraction, FU: follow-up.

Data collection

Patient data were retrieved from the patient records at the three hospitals as described before.[21] Baseline characteristics (e.g. etiology of heart failure, New York Heart Association (NYHA) functional class, comorbidities, medication) together with follow-up data (all-cause mortality, LV assist device implantation, heart transplantation) were retrieved from patients history and referral letters. Ischemic cardiomyopathy (ICM) was determined based on evidence of myocardial infarction, percutaneous coronary intervention or CABG in the medial history. LV volumes and ejection fraction were measured on echocardiographic images using the modified biplane Simpson's method. LV dimensions were indexed for body surface area. Baseline 12-lead ECGs were stored digitally in the MUSE Cardiology Information system (GE Medical System) and were evaluated for QRSd and the presence of LBBB morphology according to the ESC definition (QRS duration ≥120 ms, QS or rS in lead V1, broad (frequently notched or slurred) R waves in leads I, aVL, V5, or V6, and absent Q waves in leads V5 and V6).[23] Vectorcardiographic QRS area was calculated as

previously described (**Supplemental figure 1**).[21,24] In short, the 12-lead ECG original digital signals were extracted from the PDF-files stored in the MUSE system. Custom-made Matlab software (MathWorks Inc, Natick, MA) was then used to convert the ECG using the Kors conversion matrix into the three orthogonal vectorcardiography leads (X, Y, and Z) matrix. QRS area was subsequently calculated as the sum of the area under the QRS complex in the orthogonal vectorcardiographic leads (QRS area=$[QRS_{area,x}{}^2+QRS_{area,y}{}^2+QRS_{area,z}{}^2]^{1/2}$). The QRS area was corrected for the echocardiographic LVEDV to correct for heart size (QRSarea/LVEDV).

Study outcomes

Echocardiographic response to CRT was determined by comparing baseline and six-twelve months follow-up echocardiography. Patients with an LV end-systolic volume (LVESV) decrease of ≥15% at follow-up echocardiography were considered as volumetric responders. The composite outcome of all-cause mortality, LV assist device implantation, and cardiac transplantation, was assessed based on patient' records.

Statistical analysis

All statistical tests were performed in SPSS version 25 (IBM, Armonk, New York, USA). Continuous data were expressed using mean, standard deviation or median, interquartile range (IQR) depending on the normality of data. Categorical data were described by an absolute number of occurrences and associated frequency (%). Differences between groups were assessed using a t-test or Mann-Whitney U test, dependent on normality of the data. Pearson Chi-Square tests were used for dichotomous variables. To test the association between sex and volumetric CRT response, and sex and the composite outcome, univariable and multivariable logistic and Cox regression analyses were performed for which Odds ratios (OR) and Hazard ratios (HR) were reported, respectively. Multivariable regression analyses were performed with adjustment for potential confounders. Confounders were selected based on baseline differences between women and men, and covariates that were univariately ($p<0.1$) associated with either volumetric response or the composite outcome. Correlation tests were performed to test for multicollinearity. Covariates with signs of multicollinearity (Pearson's $r>0.8$, $p<0.05$) were excluded from the model. Covariates added to the final model regarding volumetric CRT response were; sex, ICM, device type (CRT-pacemaker or CRT-defibrillator), statin use, antiarrhythmics use, LBBB morphology, QRSd, and PR interval. The multivariable model for the composite outcome included; sex, age at implant, New York Heart Association (NYHA) functional class, ICM, kidney function, antiarrhythmic drug use, LBBB, QRSd, PR interval, and indexed LV dimensions (LVEDVi). To investigate whether a relatively larger electrical dyssynchrony in women is a confounder in the sex-CRT response relationship, the QRS area and the QRSarea/LVEDV -ratio were added separately in the multivariable model in

secondary analyses. A change in estimate criterion (odds or hazard ratio) of ≥10% was used to determine the presence of confounding. Finally, to investigate the impact of the greater volumetric CRT response in women on survival, Cox regression adjusted event curves for both sexes were acquired separately for volumetric responders and non-responders. Assumptions of the Cox model were tested by visual assessment of log-minus-log plots. Missing data were handled by a five-fold multiple imputation in order to prevent incomplete case analysis in the multivariable model. Of the variables considered in the multivariable modeling, only 3 variables had missing data (<5% missing at random). A two-sided *P* value <0.05 was considered statistically significant.

RESULTS

The baseline characteristics of women and men are displayed in **Table 1**. Women (31.4% of the study population) less frequently had an ICM (28.5% vs 58.8%, *p*<0.001), and more often had an LBBB on the ECG (88.2% vs 77.9%, *p*=0.001). QRSd was shorter (159±19ms vs 164±21ms, *p*=0.002) while QRS area was larger in women than in men (132±55μVs vs 123±58μVs, *p*=0.043). LV volumes and indexed LV volumes were 20.4% and 10.8% smaller in women (LVEDV 183 [143-235] vs 230 [176-295], *p*<0.001 and LVEDVi 99 ml/m^2 [79-131] vs 111ml/m^2 [89-146] *p*<0.001). As a consequence, the QRSarea/LVEDV-ratio was 33% larger in women as compared to men (0.76±0.46μVs/ml vs 0.57±0.35μVs/ml, *p*<0.001)(**Figure 2**).
Furthermore, women had a shorter PR interval (178±30ms vs 195±40ms, *p*<0.001), a higher resting heart rate (73±13bpm vs 71±14bpm, *p*=0.001), and a lower glomerular filtration rate (GFR) (68±31ml/min vs 75±32ml/min, *p*=0.009). Women also were less often implanted with a CRT-D compared to men (93.9% vs 97.0%, *p*=0.046), they had more symptomatic heart failure (NYHA III/IV: 70.2% vs 58.8%, *p*=0.003) and used less statins (44.3% vs 64.6%, *p*<0.001) and antiarrhythmic drugs (5.7% vs 12.5%, *p*=0.005) compared to men. Other characteristics did not differ between sexes. (**Table 1**) The differences in baseline characteristics for volumetric CRT response and the secondary endpoint are provided for both sexes in **Supplemental Tables 1 and 2**.

Volumetric CRT response

At a median follow-up time of 6.2 months 5.7-6.8], median CRT-induced LVESV reduction of the total population was 22% [1-44]. Women were more often volumetric responder (68.4% vs 52.5%, *p*<0.001) and showed more LV reverse remodeling (ΔLVESV -27±30 vs -17±30%, *p*<0.001). Women displayed more reduction in LVESV than men for any QRS area (**Figure 3**). In univariable logistic regression analysis, female sex was strongly associated with volumetric CRT response (OR 2.05 (1.47-2.86), *p*<0.001). After adjusting for possible confounders (ICM, device type, statin and

Table 1. baseline characteristics of study population

	Women n=228 (31.4)	Men n=497 (68.6)	*p*-value
Age -yr	64.7±11.0	65.6±10.1	0.279
Height - cm	166±8	177±7	<0.001
Body mass index - kg/m^2	26.8±5.7	26.6±4.3	0.631
Body surface area - m^2	1.8±0.2	2.0±0.2	<0.001
NYHA functional class			
I/II - n (%)	68 (29.8)	205 (41.2)	0.003
III/IV - n (%)	160 (70.2)	292 (58.8)	
CRT-D - n (%)	214 (93.9)	482 (97.0)	0.046
Comorbitidies - n (%)			
Ischemic cardiomyopathy	65 (28.5)	292 (58.8)	<0.001
Diabetes	50 (22.0)	115 (23.1)	0.741
Hypertension	91 (40.3)	214 (43.1)	0.468
Glomerular filtration rate - ml/min	68±31	75±32	0.009
Medication - n (%)			
Betablokker	196 (86.0)	424 (85.3)	0.817
ACE-i/ABR	209 (91.7)	456 (91.8)	0.970
Diuretics	187 (82.0)	397 (79.9)	0.499
Statin	101 (44.3)	321 (64.6)	<0.001
Antiarrhythmic†	13 (5.7)	62 (12.5)	0.005
Echocardiography			
LV ejection fraction -%	23.0±7.5	22.8±6.9	0.691
LVESV - ml	136 [103-192]	177 [131-231]	<0.001
LVESVi - ml/m^2	75 [57-105]	87 [67-114]	<0.001
LVEDV - ml	183 [143-235]	230 [176-295]	<0.001
LVEDVi – ml/m^2	99 [79-131]	114 [89-146]	<0.001
Electrocardiography			
LBBB - n (%)	201 (88.2)	387 (77.9)	0.001
QRS duration - ms	158.8±18.9	163.9±21.4	0.002
PR interval - ms	178±30	195±40	<0.001
Heart rate - bpm	74.3±14.6	80.8±14.0	0.002
Vectorcardiography			
QRS area - µVs	131.8±55.3	122.5±57.9	0.043
Correction for heart size			
QRS area/LVEDV – µVs/ml	0.76±0.46	ms	<0.001

† Amiodarone/verapamil/flecainide/sotalol ABR: angiotensin receptor blockers, ACE-i: angiotensin-converting-enzyme inhibitor, CRT-D: CRT defibrillator, EDV(i): (indexed) end diastolic volume, ESV(i): (indexed) end systolic volume, LBBB: left bundle branch block, LV left ventricular, NYHA: New York Heart Association

antiarrhythmic drug use, LBBB morphology, QRSd, and PR interval (**Supplemental table 3**), female sex remained significantly associated with volumetric CRT response OR 1.55 (1.07-2.24), p=0.023 (**Table 2, model 1**). To investigate the impact of a relatively larger electrical dyssynchrony in smaller hearts, the QRS area and the QRSarea/LVEDV-ratio were added separately to the multivariable model. The adjusted OR of female sex on volumetric CRT response changed from 1.55 to 1.38 (11.5% change) with the addition of the QRSarea/LVEDV-ratio (**Table 2**). This suggests that the QRSarea/LVEDV ratio is a confounder and contributes in part to the greater volumetric response observed in female patients. Of note, **Supplemental table 3** displays the full univariable and multivariable logistic regression analysis for volumetric response.

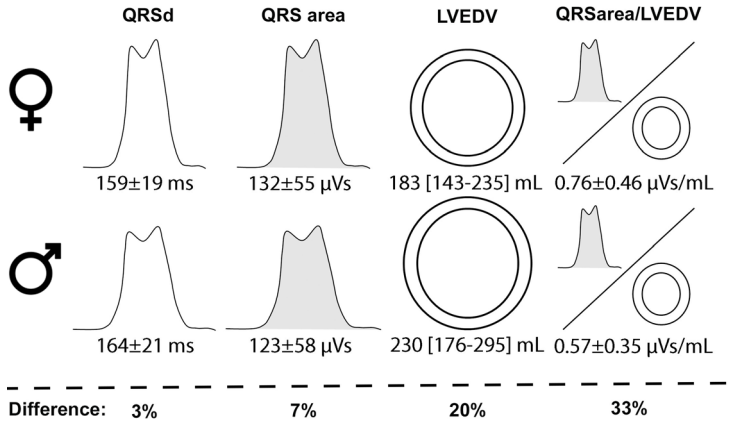

Figure 2. Sex differences in LV dimensions and LV dyssynchrony. Group mean values for electrical dyssynchrony heart size and heart size corrected electrical dyssynchrony are displayed for both sexes. Despite an overall shorter QRSd, female CRT recipients show greater absolute electrical dyssynchrony, represented by the larger QRS area. Moreover, due to the smaller overall LV dimensions, relative dyssynchrony is considerably greater in women compared to men. LVEDV: left ventricular end-diastolic volume, QRSd: QRS duration

Table 2. Multivariable logistic regression models of association of female sex with volumetric CRT response (LVESV reduction ≥15%)

Multivariable logistic regression model	OR (95% CI)	*p*-value	Fold change (%)
Model 1* Adjusted OR of female sex for volumetric CRT response	1.55 (1.07-2.24)	0.023	
Model 1* + QRS area Adjusted OR of female sex for volumetric CRT response	1.56 (1.07-2.29)	0.022	-0.6%
Model 1* + QRSarea/LVEDV-ratio Adjusted OR of female sex for volumetric CRT response	1.38 (0.95-2.02)	0.093	11.0%

*Covariates in model 1: device type, ischemic heart failure, statin and antiarrhytmics use, LBBB morphology, QRS duration and PR interval. CI: confidence interval, LVEDV: left ventricular end-diastolic volume, OR: odds ratio. Fold change reported with respect to model 1.

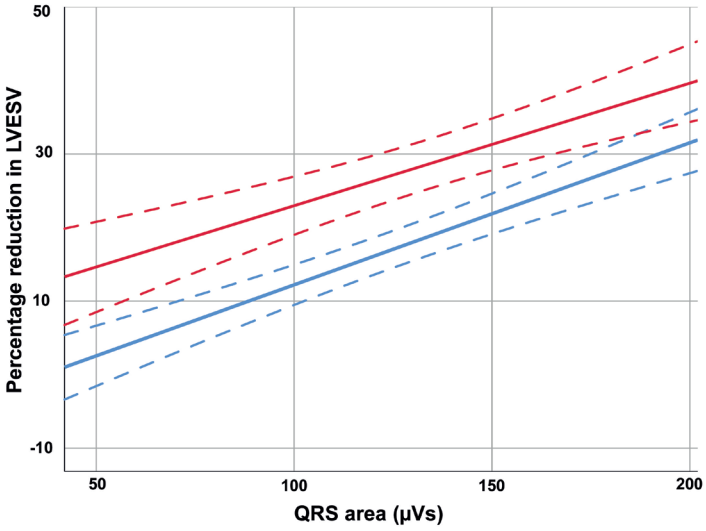

Figure 3. Left ventricular reverse remodeling according to QRS area as continuum. The mean amount of left ventricular end-systolic volume (LVESV) reduction is displayed for any QRS area with corresponding 95% confidence intervals. Women (red lines) display more reduction in LVESV for any QRS area than men (blue lines).

All-cause mortality, LVAD implant or cardiac transplantation

Over a median follow-up time of 4.2 [IQR 2.7-6.1] years, 231 patients (31.9%) reached the composite outcome of whom 54 (23.4%) were women and 177 (76.6%) were men (p=0.001). Median time to the composite outcome was significantly longer in women (4.7 [IQR 3.1-6.6] vs 3.9 [IQR 2.4-5.8] years, p=0.004). No patients in the study cohort were lost to follow-up. In univariable Cox regression analysis female sex was associated with a more favorable survival free of the composite outcome (HR 0.56 (0.41-0.76), p<0.001). After adjusting for possible confounders (age, NYHA class, ICM, kidney function, antiarrhythmic use, LVEDVi, LBBB morphology, QRSd, and PR interval)(**Supplemental table 3**), female sex remained strongly associated with lower occurrence of the composite outcome (HR 0.59 (0.42-0.85), p=0.004)(**Figure 4**). Adding QRSarea/LVEDV to the multivariable model changed the HR of female sex from 0.59 to 0.62 (5.1% change), suggesting that the larger QRSarea/LVEDV-ratio in women does not contribute to the better long-term outcomes observed in female CRT-recipients (**Table 3**). Of note, **Supplemental table 4** displays the full univariable and multivariable Cox regression analysis. Finally, to assess the impact of sex disparities in volumetric response to CRT on the occurrence of the composite outcome, adjusted event curves for both sexes were specified separately for volumetric responders and non-responders in **Figure 5**. Among both CRT responders and non-responders, female sex remained strongly associated with a reduced incidence of the composite endpoint (HR 0.59 (0.36-0.97), p=0.036 and HR 0.55 (0.33-0.90), p=0.018, respectively).

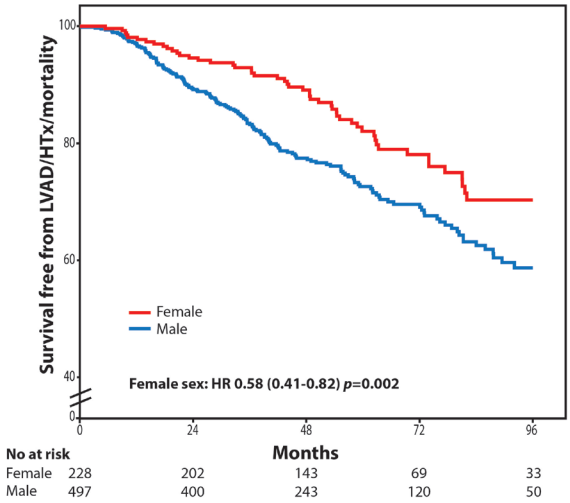

Figure 4. Adjusted event curves for association between female sex and the composite endpoint. Adjusted* event curves for association between female sex and survival free from the composite endpoint using a Cox proportional-hazards model. A significant survival benefit of women over men is displayed. *Adjusted for age, NYHA class, ischemic cardiomyopathy, kidney function, antiarrhythmic use, indexed left ventricular end-diastolic volume, left bundle branch morphology, QRS duration, PR interval and QRS area. HR: hazard ratio, Htx: heart transplant, LVAD: left ventricular assist device

Table 3. Multivariable Cox regression models of association of female sex with all-cause mortality, LVAD implant or heart transplant

Multivariable Cox regression model	HR (95% CI)	*p*-value	Fold change (%)
Model 2* Adjusted* HR of female sex for the secondary endpoint	0.59 (0.42-0.85)	0.004	
Model 2* + QRS area Adjusted* HR of female sex for the secondary endpoint	0.60 (0.42-0.86)	0.005	1.7%
Model 2* + QRSarea/LVEDV-ratio Adjusted* HR of female sex for the secondary endpoint	0.62 (0.44-0.89)	0.009	5.1%

*Covariates in model 2: age, NYHA class, ischemic heart failure, kidney function, antiarrhytmics use, LVEDVi, LBBB morphology, QRS duration, PR interval and QRS area. CI: confidence interval, LVEDVi: indexed left ventricular end-diastolic volume, HR: hazard ratio. Fold change reported with respect to model 2.

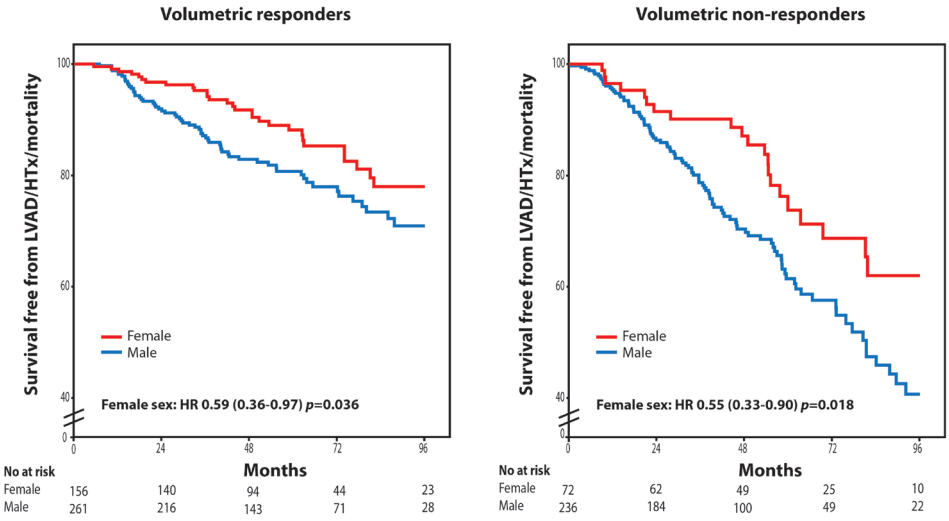

Figure 5. Adjusted event curves specified by volumetric response for the association between female sex and the composite endpoint. Adjusted* event curves for association between female sex and survival free from the composite endpoint using a Cox proportional-hazards model. A significant survival benefit of women over men is observed in both volumetric CRT responders and non-responders. *Adjusted for age, NYHA class, ischemic cardiomyopathy, kidney function, antiarrhythmic use, indexed left ventricular end-diastolic volume, left bundle branch morphology, QRS duration, PR interval and QRS area. HR: hazard ratio, Htx: heart transplant, LVAD: left ventricular assist device

DISCUSSION

In this multicenter cohort we investigated to which extent sex differences in heart size corrected electrical dyssynchrony at baseline can explain the repeatedly observed better outcomes in women. Electrical dyssynchrony was quantified by measuring the QRS area, which was adjusted for heart size using the QRSarea/LVEDV ratio. Our main findings were that i) women had a larger QRS area than men and an even more pronouncedly larger QRSarea/LVEDV ratio, ii) the larger QRSarea/LVEDV in part contributed to the better volumetric response observed in women, but iii) the superior survival in female CRT-recipients was not explained by the larger QRSarea/LVEDV ratio or their greater volumetric response.

Superior long-term survival in female CRT-recipients

The observation of better outcomes in women after CRT has led to controversies about a potential sex-specific response. While some studies ascribed the better outcome in women to baseline differences,[12,25] others implied that the better outcomes in women are intrinsic to female sex.[6,26,27] Surprising is that numerous studies failed to provide data on QRS morphology,[25–27] an important

confounder in the sex-CRT response relationship, because women more often show a typical LBBB at baseline.[28,29] Still, several studies to date have displayed that even amongst exclusively LBBB patients, women do better than men and that the superior outcome in women is not explained by the application of strict LBBB criteria.[4,8,28] The same seems true for heart failure etiology. While women less often suffer from ischemic heart failure, a subanalysis of the MADIT-CRT trial demonstrated that among CRT patients with non-ischemic heart failure, women do better than men.[14] Another contributing factor that might contribute to the improved event-free survival in female CRT-recipients is that women experience more reverse remodeling after CRT.[5,7] Work by Leyva et al, however, demonstrated that the superior long-term survival in women is only partly related to the fact that women undergo more reverse remodeling after CRT. In a large cohort study of 550 patients undergoing CRT female sex was an independent predictor of all-cause mortality (HR 0.52, p=0.0022), cardiovascular mortality (HR 0.52, p=0.0051), and death from pump failure (HR 0.55, p=0.033) when adjusting for known baseline predictors of long-term outcomes (age, NYHA class, device type, comorbidities, heart failure etiology, and LVEF) and echocardiographic LV reverse remodeling at follow-up.[6] These aforementioned findings are in line with the results of the present study and imply that it is not the greater volumetric response nor a more favorable underlying substrate (e.g. LBBB or ICM) in women that explains the superior event-free survival in female CRT-recipients. One possible explanation is that the progression of heart failure happens slower in women. This has been linked to an increased cardiac reserve in women and better preservation of cardiac function under stressed conditions.[30,31] Still, in both heart failure and demographic studies women have been shown to have a survival advantage compared to men, suggesting that the better survival in women after CRT might predominantly be attributed to factors intrinsic to the female sex.[11]

Heart size corrected LV dyssynchrony and CRT response

The notion that women may have greater LV dyssynchrony than men is not new.[4,8,32,33] Two large patient cohort studies displayed that female CRT-recipients more frequently show mechanical dyssynchrony on 2-dimensional echocardiography than their male counterparts.[12,33] Moreover, because women have smaller hearts, any single QRSd may represent greater retardation of myocardial conduction. Women may, therefore, experience on a relative basis even greater dyssynchrony than men do, which may account for their better response to CRT. This hypothesis has indeed been supported by two previous studies that corrected the QRSd for LV dimensions. Varma et al. demonstrated in 130 patients that sex differences in volumetric CRT response resolved by normalization of the QRSd for heart size using LV mass or volumes.[8] In addition to these findings, Zweerink et al. suggested that a higher QRS/LVEDV ratio in women might explain their better long-term survival.[32] This hypothesis, however, should be interpreted with caution because

the study of Zweerink et al. was not designed to investigate sex-based differences in CRT outcomes. In addition, the authors failed to index LVEDV to BSA or transform serum creatinine values to kidney function in their analysis. This is essential for a meaningful comparison between men and women since lower serum creatinine and smaller LVEDV are both traits of the female sex. Consequently, including these variables in a multivariable regression analysis severely impacts the association of female sex with the outcome measure. Yet, the assumption that it might be 'size', rather than sex, which is responsible for the greater CRT benefit in women is intriguing and has recently also been proposed by a large patient-level meta-analysis.[34] The authors implied that patient height may be the determining factor in the better survival in women by demonstrating that CRT survival was greater in shorter patients, and hence, in women. In the present study, there were, however, no differences in patient's height between volumetric responders and non-responders for neither sexes, nor did height differ between patients that did, or did not, reach the composite outcome (**Supplemental Table 1 and 2**). Baseline QRS area and QRSarea/LVEDV, on the other hand, were significantly greater among CRT responders than among CRT non-responders in both men and women, indicating that a greater dyssynchrony in smaller hearts -rather than a shorter patient statue- might play a crucial role in the superior CRT outcome in women. In this respect, this study is the first to expose sex-specific differences in CRT outcomes by quantifying electrical dyssynchrony, and hence, the electrical substrate amendable by CRT with the vectorcardiography-derived QRS area. While women had shorter QRSd than men, QRS area was larger revealing that female CRT-recipients experience more electrical dyssynchrony at baseline than men. Strong unopposed electrical forces generated within the heart are assumed to be the underlying mechanism of a large QRS area. Moreover, QRS area is lower in patients with ICM.[35,36] A larger QRS area, thus, reflects both a greater degree of electrical dyssynchrony and a more favorable substrate which is amendable by CRT. Like QRSd, QRS area is measured as a continuous variable, whereas variability in its measurement is likely to be less than in QRSd because it's largely determined by the QRS amplitude.[21,37] Accordingly, QRS area has been put forward as a better alternative to QRSd or QRS morphology to assess electrical LV dyssynchrony.[19,21,38]

Greater dyssynchrony: trait of the female sex or the result of current patient selection criteria

It is imperative to realize that the interplay between sex, LV dyssynchrony, heart size, and patient height is complex, and that it remains uncertain whether potential confounding factors of sex are masking the effect of LV dyssynchrony, or heart size on CRT response or vice versa. Furthermore, it should be acknowledged that the larger QRSarea/LVEDV-ratio could -by itself- be a trait of the female sex but could, on the other hand, also be independent of female sex and a consequence

of using the same selection criteria of QRS≥130ms (and preferably ≥150ms) for both sexes in current CRT guidelines. The latter might lead to a selection and treatment of female patients with a relatively greater LV dyssynchrony because women, on average, have smaller hearts. Because current CRT guideline recommendations are based on clinical trials which included approximately 75% men, they are biased to reflect CRT outcomes in men.[5,34] Consequently, the use of an uniform QRS duration threshold for recommending CRT in both sexes, although appropriate in men, may deny a potentially very beneficial therapy to many women with a smaller QRSd, but likely to benefit from CRT. This has raised discussion for the introduction of more lenient QRSd selection criteria in women.[39] In this respect, achieving a better understanding of the greater CRT response in women is of great importance.

Limitations

The observational and retrospective nature of the study should be acknowledged. Due to the retrospective character and lack of a control group we cannot show that women respond better to CRT, but rather that among CRT-recipients, women do better than men. Also, we did not have information on the cause of death. It would especially be of interest to investigate cardiovascular mortality because women in the general population live longer than men. Still, for a comparison of volumetric response and outcome between sexes, it can be assumed that this design is useful and allows for hypothesis generating. In addition, some selection bias might have occurred because in a proportion of the patients in the MUG database, no baseline and follow-up echocardiography were available. Also, because atrial fibrillation leads to a lower biventricular pacing rate and, hence, reduces the effect of CRT, patients with atrial fibrillation were excluded from the current analysis. Still, we investigated numerous potential confounders in the sex-CRT response relationship, including volumetric response and the PR interval, which have been shown to be associated with long-term outcome after CRT.[40,41] Importantly, to the best of our knowledge this is the first study to evaluate sex-specific differences in CRT outcomes by quantifying the underlying electrical substrate responsive to CRT with the vectorcardiography-derived QRS area. Although, we demonstrated that a part of the female advantage in volumetric response to CRT can be explained by their larger QRSarea/LVEDV ratio, other factors -which we did not study- likely influence the superior CRT response in women. A better understanding of the way in which CRT works and into the reasons why women respond better to CRT may eventually improve the selection and treatment of women with dyssynchronous heart failure. Whether the larger electrical dyssynchrony observed in women in the present study is the result of current guideline-based CRT selection criteria and whether sex-specific modifications to international guideline recommendations should be incorporated, is of interest for future research.

CONCLUSIONS

Women undergoing CRT display more LV electrical dyssynchrony at baseline as compared to men, which is most pronounced when correcting electrical dyssynchrony for heart size by echocardiographic LVEDV. The larger electrical dyssynchrony in smaller hearts, represented by the QRSarea/LVEDV-ratio, contributes in part to the greater volumetric response observed in women after CRT but not to the better long-term outcomes. When assessing long-term outcomes, female sex remained associated with the composite endpoint independent of age, heart failure etiology, comorbidities, LV dyssynchrony, heart size or volumetric response, suggesting that the better overall survival in female CRT-recipients might arise primarily from factors intrinsic to the female sex.

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SUPPLEMENTAL MATERIALS

Supplemental table 1. Baseline table of patients who did or did not show volumetric CRT response, categorized by sex .

	Women n=228		**Men n=497**		**Female**	**Male**
	Volumetric response		**Volumetric response**			
	yes - 156 (68)	no - 72 (32)	yes – 261 (53)	no – 136 (47)	***p*-value**	***p*-value**
Age -yr	65±11	64±11	65±10	66±11	0.594	0.321
Height - cm	165.5±7.6	166.3±7.8	177.4±7.5	177.5±7.0	0.474	0.891
Body mass index	26.5±5.3	27.5±6.3	26.5±4.4	26.8±4.3	0.264	0.465
Body surface area	1.8±0.2	1.9±0.2	2.0±0.2	2.0±0.2	0.226	0.503
NYHA functional class I/II - n (%)	51 (32.7)	17 (23.6)	114 (43.7)	91 (38.6)		
NYHA functional class III/IV - n (%)	105 (67.3)	55 (76.4)	147 (56.3)	145 (61.4)	0.164	0.247
CRT-D - n (%)	142 (66.4)	72 (100)	252 (96.6)	230 (97.5)	0.009	0.556
Comorbitidies						
Ischemic cardiomyopathy - n (%)	156 (24.4)	27 (37.5)	136 (52.1)	156 (66.1)	0.041	0.002
Diabetes - n (%)	29 (18.7)	21 (29.2)	62 (23.8)	53 (22.5)	0.077	0.732
Hypertension - n (%)	61 (39.6)	30 (41.7)	116 (44.4)	98 (41.7)	0.769	0.538
Glomerular filtration rate - ml/min	68±30	67±33	77±32	72±32	0.776	0.099
Medication - n (%)						
Betablokker	134 (85.9)	62 (86.1)	225 (86.2)	199 (84.3)	0.966	0.533
ACE-i/ABR	141 (90.4)	68 (94.4)	239 (91.6)	217 (91.9)	0.303	0.878
Diuretics	128 (82.1)	59 (81.9)	204 (78.2)	193 (81.8)	0.984	0.315
Statin	62 (39.7)	39 (54.2)	156 (59.8)	165 (69.9)	0.042	0.018
Antiarrhythmic†	9 (5.8)	4 (5.6)	26 (10.0)	36 (15.3)	0.948	0.075
Echocardiography						
LV ejection fraction -%	23.1±7.5	22.4±7.4	22.1±6.9	23.5±6.9	0.460	0.027
LV ESV - ml	134 [103-194]	142 [98-190]	187 [133-236]	167 [128-219]	0.895	0.208
LV ESVi - ml/m^2	74 [57-106]	82 [58-103]	90 [68-118]	84 [63-111]	0.778	0.037
LV EDV - ml	180 [143-235]	195 [138-244]	235 [180-298]	226 [175-286]	0.959	0.703
LV EDVi – ml/m^2	97 [80-134]	105 [75-128]	113 [91-148]	114 [88-141]	0.667	0.195
Electrocardiography						
LBBB - n (%)	149 (95.5)	52 (72.2)	221 (84.7)	166 (70.3)	<0.001	<0.001
QRS duration - ms	160.2±17.6	155.9±21.2	168±21	160±22	0.116	<0.001
PR interval - ms	173±27	188±34	190±34	200±45	0.002	0.006
Heart rate - bpm	72.4±12.5	75.7±14.8	70.5±13.5	70.8±14.7	0.085	0.789
Vectorcardiography						
QRS area - µVs	142.5±52.7	108.6±54.1	142.1±63.2	100.9±41.9	<0.001	<0.001
Correction for heart size						
QRS area/LVEDV – µVs/ml	0.78±0.32	0.60±0.37	0.62±0.33	0.47±0.27	<0.001	<0.001

† Amiodarone/verapamil/flecainide/sotalol ABR: angiotensin receptor blockers, ACE-i: angiotensin-converting-enzyme inhibitor, CRT-D: CRT defibrillator, EDV(i): (indexed) end diastolic volume, ESV(i): (indexed) end systolic volume, LBBB: left bundle branch block, LV left ventricular, NYHA: New York Heart Association

Supplemental table 2. Baseline table of patients who did or did not reach the secondary eindpoid. categorized by sex

	Women n=228 Secondary endpoint		Men n=497 Secondary endpoint		Female	Male
	yes – 54 (24)	**no – 174 (76)**	**yes – 177 (36)**	**no – 320 (64)**	***p*-value**	***p*-value**
Age -yr	66.3±10.7	64.2±11.1	66.6±10.4	65.1±10.0	0.220	0.105
Height - cm	167.4±8.2	165.3±7.5	177.0±6.9	177.7±7.4	0.085	0.319
Body mass index	25.0±4.6	27.4±5.9	26.1±4.1	26.9±4.4	0.007	0.058
Body surface area	1.8±0.2	1.8±0.2	2.0±0.2	2.0±0.2	0.190	0.037
NYHA functional class						
I/II - n (%)	7 (13.0)	61 (35.1)	38 (21.5)	167 (52.2)		
III/IV - n (%)	47 (87.0)	113 (64.9)	139 (78.5)	153 (47.8)	0.002	<0.001
CRT-D - n (%)	52 (96.3)	162 (93.1)	174 (98.3)	308 (96.3)	0.393	0.200
Comorbitidies						
Ischemic cardiomyopathy - n (%)	22 (40.7)	43 (24.7)	114 (64.4)	178 (55.6)	0.023	0.057
Diabetes - n (%)	9 (16.7)	41 (23.7)	44 (24.9)	71 (22.2)	0.276	0.499
Hypertension - n (%)	19 (35.2)	72 (41.9)	67 (37.9)	147 (46.1)	0.383	0.076
Glomerular filtration rate - ml/min	56±25	71±32	65±31	80±32	0.003	<0.001
Medication - n (%)						
Betablokker	47 (87.0)	149 (85.6)	147 (83.1)	277 (86.6)	0.795	0.290
ACE-i/ABR	51 (94.4)	158 (90.8)	159 (89.8)	297 (92.8)	0.398	0.247
Diuretics	51 (94.4)	136 (78.2)	159 (89.8)	238 (74.4)	0.006	<0.001
Statin	26 (48.1)	75 (43.1)	114 (64.4)	207 (64.7)	0.514	0.950
Antiarrhythmic†	4 (7.4)	9 (5.2)	26 (14.7)	36 (11.3)	0.536	0.267
Echocardiography						
LV ejection fraction -%	20.4±7.3	23.8±7.4	21.6±6.3	23.4±7.2	0.003	0.006
LV ESV - ml	173 [129-225]	128 [100-187]	198 [159-264]	166 [125-214]	0.021	<0.001
LV ESVi - ml/m^2	96 [72-121]	69 [56-99]	100 [76-132]	81 [62-104]	0.004	<0.001
LV EDV - ml	215 [168-251]	174 [138-232]	262 [202-325]	216 [171-275]	0.092	<0.001
LV EDVi – ml/m^2	121 [89-138]	95 [75-126]	131 [99-162]	107 [85-167]	0.022	<0.001
Electrocardiography						
LBBB - n (%)	45 (83.3)	156 (89.7)	126 (71.2)	261 (81.6)	0.209	0.008
QRS duration - ms	156±21	160±18	162±22	165±21	0.277	0.204
PR interval - ms	185±36	176±28	201±45	191±37	0.048	0.005
Heart rate - bpm	73.4±12.5	73.4±13.6	72.5±14.8	69.6±13.5	0.992	0.025
Vectorcardiography						
QRS area - µVs	124.1±67.5	134.2±51.0	105.7±50.0	131.9±59.9	0.100	<0.001
Correction for heart size						
QRS area/LVEDV – µVs/ml	0.61±0.34	0.76±0.34	0.43±0.25	0.62±0.32	0.005	<0.001

† Amiodarone/verapamil/flecainide/sotalol ABR: angiotensin receptor blockers, ACE-i: angiotensin-converting-enzyme inhibitor, CRT-D: CRT defibrillator, EDV(i): (indexed) end diastolic volume, ESV(i): (indexed) end systolic volume, LBBB: left bundle branch block, LV left ventricular, NYHA: New York Heart Association

Supplemental table 3. Univariable and multivariable predictors of volumetric response

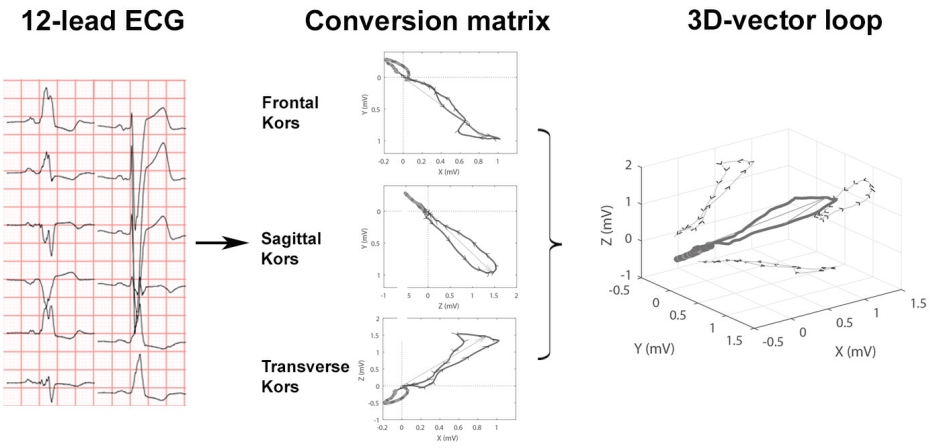
	Univariable logistic regression		Multivariable logistic regression*	
	OR (95% CI)	***p*-value**	**OR (95% CI)**	***p*-value**
Female sex	1.959 (1.408-2.725)	<0.001	1.38 (0.95-2.02)	0.093
Age - y	0.995 (0.982-1.008)	0.465		
NYHA class III/IV	0.825 (0.608-1.119)	0.216		
CRT-D	0.340 (0.137-0.846)	0.020	0.57 (0.22-1.46)	0.239
Comorbidities - n (%)				
Ischemic CMP	0.489 (0.363-0.660)	<0.001	0.82 (0.56-1.20)	0.311
Glomerular filtration rate (ml/min)	1.003 (0.998-1.003)	0.256		
Medication - n (%)				
Statin	0.558 (0.412-0.757)	<0.001	0.81 (0.56-1.17)	0.267
Antiarrhythmic†	0.592 (0.373-0.942)	0.046	0.84 (0.50-1.43)	0.524
Echocardiography				
LV ESV - ml	1.000 (0.998-1.002)	0.900		
LV EDV - ml	0.9990 (0.998-1.001)	0.478		
LV EDVi – ml/m2	1.001 ()0.997-1.005)	0.611		
Electrocardiography				
Heart rate - bpm	1.002 (0.992-1.012)	0.756		
LBBB – n (%)	3.250 (2.200-4.802)	<0.001	2.03 (1.33-3.11)	0.001
PR interval - ms	0.990 (0.986-0.994)	<0.001	0.99 (0.99-1.00)	0.006
QRSd - ms	1.014 (1.007-1.022)	<0.001	1.01 (1.00-1.02)	0.008
Vectorcardiography				
QRS area - µVs	1.015 (1.011-1.018)	<0.001		
Correction for heart size				
QRSarea/EDV -µVs/ml	4.404 (2.700-7.184)	<0.001	3.03 (1.68-5.46)	<0.001

* corresponding to model 1 + QRSarea/LVEDV-ratio according to Table 2 in manuscript.
† Amiodarone/verapamil/flecainide/sotalol ABR: angiotensin receptor blockers, ACE-i: angiotensin-converting-enzyme inhibitor, CRT-D: CRT defibrillator, EDV(i): (indexed) end diastolic volume, ESV(i): (indexed) end systolic volume, LBBB: left bundle branch block, LV left ventricular, NYHA: New York Heart Association, OR: odds ratio

Supplemental table 4. Univariable and multivaribale predictors of the composite endpoint

	Univariable Cox regression		Multivariable Cox regression*	
	HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**
Female sex	0.573 (0.421-0.780)	<0.001	0.62 (0.44-0.89)	0.009
Age - y	1.023 (1.009-1.036)	0.001	1.00 (0.98-1.02)	0.95
NYHA class III/IV	1.846 (1.323-2.578)	<0.001	1.66 (1.15-2.38)	0.006
CRT-D	1.691 (0.696-4.108)	0.246		
Comorbidities - n (%)				
Ischemic CMP	1.461 (1.121-1.903)	0.005	0.83 (0.60-1.14)	0.250
Glomerular filtration rate (ml/min)	0.984 (0.979-0.989)	<0.001	0.98 (0.98-0.99)	<0.001
Medication - n (%)				
Statin	1.105 (0.847-1.443)	0.461		
Antiarrhythmic†	1.561 (1.056-2.306)	0.025	1.26 (0.83-1.92)	0.279
Echocardiography				
LV ESV - ml	1.003 (1.002-1.005)	<0.001		
LV EDV - ml	1.003 (1.001-1.004)	<0.001		
LV EDVi – ml/m2	1.007 (1.004-1.009)	<0.001	1.00 (1.00-1.01)	0.050
Electrocardiography				
Heart rate - bpm	1.005 (0.997-1.014)	0.238		
LBBB – n (%)	0.612 (0.456-0.823)	0.001	0.84 (0.60-1.19)	0.333
PR interval - ms	1.007 (1.004-1.010)	<0.001	1.00 (1.00-1.01)	0.288
QRSd - ms	0.993 (0.986-0.999)	0.024	0.99 (0.99-1.00)	0.137
Vectorcardiography				
QRS area - µVs	0.994 (0.991-0.996)	<0.001		
Correction for heart size				
QRSarea/EDV -µVs/ml	0.279 (0.173-0.449)	<0.001	0.32 (0.26-0.63)	0.001

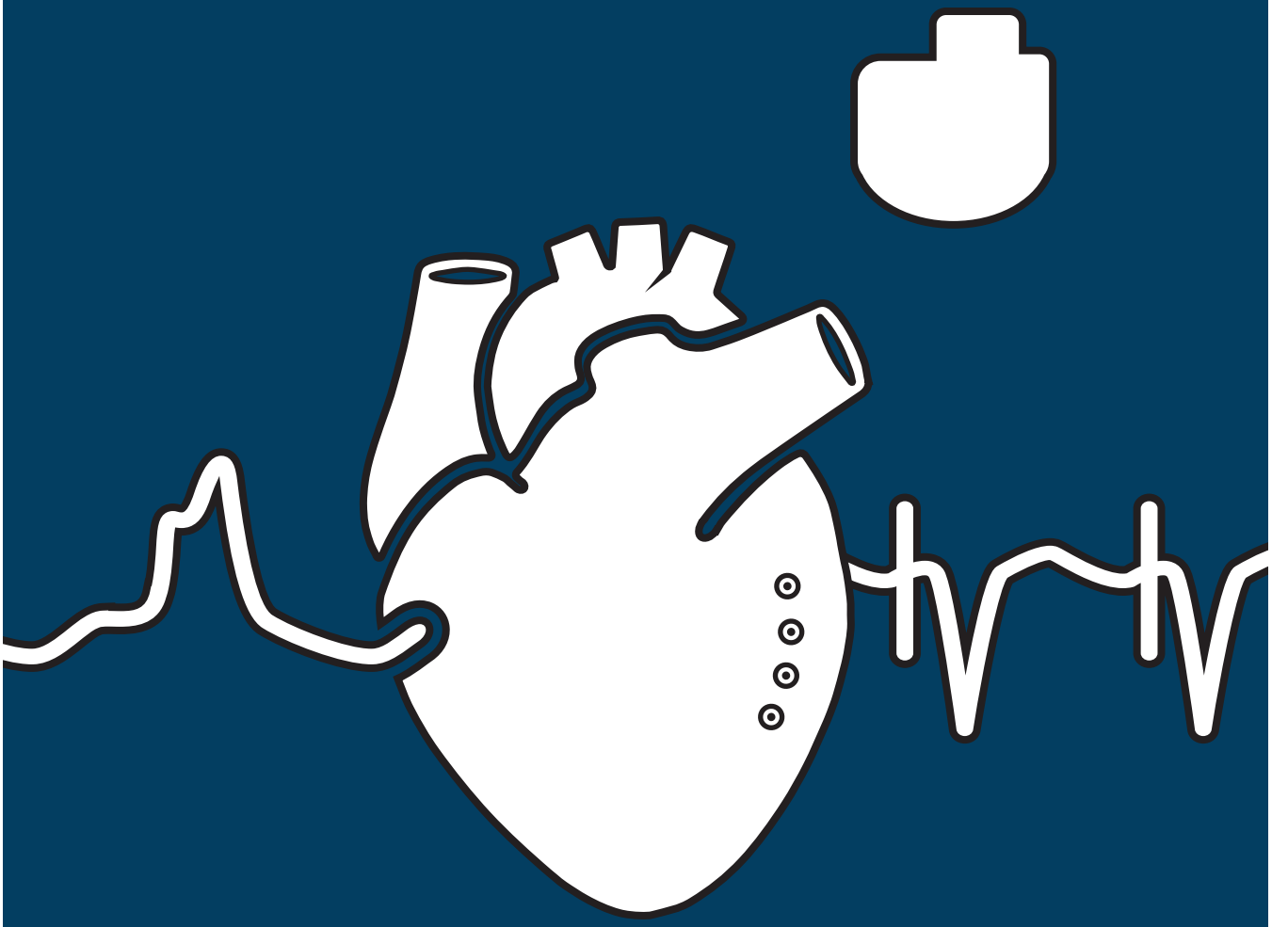
* corresponding to model 2 + QRSarea/LVEDV-ratio according to Table 2 in manuscript.
† Amiodarone/verapamil/flecainide/sotalol ABR: angiotensin receptor blockers, ACE-i: angiotensin-converting-enzyme inhibitor, CRT-D: CRT defibrillator, EDV(i): (indexed) end diastolic volume, ESV(i): (indexed) end systolic volume, HR: Hazard ratio, LBBB: left bundle branch block, LV left ventricular, NYHA: New York Heart Association

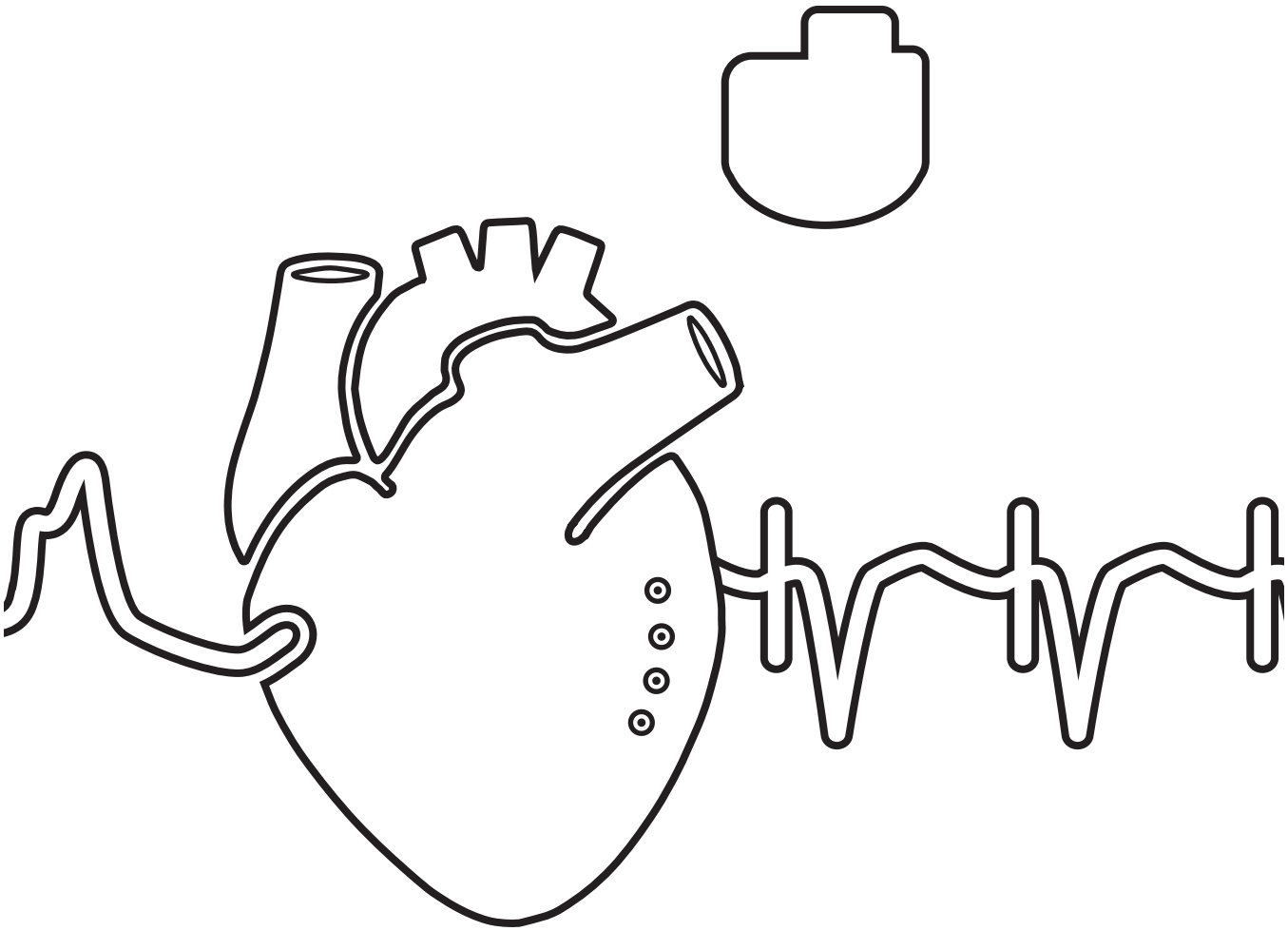


Supplemental figure 1. Conversion of 12-lead electrocardiogram (ECG) by the Kors conversion matrix into the three orthogonal vectorcardiography (VCG) leads matrix and a three-dimensional vector loop. QRS area can be subsequently calculated as the sum of the area under the QRS complex in the orthogonal vectorcardiographic leads (QRS area=[$QRS_{area,x}^{2}$+$QRS_{area,y}^{2}$+$QRS_{area,z}^{2}$]$^{1/2}$).

Part two

Image-guided CRT delivery

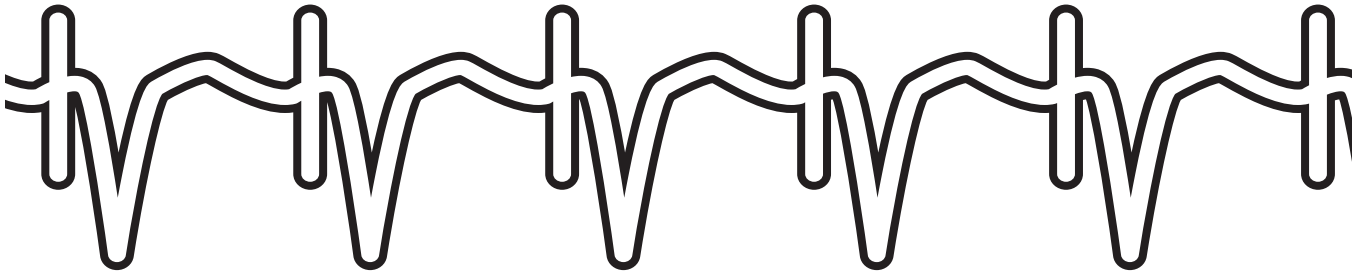




Chapter 5

Feasibility and potential benefit of pre-procedural CMR imaging in patients with ischaemic cardiomyopathy undergoing cardiac resynchronization therapy

Netherlands Heart Journal 2020;28:89-95.



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ABSTRACT

Purpose

To determine the feasibility and potential benefit of a full cardiac magnetic resonance (CMR) work-up for assessing the location of scarred myocardium and the region of latest contraction (LCR) in patients with ischaemic cardiomyopathy (ICM) undergoing cardiac resynchronisation therapy (CRT).

Methods

In 30 patients, scar identification and contraction timing analysis was retrospectively performed on CMR images. Fluoroscopic left ventricular (LV) lead positions were scored with respect to scar location, and when placed outside scar, with respect to the LCR. The association between the lead position with respect to scar, the LCR and echocardiographic LV end-systolic volume (LVESV) reduction was subsequently evaluated.

Results

The CMR work-up was feasible in all but one patient, in whom image quality was poor. Scar and contraction timing data were succesfully displayed on 36-segment cardiac bullseye plots. Patients with leads placed outside scar had larger LVESV reduction (-21±21%, *n*=19) compared to patients with leads within scar (1±25%, *n*=11), yet total scar burden was higher in the latter group. There was a trend towards larger LVESV reduction in patients with leads in the scar-free LCR, compared to leads situated in scar-free segments but not in the LCR (-34±14% vs -15±21%, *p*=0.06).

Conclusions

The degree of reverse remodelling was larger in patients with leads situated in a scar-free LCR. In patients with leads situated within scar there was a neutral effect on reverse remodelling, which can be caused both by higher scar burden or lead position. These findings demonstrate the feasibility of a CMR work-up and potential benefit in ICM patients undergoing CRT.

INTRODUCTION

Cardiac resynchronisation therapy (CRT) is an effective therapy for patients with chronic heart failure, impaired left ventricular (LV) ejection fraction and prolonged QRS duration.[1] Yet, 30-40% of patients do not benefit from the treatment [2]. Patients with ischaemic cardiomyopathy (ICM) derive less benefit from CRT, with 50% of patients displaying volumetric or clinical non-response.[2-5] Both a larger scar burden and pacing in or near an area with myocardial scar are associated with a suboptimal response to CRT.[6–10] On the other hand, echocardiographic studies suggested that pacing in the region of latest contraction (LCR) is associated with improved CRT response.[11,12] In current clinical practice, the LV lead is implanted empirically at the basal lateral segment, where statistically the best response is obtained. For individual ICM patients, the location of myocardial scar represents an additional requirement for the location of the LV lead. Given the wide variation in scar distribution and scar burden, as well as a heterogeneity of electrical activation patterns, pre-procedural determination of the location of myocardial scar and mechanical delay may be of key importance in these patients. With advancements in implanting techniques, such as real-time image-guided LV lead delivery, the snare technique and multipoint pacing, tailor-made individualised therapy has become available to patients undergoing CRT.[13-16] These advances call for image post-processing techiques that can determine the location of myocardial scar and delayed contraction, so that these areas can either be avoided or targeted. Cardiac magnetic resonance imaging (CMR) has been suggested as a promising tool for this purpose. Late gadolinium enhancement (LGE) CMR is the gold standard for determining the location and transmurality of scar tissue. Furthermore, tissue tracking software packages, such as CMR feature tracking (FT), can be used to perform LV contraction timing analysis on standard CMR-CINE images.[17,18] In the present study, we therefore investigated the feasibility and potential benefit of a CMR-based approach to identify scar location, scar transmurality, and LV contraction timing. Furthermore, we assessed the effect of tissue characteristics (e.g. scar and delayed contraction) at the LV pacing electrode on LV reverse remodelling after CRT.

METHODS AND MATERIALS

Patient selection

Patients with ICM that had undergone CRT implantation and had a pre-implantation CMR scan and pre- and post-implant echocardiography acquisition were retrospectively included in the study. Patients received a CRT device in accordance with the ESC guidelines between 2006 and 2016 at the University Medical Centre Utrecht.[19] Standard CRT device implantation was performed

with the LV lead placed empirically in a coronary vein overlying the LV free wall, the right atrial lead in the right atrial appendage and the right ventricular lead in the right apicoseptal segment. Patient medical records were screened for an ischaemic origin of heart failure based on the presence of ischaemic delayed enhancement on CMR-LGE sequences, prior coronary artery bypass grafting, or percutaneous coronary intervention. The study was approved by the local medical ethical committee (METC), by whom the need for informed consent was waived.

Study design

In all patients, the location of myocardial scar, the LCR and the location of the LV pacing electrode were determined and scored on cardiac bullseye plot models. This was done by dividing the LV myocardium into a custom-made 36-segment bullseye plot representation (**Figure 1 and 2**). Subsequently, the association of the LV lead position with respect to the CMR-defined location of scar, LCR and its relation to LV reverse remodelling was assessed. LV reverse remodelling was evaluated in terms of LV end-systolic volume (LVESV) reduction.

LV lead position

Assessment of the position of the programmed LV pacing electrode on fluoroscopic projections made during CRT implantation was performed by two investigators blinded to all other study data (interobserver variability κ=0.92). The 30° right anterior oblique (RAO) view was used to determine the long axis position of the LV lead (basal, mid or apical), and the 40° left anterior oblique (LAO) view was used to determine the circumferential position of the LV lead on the free wall (anterior, anterolateral, lateral 1, lateral 2, inferolateral and inferior) (**Figure 2**).

CMR analysis

CMR scans were performed on a 1.5T MRI scanner (Achieva, Philips Medical Systems, Best, The Netherlands) using a standardised protocol as described in detail previously[14] Scar segmentations were processed using Segment CMR software (Medviso, Lund, Sweden). With this approach, scar transmurality per myocardial segment was evaluated in each patient, as well as total LV scar burden (**Figure 1**). Scar-free segments were defined as segments with scar transmurality of 0-5%. This was done to correct for artefacts and noise from, for instance, blood pool or epicardial fat. For detection of the segments of latest mechanical contraction, time to peak (TTP) analysis was performed on short-axis CMR-CINE images using CMR-FT software (TomTec Arena, 2D Cardiac Performance Analysis MR, Unterschleißheim, Germany) as described previousl.[14] In short: endo- and epicardial borders of the short-axis CMR-CINE sequences were drawn manually in the end-diastolic frame for all slices. CMR-FT software then automatically followed the myocardial borders throughout the remainder of the cardiac cycle. This resulted in automatically generated

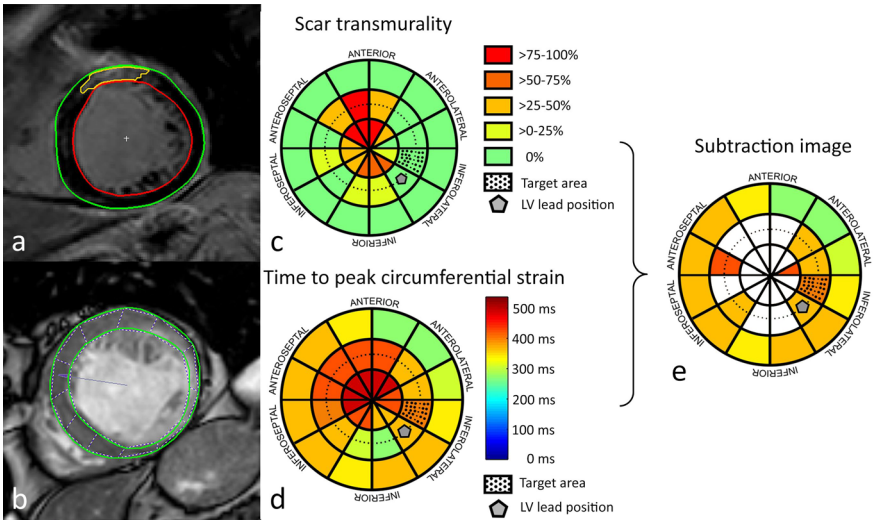

Figure 1. Cardiac magnetic resonance (CMR) processing.
(**a**) Segmentation of late gadolinium enhancement CMR sequences used to determine myocardial scar transmurality and position. (**b**) Feature tracking of CMR-CINE sequences used for strain analysis and determination of the area of latest time-to-peak circumferential strain. (**c, d**) 36-segment cardiac bullseye plots depicting segmental scar transmurality (**c**) and time-to-peak circumferential strain (**d**). The subtraction image (**e**) shows the contraction timing as shown in (**d**) with subtraction of scarred segments from (**c**). The left ventricular target area is depicted as a *dotted* segment and the left ventricular lead position is marked by a *pentagon*. *LV* left ventricular

circumferential strain data, which were manually checked and corrected when necessary to ensure optimal strain data. Scar transmurality and TTP-strain data were expressed on cardiac bullseye plots using an in-house-developed software program running in MATLAB and Statistics Toolbox (The MathWorks, Inc., Natick, MA, USA) (**Figure 1**). The location of the fluoroscopic LV pacing electrode was scored in a blinded fashion as within an area of scar ('within scar') or at a scar-free site ('outside scar'). In patients with an LV lead in a scar-free segment, the LV lead location was subsequently scored with respect to the segment with the highest TTP strain (latest contracting region) and defined as 'within the LCR' or 'outside of the LCR'.

Statistics

Statistical analysis was performed using IBM SPSS Statistics 25 software (IBM, Armonk, NY, USA). Continuous variables were tested for normality with a Shapiro-Wilk test, and were described using mean±standard deviation or, in the case of non-normal distribution, with the median (interquartile range). Categorical data were described by an absolute number of occurrences and associated frequency (%). Between-group comparisons were performed with Mann-Whitney U tests (continuous data with non-normal distribution), unpaired Student *t*-test (normally distributed data) and Pearson

chi-square test or, if there was an expected cell count of <5, Fisher's exact test (dichotomous variables). A *p*-value of <0.05 was considered to be significant and all tests were two-tailed.

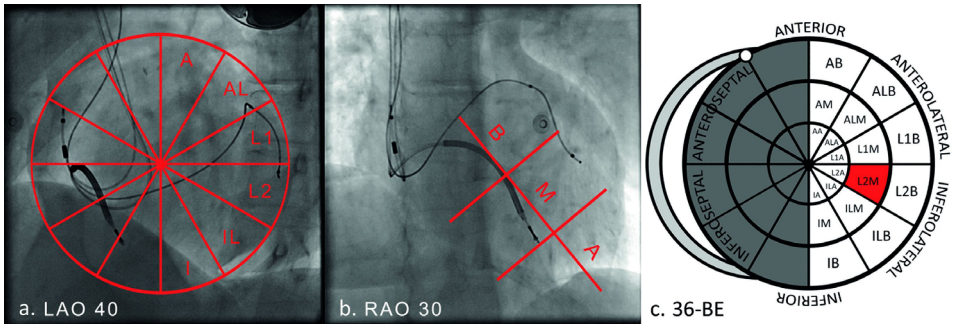

Figure 2. Identification of the left ventricular lead position on fluoroscopy images. (**a**)Left anterior oblique (*LAO*) 40º view of the heart with the lateral part of the left ventricle divided into six segments (*A* anterior, *AL* anterolateral, *L1* lateral 1, *L2* lateral 2, *IL* inferolateral, *I* inferior) with a grid placed over the fluoroscopy image to determine the segment of pacing. (**b**) Right anterior oblique (*RAO*) 30º view of the heart divided in three levels (*B* basal, *M* mid, *A* apical). (**c**) 36-segment cardiac bullseye (*BE*) plot representing the fusion of the LAO 40º view and RAO 30º view. The distal pacing electrode, which was configurated for biventricular pacing, is located in the *red* segment

RESULTS

Baseline characteristics

A total of 35 patients met all the inclusion criteria. In four patients echocardiography quality was insufficient. CMR processing was feasible in all but one patient, in whom CMR quality was insufficient to perform FT analysis. Therefore, 30 patients were included in the analysis; their baseline characteristics are described in **Table 1**.

LV lead position in relation to myocardial scar, delayed contraction and LVESV reduction

Eleven patients (37%) had LV leads situated in scarred myocardium. Of these, three patients had the LV lead placed in a segment with >75% scar transmurality, two in an area with >50-75% scar transmurality, four in an area with >25-50% scar transmurality and two in an area with >0-25% scar transmurality. Patients in whom the LV lead was placed in a scar-free segment (*n*=19) had a significantly greater LVESV reduction at follow-up compared to patients in whom the LV lead was placed within scar (-21±21% vs 1±25% respectively, *p*=0.02). There was a trend towards larger LVESV reduction in patients with LV leads placed in a scar-free segment as well as in the LCR compared to patients with leads in a scar-free segment but not in the LCR (-34±14% vs -15±21%, *p*=0.06) (**Figure 3**).

Table 1. Baseline characteristics

	All patients	LV lead in scar-free region and LCR	LV lead in scar-free region, not in LCR	LV lead within scar
Patient characteristics	**(*n*=30)**	**(*n*=6)**	**(*n*=13)**	**(*n*=11)**
Age at implantation (years)	69.9±5.8	68±7	72±5	68±6
Male gender, ***n*** (%)	24 (80)	4 (66.7)	10 (76.9)	10 (90.9)
LBBB conduction, ***n*** (%)	23 (76.7)	5 (83.3)	10 (76.9)	8 (72.7)
QRS duration (ms)	150±19	151±29	146±18	154±14
NYHA, ***n*** (%)				
I/II	13 (43.3)	2 (33.3)	6 (46.2)	5 (45)
III/IV	15 (50)	3 (50)	7 (53.8)	5 (45)
Scar burden (%) (interquartile range)	19 (14-24)	13 (5-31)	14 (12-22)*	21 (18-44)*
LV end-systolic volume (ml)	151±56	174±79	143±39 (p=0.06)	148±62
LV end-diastolic volume (ml)	198±63	215±91	193±41	196±72
LV ejection fraction (%)	24.8±7.0	20±5	26±7	26±7*
Comorbidities, *n* (%)	10 (33.3)			
Atrial fibrillation	9 (30)	1 (16.7)	5 (38.5)	3 (27.3)
Hypertension	16 (53.3)	5 (83.3)	8 (61.5)*	3 (27.3)*
Smoking	19 (63.3)	5 (83.3)	7 (53.8)	7 (63.6)
Medication, *n* (%)				
Beta blocker	21 (70)	4 (66.7)	11 (84.6)	6 (54.5)
ACE-i/ARB	29 (96.7)	5 (100)	14 (100)	10 (90.9)
Diuretics	25 (83.3)	5 (83.3)	12 (92.3)	8 (72.7)

Data presented as mean with standard deviation, median with interquartile range
* Significant difference ($p<0.05$) *LBBB* left bundle branch block according to ESC 2013 criteria[2], *NYHA class* New York Heart Association functional classification, *LV* left ventricular, *ACE-i* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker

Myocardial scar burden

The amount of reverse remodelling after CRT is affected not only by the presence or absence of myocardial scar or significant mechanical delay at the LV pacing electrode, but also by the total LV scar burden. Median LV scar burden was 19% (14-24). Scar burden was significantly higher in patients with leads within scar compared to patients with leads in scar-free myocardial segments [21% (18-44) vs 15% (10-22), p=0.02]. Scar burden did not vary between patients with leads in a scar-free segment as well as in the LCR and patients with leads in a scar-free segment but outside of the LCR [15% (5-35) vs 15% (11-22), p=0.677).

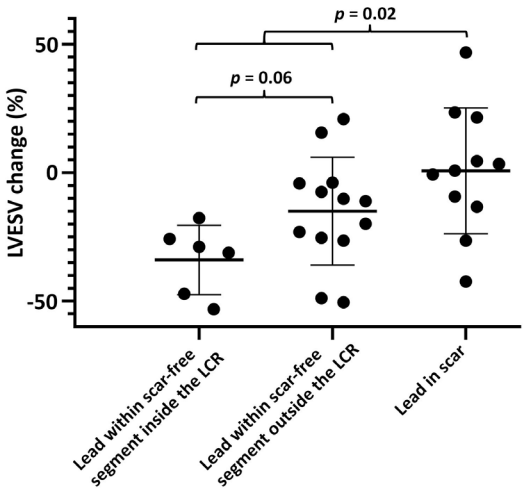

Figure 3. Echocardiographic response versus lead location in relation to the myocardial scar and the region of latest contraction (*LCR*) Relation between scar location, the location of the LCR, the LV pacing electrode and its relation to left ventricular end systolic volume (*LVESV*) change

DISCUSSION

The present study demonstrates the feasibility and potential benefit of a CMR work-up for the assessment of the optimal site for LV pacing based on myocardial scar transmurality and the area of latest contraction. For the visualisation of scar and delayed contraction, 36-segment cardiac bullseye plots were used. LVESV reduction was most evident in patients with LV leads situated in scar-free segments. In addition, there was a trend towards improved LVESV reduction when the LV lead was placed outside of scar and in the LCR compared to outside of scar and outside the LCR. Because scar burden did not differ significantly between these groups, it is possible that this trend is based on a favourable lead position in these patients. In patients with LV leads placed within scar there was an overall neutral effect on reverse remodelling. This can be caused by both higher scar burden or the LV lead position. These results are in line with those of previous publications that show that pacing within scar is associated with CRT non-response, while pacing outside of scar and in the area with most delayed contraction leads to superior results.[9-12,20]

Pre-procedural identification of target sites for LV lead delivery

Despite the promising results from echocardiographic studies showing the benefit of targeted LV lead placement, such as the TARGET and STARTER trials, no prospective, randomised clinical studies currently have been published using CMR to guide LV lead delivery in CRT.[11,12] An important

limitation of echocardiography is the inability to visualise scar. Yet, in ICM patients undergoing CRT, scar identification is of key importance given the association between scar and poor outcomes.[6–10] CMR, in contrast to echocardiography, is a useful imaging modality to identify and quantify both scar and dyssynchrony in a three-dimensional fashion and, therefore, may represent the optimal imaging modality for treatment planning.[20,21] In line with our results, Taylor et al. demonstrated in a retrospective study that an LV lead position over non-scarred, late-contracting segments, assessed with CMR, was associated with improved echocardiographic response and superior outcomes in CRT patients.[20] In contrast to the present study, only 50% of patients had ICM. Importantly, Taylor et al. did not assess total LV scar burden and its impact on the relation between the LV lead location and CRT response. In addition, a novelty of the present study is that we used smaller LV segments to visualise scar and mechanical delay. When displaying these data on American Heart Association 17-segment cardiac bullseye plots, we believe that the accuracy of CMR is not fully exploited; hence we created smaller LV segments.

Clinical implications

This study shows that CMR is a potentially useful tool that could be used to identify target sites for LV stimulation and, hence, prospectively plan and guide LV lead delivery in patients undergoing CRT implantation. This is especially valuable in patients with scarred myocardium, in whom it is unlikely that a single, empirical location for LV lead placement will adequately resynchronise all patients. Eleven patients (37%) in our study had LV leads positioned in scarred myocardium while a pre-implantation CMR-LGE scan was at the implanting cardiologist's disposal. These data suggest that pre-procedural visual inspection of the plain MRI dataset can not always prevent lead implantation in scarred segments. More advanced, image-guided LV lead implantation, in which scarred myocardium or target sites for LV lead delivery are projected on top of the live fluoroscopy during implantation, might overcome this problem.[13,14,21] When retrospectively assessing the availability of a suitable coronary branch on fluoroscopy in the current study, a suitable alternative target vein was available in a scar-free segment in nine out of these 11 patients. This is an interesting finding because it further fuels the concept of careful assessment of CMR images before performing CRT implantation. Still, we recognise that we do not know whether acceptable capture thresholds without phrenic nerve stimulation would have been available in non-scarred segments in these nine patients.

Limitations and challenges

The two main limitations of this study are the retrospective design and small sample size. This is caused by the fact that we included only patients with myocardial scar on CMR-LGE scans that were performed before CRT implantation. Differences in baseline characteristics between patients

could have influenced our results. For example, patients with LV leads placed within scar had more unfavourable characteristics at baseline (e.g. higher scar burden, lower frequency of left bundle branch block and more males). The advantage of CMR-FT is that it is a relatively easy technique for contraction timing analysis since it can be performed on CMR-CINE images, which are obtained during standard cardiac imaging protocols. Still, there are some limitations when assessing TTP-strain data. Both electrical substrates (which are generally responsive to CRT) and non-electrical substrates, such as hypocontractility and myocardial scar (which do not respond to CRT) may cause TTP-strain delay.[22] To avoid noise from scarred segments causing TTP-strain delay, we determined contracting timing only in segments outside scarred myocardium (**Figure 1e**). Due to between-group differences and the restrospective study design we cannot draw firm conclusions regarding the superior effect of placing the LV lead in a CMR-defined LV target segment. Yet, the present study is a feasibility study of a full-CMR work-up. Larger trials are needed to further determine whether this approach leads to improved CRT response.

CONCLUSION

This study demonstrates the feasibility and potential benefit of a CMR work-up to determine optimal LV pacing sites in ICM patients undergoing CRT implantation. Patients in whom the LV lead was placed in a scar-free region with most delayed contraction showed marked LV reverse remodelling, while in patients with leads in scarred segments there was an overall neutral effect on LVESV change.

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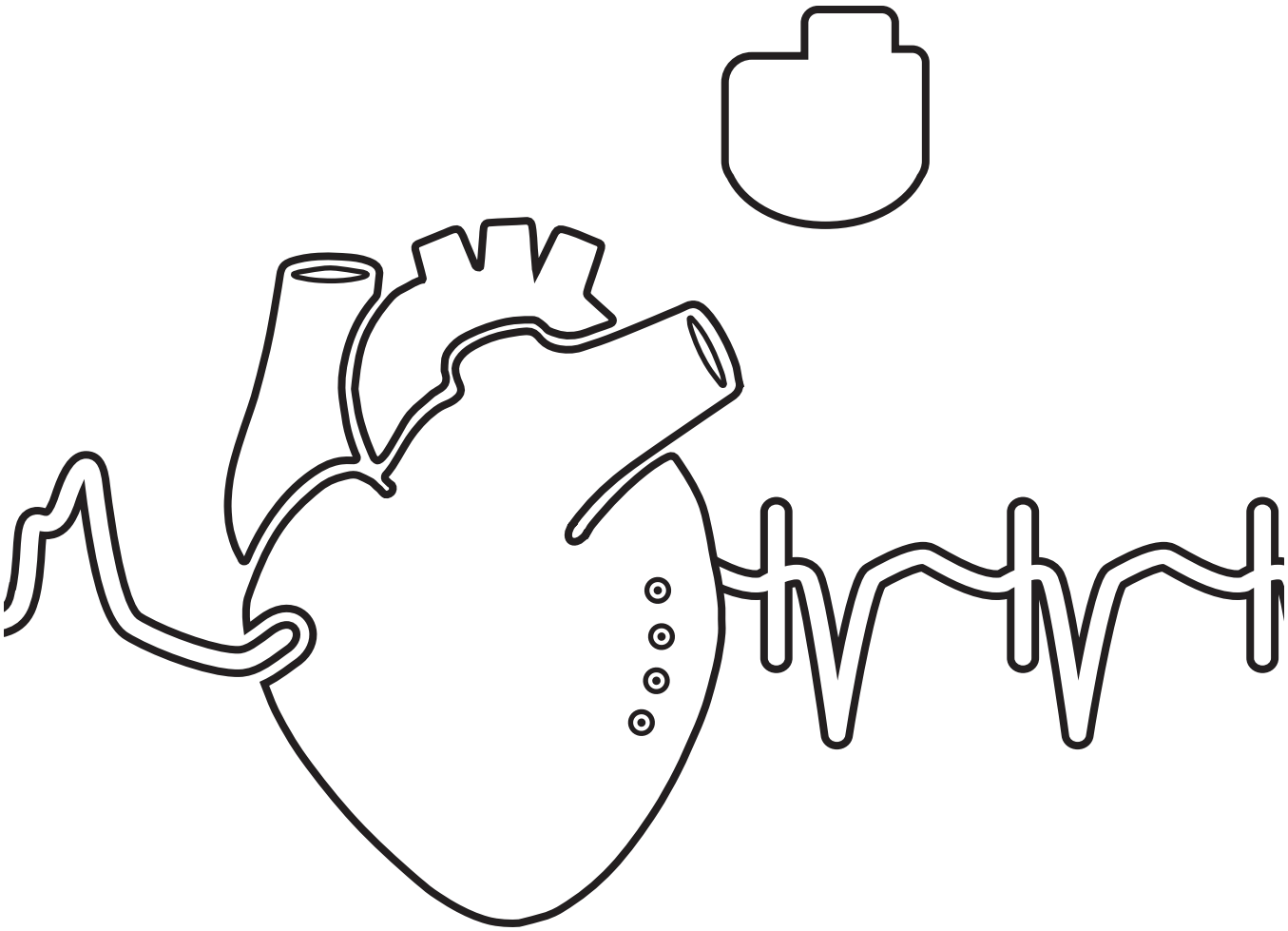

Chapter 6

Multimodality Imaging for Real-Time Image-Guided Left Ventricular Lead Placement during Cardiac Resynchronization Therapy Implantations

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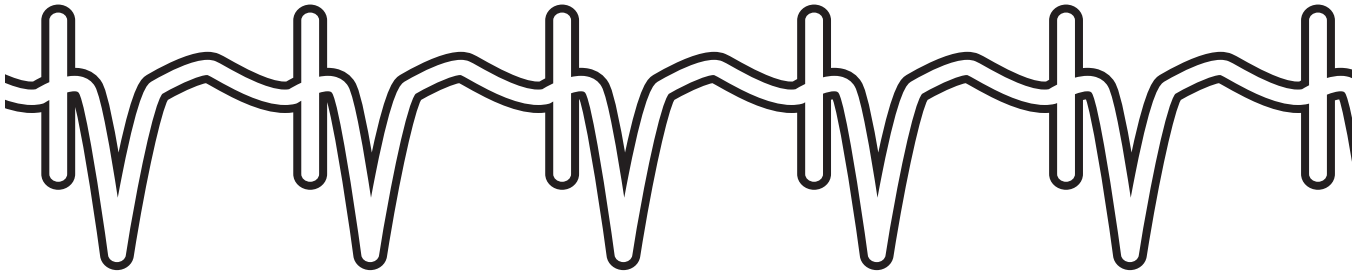

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The first two and last two authors contributed equally to this manuscript.

ABSTRACT

Purpose

To evaluate the feasibility of intra-procedural visualization of optimal pacing sites and image-guided left ventricular (LV) lead placement in cardiac resynchronization therapy (CRT).

Methods

Pre-procedurally defined optimal pacing sites were visualized intra-procedurally in fifteen patients (10 males, 68±11 years, 7 with ischemic cardiomyopathy and ejection fraction of 26±5%). Cardiac magnetic resonance (CMR) derived scar and dyssynchrony maps were created for all patients. In six patients the anatomy of the left phrenic nerve (LPN) and coronary sinus ostium was assessed via a computed tomography (CT) scan. By overlaying the CMR and CT dataset onto live fluoroscopy, aforementioned structures were visualized during LV lead implantation. In the first nine patients, the platform was tested, but no real-time image-guidance was implemented. In the last six patients real-time image-guided LV lead placement was performed.

Results

Real-time visualization of target areas for LV lead delivery was feasible in all patients. CRT implant and fluoroscopy times were similar to previous procedures and all leads were placed close to the target area but away from scarred myocardium and the LPN. Patients that received real-time image-guided LV lead implantation were paced closer to the target area compared to patients that did not receive real-time image-guidance (8mm [IQR: 0-22] versus 26mm [IQR 17-46], p=0.04), and displayed marked LV reverse remodeling at six months follow up with a mean LVESV change of -30±10% and a mean LVEF improvement of 15±5%.

Conclusions

Real-time image-guided LV lead implantation is feasible and may prove useful for achieving the optimal LV lead position.

INTRODUCTION

Cardiac resynchronization therapy (CRT) has had a major beneficial effect on the treatment of patients with symptomatic heart failure, severe left ventricular (LV) dysfunction, and prolonged QRS duration. Nevertheless up to 30-45% of patients do not obtain a clinical or echocardiographic benefit from CRT.[1] Improving CRT response rate has been the main focus of many researchers in the field, whom have demonstrated that improved response can be achieved by targeting optimal pacing sites for LV stimulation.[2–4]

LV lead placement in or near an area of myocardial scar worsens outcomes,[4–6] while pacing in or near an area of latest mechanical contraction improves both response rate and prognosis after CRT.[2,3] Still, the fluoroscopic projections used during CRT implantation provide no tissue characteristics, and therefore no information regarding the optimal site for LV pacing. Consequently, LV leads are mostly placed empirically on the posterolateral wall in patients undergoing CRT. However, there is a substantial inter-individual variation regarding the optimal pacing site as a result of myocardial scar regions and diversity in intrinsic electrical activation of the myocardium. Cardiac magnetic resonance (CMR) imaging has been proposed as a promising tool for LV target area identification since it is able to assess myocardial scar tissue with late gadolinium enhancement (LGE) and mechanical dyssynchrony with feature tracking.[6] Yet, LV lead delivery into target areas remains difficult due to left phrenic nerve (LPN) stimulation. And restrictions caused by coronary vein anatomy.

Aforementioned challenges call for additional techniques that offer real-time visualization of optimal pacing sites during CRT device implantation. In the present study, we test the feasibility of a custom-made treatment-guidance platform (CARTBox[7], CART-Tech B.V., Utrecht, The Netherlands) for real-time visualization of scar location, latest contracting area, and LPN position onto live fluoroscopy during CRT implantation procedures.

METHODS

Study population

Fifteen patients with an indication for CRT according to the current ESC guidelines were prospectively enrolled.[8] Patients with severely impaired renal function (GFR < 30 ml/min/1.73m^2), and patients with a contraindication for cardiac magnetic resonance (CMR), as well as patients with persistent atrial fibrillation, were excluded. All subjects gave written informed consent. The study was performed according to the Declaration of Helsinki and was approved by the local institutional review board and ethics committee.

Study design

In this prospective feasibility study, LV target areas were determined on pre-procedurally acquired CMR and computed tomography (CT) scans using a custom-made platform, CARTBox (CART-Tech B.V., Utrecht, The Netherlands). After LV target area identification, target areas were co-registered with live fluoroscopy during CRT implantations.

The study was conducted in four steps to test the feasibility of the various features of CARTBox in a stepwise approach **(Figure 1)**. During steps 1-3 (including three patients per step, thus nine patients in total) *specific* tissue characteristics (scar, delayed mechanical activation, the LPN and coronary sinus ostium) (CSO) were identified on a pre-procedural CMR or CT scan. Based on the location of scar, delayed activation, and the LPN, a target area for LV lead delivery was chosen. Importantly, LV lead target area and tissue characteristics were fused with live fluoroscopic imaging, however they were not visible for the implanting cardiologist. Therefore, this group, in whom we performed treatment planning but no real-time image-guidance, is further mentioned as the non-target group. In step 4 (six patients) *all* aforementioned tissue characteristics were determined and displayed in conjunction with live fluoroscopy in the catheterization theatre during LV lead implantation. Thus enabling the implanting cardiologist to perform image-guided LV lead placement in a targeted treatment group (target group).

In all patients implantation characteristics (radiation dose, procedure and fluoroscopy time, and peri-procedural complications) were collected together with electrical properties at the stimulation electrode (pacing threshold, LPN stimulation threshold, paced QRS duration and the electrical delay, which was measured as the interval from Q on the surface ECG to local sensing at the LV electrogram (QLV), divided by QRS duration (QLV/QRS). Echocardiography was performed before and six months after implantation to determine the presence of LV reverse remodeling (defined as a ≥15% reduction in LV end-systolic volume).

Cardiac magnetic resonance imaging

CMR was performed 1-7 days prior to CRT implantation in all patients, using a 1.5T Philips Ingenia scanner (Philips Healthcare, Best, The Netherlands). Gold standard late gadolinium enhancement (LGE) CMR scans were made to determine the size and the location of the myocardial scar. Short axis steady-state-free-precession cine images were made to determine areas of latest contraction, using feature tracking (CMR-FT) software (TomTec Arena, 2D Cardiac Performance Analysis MR, Version 1.2, Unterschleissheim, Germany). The settings during the CMR acquisitions were as follows. Cine: repetition time/echo time=3.4ms/1.7ms, flip angle=60°, voxel size=1.67x1.67mm, field of view=32x32cm, 192x192 matrix, 8mm slice thickness, 30 phases/R-R interval, electrocardiogram-gated. LGE: repetition time/echo time=3.2ms/1.6ms, flip angle=15°, voxel size=2.1x2.1mm, field of view=46x46cm, 220x220 matrix, 8mm slice thickness. Cine and LGE scans were made at the same positions with the same orientation.

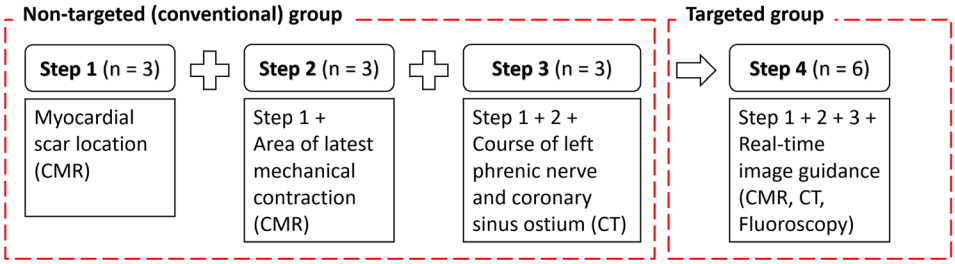

Figure 1. Schematic overview of study. Each step resembles a phase during the study. In step 1 a CMR scan was made to assess the location of myocardial scar tissue (patients 1-3). In step 2 scar identification and contraction timing analysis was performed on CMR images (patients 4-6). In step 3 a CT scan was added to identify the left phrenic nerve and coronary sinus ostium (patients 7-9). In step 1-3 the feasibility of CARTBox was tested for identification and live visualization of the structures. In step 4, steps 1-3 were combined and used for real-time image-guidance of left ventricular lead placement (patients 10-15). CMR: cardiac magnetic resonance; CRT: cardiac resynchronization therapy; CT: computed tomography.

Cardiac computed tomography

CT scans were performed 2-14 days prior to CRT implantation in nine patients for the identification of LPN and CSO. CT images were acquired using Turbo Flash in a Siemens Somatom Force 384 (2x192) row scanner (Siemens Healthcare, Forchheim, Germany). The CT protocol was optimized for visualization of contrast in the venous system using a double bolus technique to ensure opacification of the CSO. The first bolus of 60mL of iodinated contrast medium (saline:contrast ratio: 1:2, 300mg of iodine/mL, Ultravist; Bayer AG, Berlin, Germany) was administered at the start and the second bolus of 80mL was injected after 40s. Both boluses were injected at a rate of 6mL/s into the basilic vein. CT scanning was triggered by using a bolus-tracking technique, with the region-of-interest placed in the descending aorta. Image acquisition started 11s after the attenuation reached the predefined threshold of 200HU. Scanning time was approximately 0.25s. The reference tube potential and tube current were set to 100kV and 350mAs, respectively. Both were regulated by automatic potential and tube current programs (Care kV and Care dose 4D). Images were reconstructed with a 1.0mm slice thickness and a 0.4x0.4mm pixel spacing with a Bv40d reconstruction kernel.

Image processing

Image processing with CARTBox consisted of three steps **(Figures 2 and 3)**. The first step consisted of the segmentation of a) scarred myocardium and dyssynchrony on CMR images, and b) the identification of the LPN and CSO on CT-scans.

a) To start, the LV endo- and epicardium of the end-diastolic short axis CMR cine and LGE images were automatically segmented. The full width at half maximum method was used for the segmentation of myocardial scar on LGE images **(Figure 3B)**.[9] Segmentations were manually

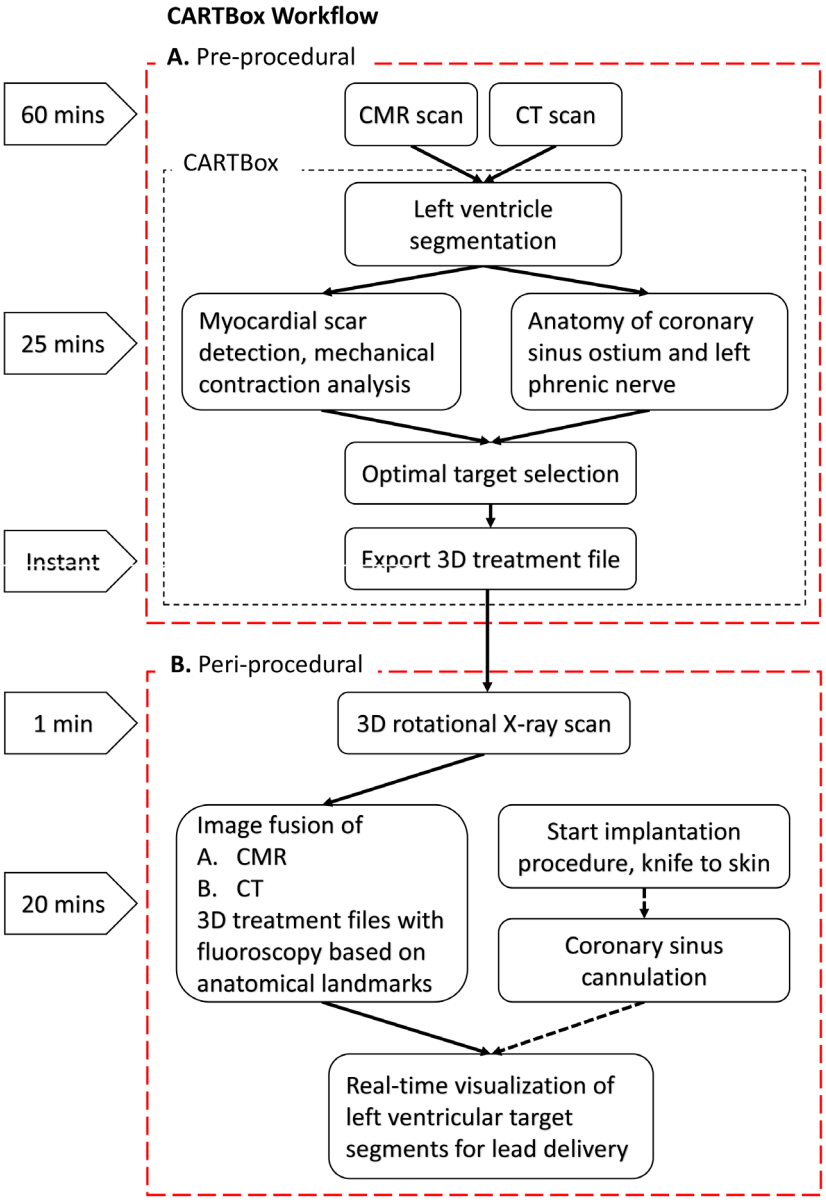

Figure 2. CARTBox workflow and time requirement. The pre-procedural workflow **(Panel A)** consists of the acquisition of cardiac MRI and CT (60 minutes in total), and image processing in CARTBox. The image processing, required to identify the optimal site for LV stimulation, and necessary to produce a detailed 3D-model of the heart, takes approximately 25 minutes per scan. The implantation procedure **(panel B)** starts with acquiring a 3D-rotational X-ray scan (minutes). The 3D-treatment files are then semi-automatically fused with the 3D-rotational scan based on anatomy landmarks. This takes approximately 20 minutes and can be performed during RV lead implantation and coronary sinus cannulation. Using this approach, LV target areas can be visualised on live fluoroscopic images during LV lead implantation. CMR: cardiac magnetic resonance; CT: computed tomography.

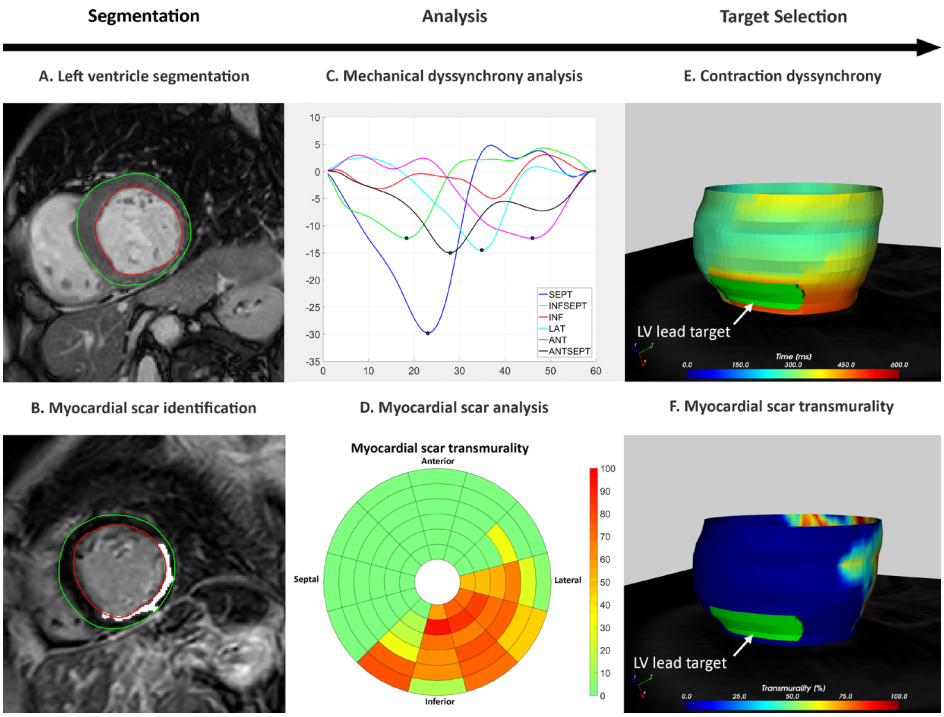

Figure 3. CARTBox workflow in images. A: Segmentation of left ventricle. **B:** Myocardial scar detected on CMR LGE scans. **C:** Contraction timing analysis displaying delayed contraction of anterior and lateral segments.. **D:** Transmurality of scar showing inferolateral infarct of the left ventricle. **E&F:** 3D-Model of contraction timing **(E)** and scar transmurality **(F)** with manual selected target segment (green). ANT: anterior; ANTSEPT: anteroseptal; INF: inferior; INFSEPT: Inferoseptal; LAT: lateral; LV: left ventricle; SEPT: septal.

adjusted if necessary. For detection of the latest mechanical contracting segments, time to peak analysis was performed on the short axis CMR cine images using CMR-FT software[10,11]. Time to peak endocardial circumferential strain was used for the identification of latest contracting segments **(Figure 3C)** because circumferential strain is believed to produce higher intra- and interobserver reproducibility than segmental radial strain analysis.[12,13] After image processing, scar transmurality and contraction timing data were projected on a 3D-epicardial surface mesh **(Figure 3E-F)**. b) After CMR processing, the location of the CSO and course of the LPN were segmented manually from CT data. A board-certified cardiac radiologist (FMH) reviewed the results of the segmentation processes.

In the second step, the implanting cardiologist selected the optimal area for LV lead delivery based on the course of the LPN and the 3D-CMR surface mesh containing scar transmurality [%] and contraction timing [ms] data **(Figure 3E-F).** Optimal pacing sites were chosen in an area

with 0% scar transmurality and most delayed contraction. Septal segments were excluded as target areas. In the final step, two 3D-treatment files were created by CARTBox in the standard DICOM format. One 3D-treatment file contained myocardial scar transmurality and the LV target segments **(Figure 4A)**. The other 3D-treatment file consisted of the anatomy of the LPN and CSO **(Figure 4B)**.

Image fusion

Prior to CRT implantation, a 3D-rotational scan was made in the catheterization theatre. In a single gantry rotation of 200°, a 3D CT-like dataset is acquired by using the Siemens Artis Zee (Syngo X workplace version B21), which allows 3D fusion of CMR and CT images with live fluoroscopy. After fusing the 3D-treatment datasets, 3D representations of the specific anatomical aspects (i.e. myocardial scar, LV lead target, LPN and/or CSO) were visualized in conjunction with the fluoroscopy images by assigning a unique color for each anatomic structure. **(Figure 4)**. After registration the targets rotate accordingly upon rotation of the C-arm. The fused images were shown in a separate part of the screen in the catheterization theatre. Directly after CRT device implantation, a second 3D-rotational scan was acquired to measure the distances between the final LV pacing electrode location and the locations of the scar, LV lead target area, and LPN.

CRT implantation

CRT device implantation was performed transvenously under local anesthesia. The right atrial and right ventricular leads were placed at conventional locations in the right atrium appendage and the right ventricular apicoseptal segment, respectively. After CS cannulation and coronary venous angiogram, a quadripolar LV lead was placed in one of the coronary veins overlying the LV free wall. After LV lead placement, all leads were connected to a CRT device.

Statistical analysis

Statistical analysis was performed with SPSS (SPSS statistics 23.0, IBM, New York, USA). Each variable was tested for normality with a Shapiro-Wilk test. Continuous variables with a Gaussian distribution were described using mean, standard deviation and those with non-normal distribution were described with the median, interquartile range (IQR). Categorical data were described by an absolute number of occurrences and associated frequency (%). Differences between groups were assessed using nonparametric testing with Mann-Whitney U test for continuous data with non-normal distribution, and unpaired Student *t*-test for continuous variables with a Gaussian distribution. Pearson Chi-Square test was used for dichotomous variables. A *p*-value below 0.05 was considered significant.

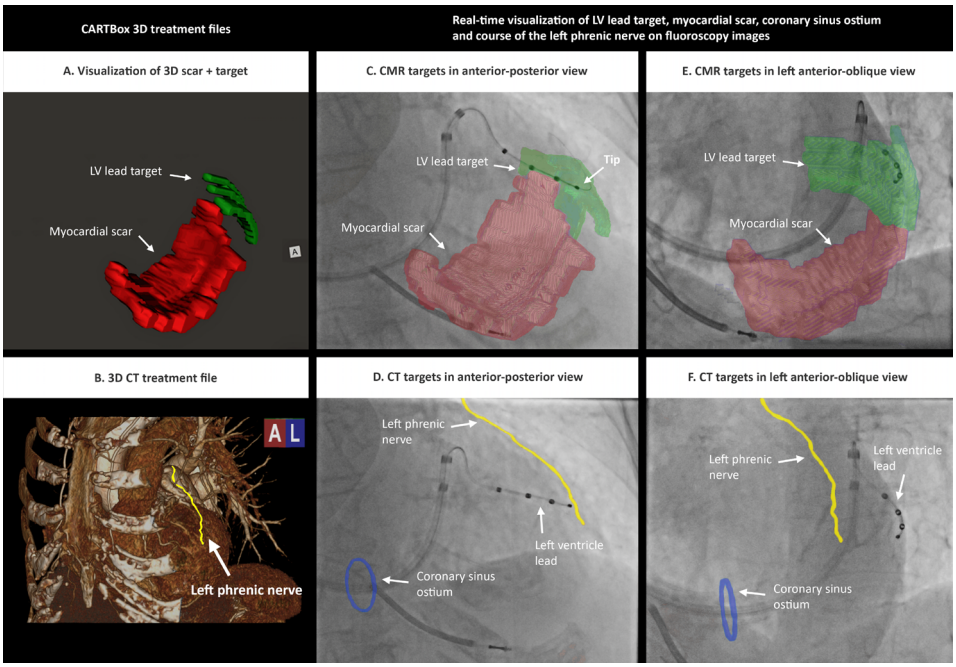

Figure 4. Real-time visualization of CMR and CT targets. A-B: 3D-treatment file of CMR data **(A)** and CT data **(B). C-F:** After 3D image fusion of the 3D-treatment dataset with fluoroscopy, the LV lead targets and scar segments **(C,E)** together with left phrenic nerve and coronary ostium **(D,F)** are visualized on live fluoroscopy during the LV lead implantation. CMR: cardiac magnetic resonance; CT: computed tomography.

RESULTS

Fifteen patients, of whom baseline characteristics are provided in Table 1, underwent de novo CRT implantation with a quadripolar LV lead. Patients were aged 68±11 years, ten were male, eleven had a left bundle branch block, and seven had ischemic cardiomyopathy (ICM) with a mean scar burden of 21±13% **(Table 1)**. Median size of the pre-procedurally defined LV target area was 10% [6-11] of total LV surface. In all patients, CARTBox was successfully applied and merging of the treatment file with live fluoroscopy images did not lengthen the procedure. Merging was performed during pocket preparation and right ventricular lead implantation. Image fusion took an average of 14±4 minutes for merging of the CT-scan, and 10±6 minutes for merging the CMR scan. CSO visualization was successful in all patients that received a pre-procedural CT and had an overall fair agreement with the CSO at fluoroscopy images. There were no intra- or post-operative complications and no reported adverse effects on renal function.

Table 1. Demographic data

	All patients (n=15)	Target group (n=6)	Non-target group
Male gender (%)	10 (67)	3 (50)	7 (78)
Age (years)	68 ± 11	67 ± 13	69 ± 9
Body mass index (kg/m$^{2)}$	26±5	27±6	26±4
NYHA functional class (n,%)			
II	12 (80)	5 (83)	7 (78)
III	3 (20)	1 (17)	2 (22)
Left bundle branch block* (n, %)	11 (73)	5 (83)	6 (67)
QRS duration (ms)	162 ± 23	165 ± 26	160 ± 22
PR interval (ms)	188 ± 34	164 ± 27†	203 ± 29
LV ejection fraction (%)	26±5	27±6	25 ± 5
LV end diastolic volume (ml)	209 [165-250]	175 [142-216]	222 [184-327]
LV end systolic volume (ml)	149 [123-198]	128 [96-169]	162 [135-250]
Ischemic cardiomyopathy (n, %)	7 (47)	2 (33)	6 (67)
Scar burden (%)	18 [13-28]	30 [15-45]	18 [7-28]

Values are in mean ± SD, median [interquartile range] and n (%). Significant differences between groups (p<0.05) are indicated with a† LV: left ventricular; NYHA: New York Heart Association. *Definition according to Strauss criteria.

LV implantation characteristics

The implantation characteristics and outcome data of patients who received real-time image-guided LV lead placement (target group) are displayed in Table 2. Total and LV implantation duration in this group were 146±38 minutes and 47±18 minutes respectively, fluoroscopy time was 36±15 minutes. CRT implantation duration and fluoroscopy times were not statistically different from recent historical controls (185±40 minutes, p=0.07, and 27±12 minutes, p=0.17 respectively).Total radiation dose was 6758±4201 cGycm^2 , the radiation dose of the pre-implantation and post-implantation 3D-rotational scan were 1188±262 cGycm^2 and 1313±333 cGycm^2 (**Table 2**). The radiation dose of the CRT implantation without 3D-rotational scan was 5753±3038 cGycm^2.

Results of image-guided CRT implantation

In all patients that received real-time image guidance, LV leads were placed out of scar, away from the LPN and within, or in close proximity to the CMR defined target area. In three out of six patients the LV lead was implanted within the target segment, in the other three patients, the LV lead was placed adjacent to the target area. In patients from the target group, LV leads were placed significantly closer to the target area compared to patients from the non-target group (8mm [IQR: 0-22] versus 26mm [IQR 17-46], p=0.04), while distance of the LV lead to scar and the LPN did not differ between groups . The electrical properties in the target group did not vary from the non-

Table 2. CRT implantation and follow up characteristics

	TARGET group (n=6)	NON-TARGET group (n=9)	p-value
Distance to target sites			
Distance to target (mm)	8 [0-22]	26 [17-46]	0.04
Distance to infarct (mm)	22 [21-23] (n=2)	26 [14-51]	0.51
Distance to left phrenic nerve (mm)	44 [18-54]	44 [36-n/a]	0.61
Implantation characteristics			
Implantation duration (min)	146±38	127±35	0.38
LV lead implantation duration (min)	47±18	55±28	0.57
Fluoroscopy time (min)	36±15	28±12	0.30
Total radiation dose (cGycm^2)	6758±4201	8242±6446	0.70
Pre-procedural 3D-angiogram radiation (cGycm^2)	1188±262	1449±452	0.41
Post-procedural 3D-angiogram radiation (cGycm^2)	1313±333	1491±439	0.57
Radiation dose CRT only (cGycm^2)	5753±3038	5303±5847	0.91
LV lead electrical properties			
Paced QRS duration (ms)	153±22	170±22	0.18
Decrease QRS duration (ms)	-12±13	-9±27	0.10
Pacing threshold (V)	0.65±0.39	0.58±0.20	0.64
QLV (ms)	150±8	130±30	0.23
Ratio QLV/QRS (%)	85±10	81±16	0.66
Echocardiographic follow up			
LV end-systolic volume change (%)	-30±10	-19±19	0.28
LV ejection fraction change from baseline (%)	15±5	10±12	0.30

Values are in mean ± SD, median [interquartile range]. LV: left ventricular; QLV: Interval from Q on the surface ECG to local sensing at the LV electrogram

target group and they were as follows: mean pacing thresholds: 0.65±0.39V vs 0.58±0.20V, paced QRS duration: 153±22ms versus 170±22ms, change in QRS duration from baseline: -12±13ms versus -9±27ms, and QLV: 150±8ms versus 130±30ms (QLV/QRS ratio 85±10% versus 81±16) **(Table 2)**. At six months follow up, all patients from the target group showed echocardiographic response to CRT with a mean LVESV change of -30±10% and a mean LVEF improvement of 15±5%.

DISCUSSION

This study demonstrates the feasibility of multimodality image fusion, for treatment planning and real-time image-guided LV lead delivery towards optimal pacing sites during CRT implantation procedures. Optimal pacing sites were pre-procedurally identified on CMR (i.e. latest contracting

segment and scar location) and CT scans (i.e. anatomy of the LPN and CSO) and were intra-procedurally fused with live fluoroscopic projections. This allowed the implanting cardiologist to place the LV lead out of scar, away from the LPN and closer to the CMR defined target area compared to CRT implantation without real-time image-guidance, while implantation duration and fluoroscopy time were not increased compared to historical controls.

Targeting LV lead towards predefined optimal pacing sites

Previous work demonstrated significantly more LV reverse remodeling, lower cardiac mortality and fewer heart failure hospitalizations in patients paced from within a target segment with significant electrical or mechanical delay.[2,3,6,14] Measuring the QLV is a relatively simple technique for assessing LV activation delay, however, it provides limited information of total LV electrical activation because usually measurements are only performed at the LV anatomical target region. CMR-scans on the other hand can provide detailed information with regards to mechanical dyssynchrony and myocardial scar location. This supports the role of CMR for image-guided LV lead delivery in patients undergoing CRT implantations. Yet, only two previous studies established real-time visualization of target areas on fluoroscopy images during CRT implantation.[15,16] Using a similar approach to our study, both studies showed the feasibility of real-time image-guided LV lead implantation. Importantly, they did not assess the course of the LPN, moreover, they assessed latest contracting segments by an automatic segmentation algorithm differentiating between the myocardium and the blood pool and in doing so assessed the time to minimum segmental endocardial volume. In our study, we used CMR-FT, the CMR equivalent of speckle-tracking echocardiography for contraction timing analysis. CMR-FT is a relatively easy technique for myocardial contraction timing analysis since the cine images are obtained during standard cardiac imaging protocols.[6,17] In validation studies CMR-FT showed good agreement with CMR-tagging, the gold standard technique for the non-invasive assessment of myocardial deformation which requires separate acquisition of images.[13,18]

In the present study, real-time image-guided LV lead implantation enabled placing the LV lead closer to the target segment compared to LV lead implantation without real-time image-guidance (treatment planning only). LV lead delivery within a pre-procedurally defined target segment, however, remains challenging. We were able to place three out of six LV leads within the CMR target segment using the overlay with fluoroscopy. The lack of a suitable coronary vein at the target site can be an important factor that may prevent LV lead delivery to a target segment. Additionally, in the present study, we didn't adhere to the American Heart Association (AHA) 17-segment to determine LV lead target segments,[19] but we performed the data processing into smaller LV segments and allowed the cardiologist to freely choose a subset of the LV segments to construct a well visible LV target area. Data processing into smaller segments allows for a more

precise delineation of scar tissue, and subsequently, more precise target area definition. Placing the LV within a smaller target segment, however, is more challenging. Real-time image-guidance enabled us to place the LV lead as close to the target site as possible in all patients. Whether more precise targeting leads to improved CRT outcomes needs yet to be determined.

Limitations and challenges

This study was designed to demonstrate the feasibility of a novel treatment guidance platform for real-time visualization of optimal pacing sites during CRT implantation. Because the study was not designed or powered to demonstrate the superiority of real-time image-guided LV lead placement, no definite conclusions can be drawn regarding outcome data on implantation characteristics and end points. While, all patients that received real-time image-guided LV lead implantation were echocardiographic responder at follow up, other important factors probably have attributed to the high rate of reverse remodeling in patients from the target group. For instance, patients with persistent atrial fibrillation were excluded from study participation and patients from the target group had relatively favorable patient characteristics (e.g. more frequently LBBB, non-ICM and lower intracardiac volumes).

Furthermore, we recognize that a relatively high radiation dose was used due to the additional 3D-rotational scans and pre-implantation CT imaging. The radiation dose of the CRT implantation without 3D-rotational scans was comparable to previous work.[20,21] In the present study, 3D-rotational scans were acquired before and after CRT implantation, however for visualization of optimal pacing sites onto fluoroscopic projections, performing a single 3D-rotational scan is sufficient. This adds approximately 20% of radiation dose to a CRT implantation. Detrimental effects of radiation, occur at a dose area product larger than 40 000 cGycm^2 (assuming an effective radiation area of 100cm^2)[20] whereas, the threshold dose for skin erythema is 20 000 cGycm^2.[21] Using CARTBox, in the present study radiation dose thus remained well below the above-mentioned thresholds. In addition, performing a CT-scan is not standard care in patients undergoing CRT device implantation and is associated with increased cost and a slightly increased healthcare risk due to ionizing radiation (average 20-80cGycm^2) and the use of an iodinated contrast agent. Iodinated contrast agents may cause kidney dysfunction, especially in patients with pre-existing renal impairment. According to large, epidemiologically representative patient populations with chronic heart failure, about 10% of patients will have severe renal dysfunction (GFR<30ml·min·1.73m^2).[22] Therefore, performing both a CT scan and a CRT implantation may not be feasible in all patients eligible for CRT. Although the CARTBox platform can easily be implemented using CMR only, we chose to implement the CT scan in the current study, because visualizing the course of the LPN and CSO before implantation could potentially simplify CS cannulation, prevent LPN stimulation and accompanied LV lead relocation, and consequently, reduce implant times. Pre-procedural detailed evaluation of the coronary venous anatomy on CT

images could take the concept for targeted LV lead implantation even further. However, the timing of the intravenous contrast administration to the venous phase is not a standard procedure and is especially difficult in heart failure patients. Furthermore, even when performed optimally, it does not permit the visualization of the smaller venous branches. Therefore in the present study, we did not evaluate the CS anatomy preoperatively on CT, but chose to use the CS venogram instead, which is acquired during CRT implantation and which is the current standard to visualize complete CS anatomy. Importantly, emerging technologies in CMR and CT scan protocols and image analysis algorithms (i.e. detection of myocardial scar and dyssynchrony on cardiac CT[23] and the anatomy of the LPN and coronary sinus on CMR[24]) could in the near future negate the necessity for both pre-procedural CMR and CT. This would especially be of value in patients with a contra-indication for CMR or CT, such as patients with impaired renal function, claustrophobia, documented allergy to gadolinium, or patients with non-MRI conditional devices.

Future implications

Despite the aforementioned challenges, and based on the superior patient outcomes of targeted LV lead placement, demonstrated by previous studies,[2,3,6,15] we believe that the technology of real-time image-guided LV lead implantation towards optimal pacing sites is clinically promising. Technical advancements such as the development of the snare technique and octopolar LV leads, together with other pacing techniques, such as endocardial pacing, will probably allow for a more precise delivery of LV leads into predefined, smaller, target areas. Technologies that enable visualization of optimal pacing sites, therefore, may become of high value for implanting physicians. Moreover, further developments of CARTBox have enabled the use of merging the 3D-CMR or CT treatment dataset with standard fluoroscopy set-ups to omit the need for a 3D-rotational scan. This reduces ionizing radiation, and increases the uptake of the technology in CRT implanting hospitals.

CONCLUSIONS

Real-time image-guided LV lead placement by fusion of CMR- and CT-images with fluoroscopy images during CRT device delivery is feasible and endorses placing the LV lead closer to the target segment and out of scar compared to treatment planning only. Merging of target segments on to live fluoroscopy can be performed rapidly without prolongation of procedure time. Further investigation of this technology in clinical practice with larger patient cohorts is necessary to determine whether real-time image-guided LV lead delivery leads to improved patient outcomes and whether this approach is cost effective.

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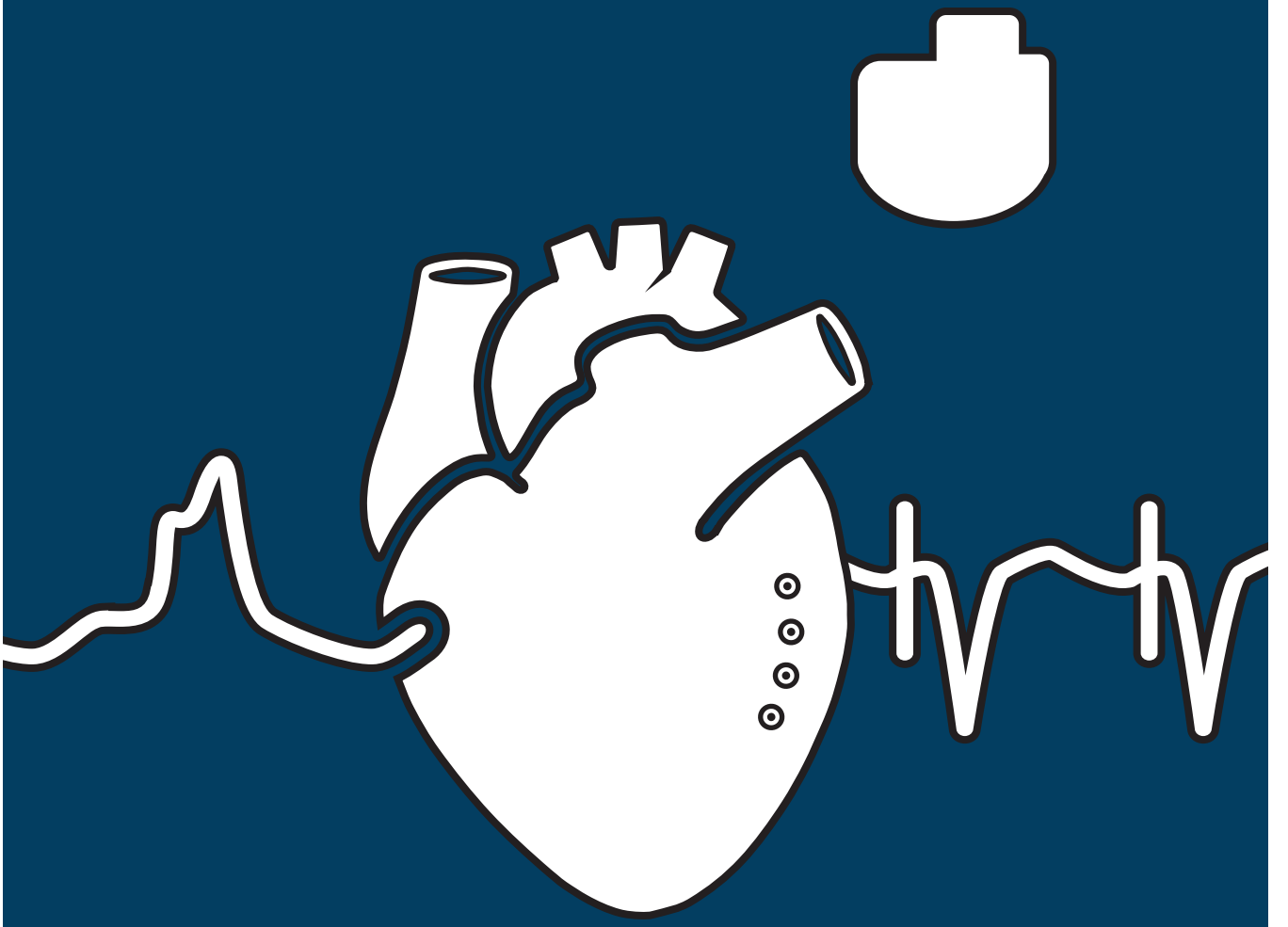
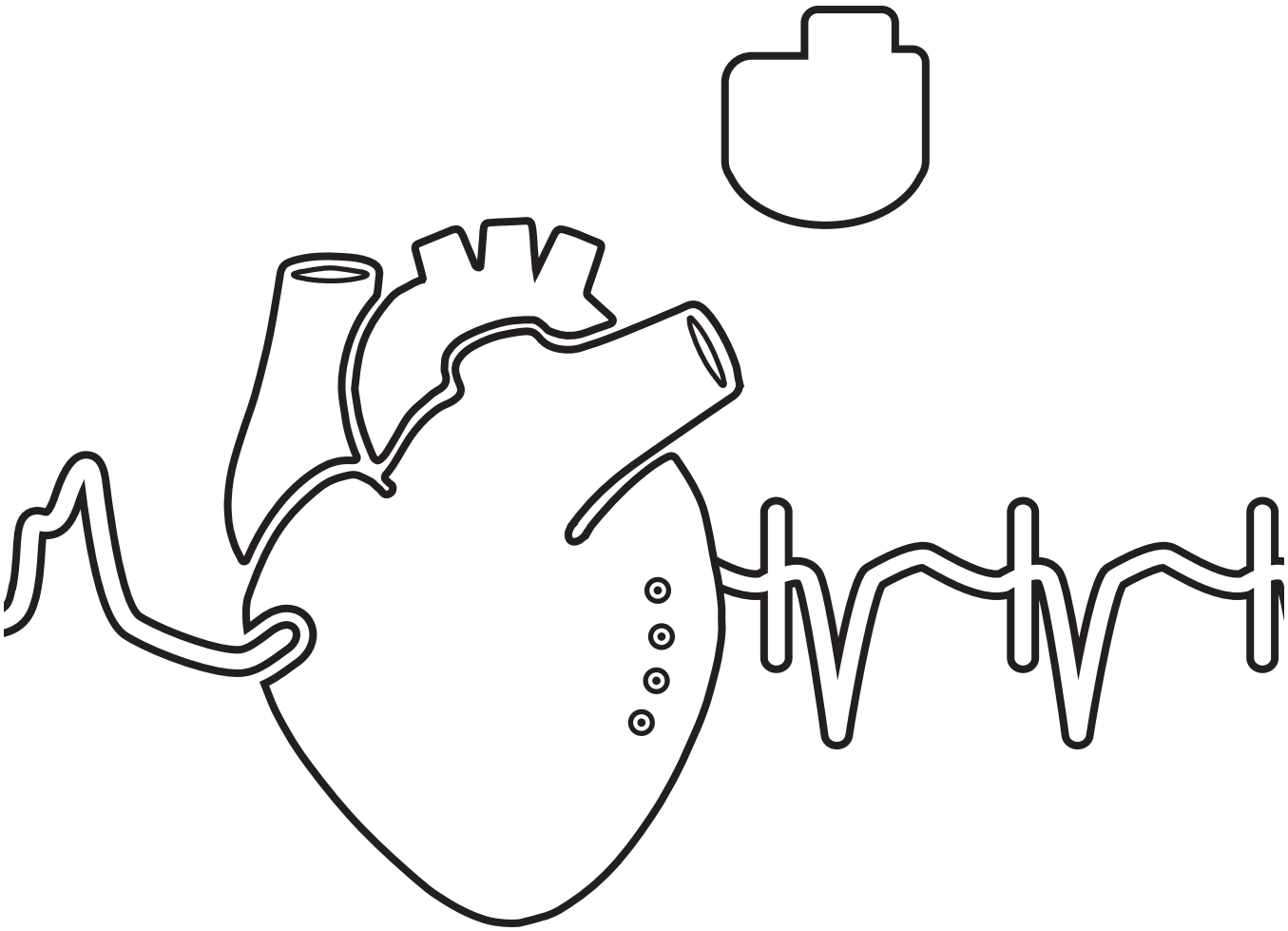
Part three

Optimizing device programming





Chapter 7

Hemodynamic Optimization in Cardiac Resynchronization Therapy: Should We Aim For dP/dt_{max} or Stroke Work?

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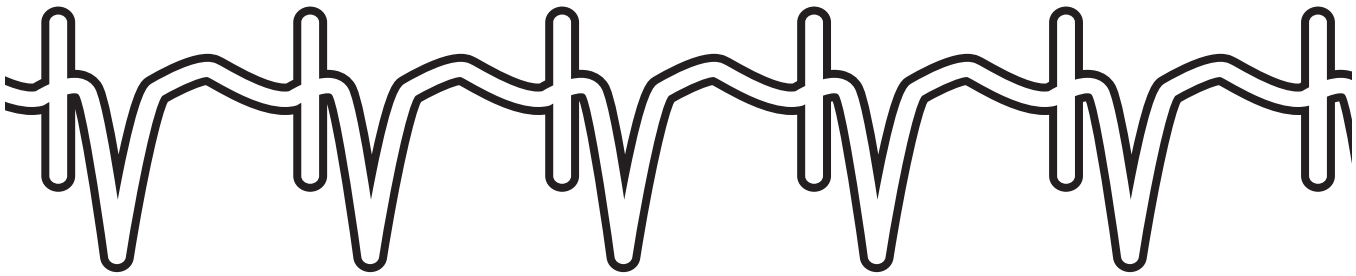

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ABSTRACT

Background

Hemodynamic optimization may increase benefit from cardiac resynchronization therapy (CRT). Typically, maximal LV pressure rise dP/dt_{max} is used as an index of ventricular performance. Alternatively, stroke work (SW) can be derived from pressure-volume (PV) loops. This study (1) evaluates the acute effect of dP/dt_{max} versus SW guided CRT optimization, and (2) relates acute hemodynamic changes to long-term CRT response.

Methods

Forty-one patients underwent CRT implantation followed by invasive PV loop measurements. The stimulation protocol included sixteen LV pacing configurations using each individual electrode of the quadripolar lead with four atrioventricular (AV) delays. Conventional CRT was defined as pacing from the distal electrode with an AV delay of ~120ms.

Results

Compared to conventional CRT, dP/dt_{max} guided optimization resulted in one-third additional dP/dt_{max} increase (17±11% vs. 12±9%; $p<0.001$). Similarly, SW guided optimization resulted in one-third additional SW increase (80±55% vs. 53±48%; $p<0.001$). Comparing both optimization strategies, dP/dt_{max} favored contractility (8±12% vs. 5±10%; p=0.015) whereas SW optimization improved ventricular-arterial (VA) coupling (45% vs. 32%; $p<0.001$). After six months, mean LV ejection fraction (LVEF) change was 10±9% with 23 (56%) patients becoming CRT (super) responders (≥10% LVEF improvement). Whereas acute changes in SW were predictive for long-term CRT response (AUC 0.78; $p=0.002$), changes in dP/dt_{max} were not (AUC 0.65; $p=0.112$).

Conclusions

Pressure-volume guided hemodynamic optimization in CRT results in approximately one-third SW improvement on top of conventional CRT, caused by a mechanism of enhanced ventricular-arterial coupling. dP/dt_{max} optimization, on the other hand, favored LV contractility. Ultimately, acute changes in SW showed larger predictive value for long-term CRT response compared to dP/dt_{max}.

INTRODUCTION

Optimization of cardiac resynchronization therapy (CRT) after implantation includes individualized programming of the atrioventricular (AV) and interventricular (VV) delay, selection of the most beneficial LV pacing electrode, or stimulation by multiple electrodes (i.e. multipoint pacing). Multiple optimization strategies are presently available and the best method remains to be established. Electrical (e.g. QRS duration/area; Q on surface ECG to LV sensing interval, QLV) and echocardiographic (e.g. stroke volume; mitral flow) parameters are most widely used in clinical practice although convincing scientific evidence for these methods is lacking. Alternatively, acute CRT response can be assessed by invasive hemodynamic testing in order to optimize device settings.[1] Typically, the maximum rate of LV pressure rise (dP/dt_{max}) is used as an index of ventricular performance.[2] To this purpose, a pressure guidewire is inserted in the LV cavity to perform measurements in a relatively easy and reliable manner. Alternatively, pressure-volume (PV) loops can be obtained by the use of a conductance catheter. A major advantage of the PV approach is that functional measures are provided with information on preload, afterload and contractility allowing to assess underlying physiological mechanisms. Stroke work (SW) incorporates all pressure and volume changes throughout the cardiac cycle and provides a comprehensive appraisal of LV pump function.[1,2]

At present, a direct comparison between invasive CRT optimization strategies is lacking. This study aims to (1) evaluate the acute effect of dP/dt_{max} versus SW guided CRT optimization, and (2) relate acute changes in hemodynamic parameters to long-term CRT response.

METHODS

Study population

This study is part of the OPTICARE-QLV (Optimization of Cardiac Resynchronization Therapy with a Quadripolar Left Ventricular Lead) study, a multicenter, prospective, observational study. The main aim of the OPTICARE-QLV study was to relate electrical parameters (Q on surface ECG to LV sensing interval, QLV) to acute hemodynamic response in CRT with quadripolar LV leads, using conductance catheter measurements.[3] Inclusion criteria were moderate to severe heart failure (NYHA class II or III) despite optimal medical therapy, LV ejection fraction ≤35%, sinus rhythm, and left bundle branch block (LBBB) according to the Strauss criteria. The study was performed according to the Declaration of Helsinki and in agreement with the local medical ethics committees. All subjects gave written informed consent.

Baseline procedures

All patients underwent ECG-, echocardiographic-, and cardiac magnetic resonance imaging (CMR) examination prior to device implantation. CRT implantation was performed under local anesthesia following standard procedures. Right ventricular (RV) and right atrial (RA) leads were placed at conventional positions. The quadripolar LV lead (Quartet 1458Q, St. Jude Medical, Saint Paul, Minnesota, United States) was targeted at an anterolateral, lateral, or posterolateral position using the tributaries of the coronary sinus. After lead placement, fluoroscopy images were made in the left anterior oblique (LAO) 40° and in the in the right anterior oblique (RAO) 30° angle to determine the specific position of each quadripolar LV lead electrode.

Stimulation protocol

Immediately after device implantation, a dedicated 7F conductance catheter (12 electrodes; 8, 10 or 12mm spacing; CD Leycom, Zoetermeer, The Netherlands) was inserted via the femoral artery and placed in a stable position in the LV apex. PV loops were recorded during each run of biventricular pacing in-between of baseline recordings with intrinsic conduction (i.e. LBBB). To ensure a stable rhythm, RA pacing with 5-10 bpm above the intrinsic heart rate was maintained throughout the stimulation protocol. The stimulation protocol included four LV pacing configurations using each individual electrode of the quadripolar lead (i.e. D1: distal electrode; M2: mid-distal electrode; M3: mid-proximal electrode; P4: proximal electrode) as cathode and the RV shock-coil as anode. Per pacing configuration, four AV-delays of approximately 80%, 60%, 40% and 20% of the intrinsic AV conduction (RA pacing to RV sensing interval) were programmed, resulting in a total of 16 "pacing runs" (**Figure 1**). The order in which the electrodes were tested was randomized between patients. The VV-delay was fixed at 40ms LV pre-activation.[4]

Hemodynamic measurements

PV loops were constructed using Conduct NT software (version 2.8.1). Approximately 60 representative cardiac cycles per pacing run were averaged, disregarding all inappropriate beats. Baseline-loops were averaged from 30 beats recorded prior and afterwards each pacing run. Subsequently, baseline-loops were calibrated by CMR-derived LV volumes. Patients were excluded if the baseline-loop showed non-physiological characteristics (volume changes during the isovolumic phases) resulting in a hourglass-shaped baseline loop, as judged by two independent experts. LV pump function was quantified by both SW derived from PV loops and the pressure derivative dP/dt_{max}. To account for baseline drift, the effect of each biventricular pacing setting was calculated as the relative change in LV pump function compared with the mean of the two flanking baseline measurements. Optimization curves were used to identify the pacing configurations with the highest increase in SW and dP/dt_{max}, respectively (**Figure 1**). PV indices were compared between the optimal SW and dP/dt_{max} configuration, as well as the conventional

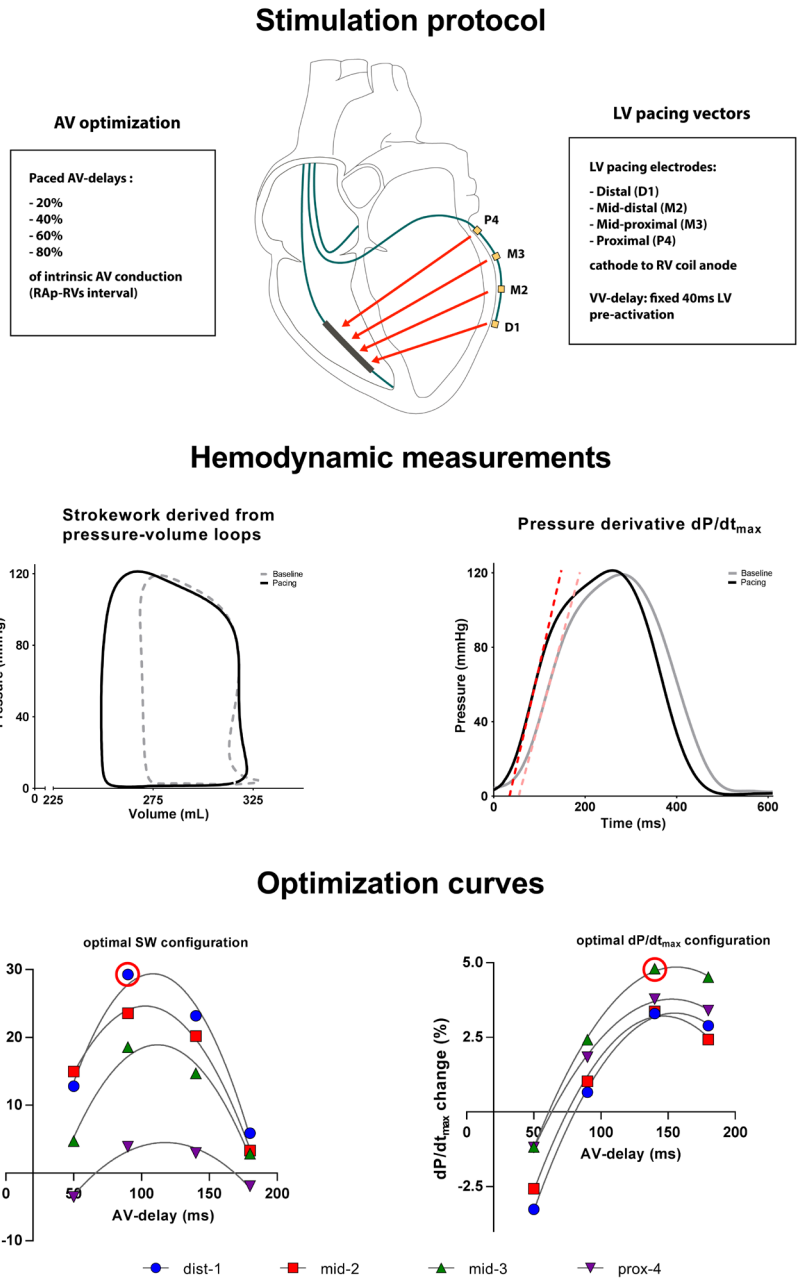

Figure 1. Hemodynamic optimization protocol. The stimulation protocol included four LV pacing configurations using each individual electrode of the quadripolar lead (D1: distal electrode; M2: mid-distal electrode; M3: mid-proximal electrode; P4: proximal electrode). Per electrode, four AV-delays were programmed of approximately 80%, 60%, 40% and 20% of the intrinsic AV conduction. Per setting, acute response to CRT was measured by change in SW and dP/dt_{max}. The pacing configuration with the highest increase in SW and dP/dt_{max} was used for comparison.

CRT configuration. Conventional CRT was defined as pacing the distal electrode with an AV delay of ~120ms. dP/dt_{max} was calculated as the maximum rate of LV pressure rise and SW was directly calculated as the area of the PV loop. In addition, maximal pressure (P_{max}), minimal pressure (P_{min}), pressure rise ($dP_{max-min}$), end-diastolic volume (EDV), end-systolic volume (ESV), stroke-volume (SV), and ejection fraction (EF) were measured. For volumetric measurements, end-diastole was defined at the time of dP/dt_{max} and end-systole was defined at the time of dP/dt_{min}. Effective arterial elastance (E_A) was calculated as end-systolic pressure divided by SV. LV end-systolic elastance (E_{ES}) was estimated by end-systolic pressure divided by end-systolic volume.[5] The specific end-systolic PV point for these measurements was defined as the maximum ratio of LV pressure to volume. Ventricular-arterial (VA) coupling was quantified as E_A/E_{ES}, and mechanical efficiency was calculated as the ratio of SW to the pressure-volume area (PVA) where PVA is the sum of SW and potential energy (PE).[6] The setting programmed in the device before discharge was left to the discretion of the operator. Typically, this was the optimal SW electrode with an adequate sensing signal and capture threshold without evidence of phrenic nerve stimulation.

Echocardiography

Echocardiography was performed before, and six months after CRT implantation. Echocardiographic images were analyzed by a dedicated core lab (University Medical Center Utrecht). LV volumes were measured using the biplane Simpson's method by two experienced observers and calculated as averages of multiple (2-3) consequent beats. Long-term CRT response was calculated as the absolute percent change in LVEF between baseline and follow-up. Patients with ≥10% increase in LVEF were classified as CRT super-responders as this cut-off value is widely used.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) in case of normal distribution or otherwise as median and interquartile range. Categorical variables are presented as absolute numbers and percentages. Pearson's and Spearman correlations were calculated depending on whether distribution was normal or not. The paired t-test or Wilcoxon signed rank test was used to compare hemodynamic variables between the optimal SW, optimal $dP/dt_{max,}$ and conventional CRT settings. Cohen's Kappa () coefficient was calculated as the level of agreement between the optimal LV lead pacing electrode and electrode position between groups. Receiver operating characteristics (ROC) curve analysis was used to determine the predictive value of hemodynamic parameters for long-term CRT response. The commercially available Statistical Package for Social Sciences software (IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY, USA) was used for statistical analysis. A *p*-value of <0.05 was considered statistically significant.

RESULTS

Patient population

A total of fifty-one patients were enrolled in the main study, of whom ten were excluded from this analysis. Nine patients were excluded because of unreliable baseline PV loops and one patient was lost to follow-up due to a psychiatric disorder. Patients with unreliable baseline-loops demonstrated larger LVEDV (396±96ml vs. 287±82ms; p=0.002) and lower LVEF (16±2% vs. 26±8%; p=0.001) on CMR compared to patients included in the study. Patient characteristics of the remaining forty-one patients are presented in **Table 1**.

Acute changes in hemodynamic parameters

During conventional CRT (D1 electrode; AV delay ~120ms), dP/dt_{max} increased by 12±9% and SW improved by 53±48% (**Table 2; Figure 2**). Compared to conventional CRT, dP/dt_{max} guided optimization (i.e. the setting that resulted in best dP/dt_{max}) resulted in one-third additional dP/dt_{max} change (17±11%; p<0.001), but with a similar SW change (52±45%; p=0.754). The highest dP/dt_{max} was achieved with electrode D1 in twelve (29%), M2 in twelve (29%), M3 in eight (20%) and P4 in nine (22%) patients, (**Table S1** of the supplemental material). The AV-delay that resulted in optimal dP/dt_{max} was longer compared to conventional CRT (165±41ms vs. 119±13ms; p<0.001). Compared to conventional CRT, SW guided optimization (i.e. the setting that resulted in best SW) resulted in comparable dP/dt_{max} changes (12±10%; p=0.679), but one-third additional SW increase (80±55%; p<0.001). The largest SW was achieved with electrode D1 in twenty-two (54%), M2 in five (12%), M3 in five (12%) and P4 in nine (22%) patients. On average, the optimal SW AV-delay did not significantly differ from conventional CRT (132±58ms vs. 119±13ms; p=0.191).

Comparing both optimization strategies, the optimal dP/dt_{max} configuration differed from the optimal SW configurations by a lack of agreement in pacing electrode (-0.3) and a significant difference in AV delay (165±41ms vs. 132±58ms; p=0.001). When evaluating the relation between acute changes in SW and dP/dt_{max} for all pacing configurations of the entire population (n=635), a weak correlation was found (R = 0.24; p<0.001), illustrated in **Figure S1** of the supplemental material. Comparing SW and dP/dt_{max} changes in a per-patient analysis, only nine (22%) patients demonstrated a positive correlation with a correlation coefficient ≥0.5 (**Figure S2**). Comparing changes in hemodynamic parameters between dP/dt_{max} and SW guided strategies, the former showed a larger pressure increase (6±4% vs. 3±5%; p<0.001) whereas SW optimization resulted in a larger SV augmentation (85±70% vs. 51±56%; p<0.001), see **Figure 3**.

To study interactions between the LV and the arterial system, **Table 3** summarizes changes in VA coupling between optimization strategies. Whereas dP/dt_{max} optimization was associated with larger E_{ES} increase compared to SW optimization (8±12% vs. 5±10%; p=0.015), SW optimization showed relatively larger reduction in E_A (44±44% vs. 26±35%; p<0.001). VA coupling at baseline

Table 1. Patient characteristics at baseline and echocardiographic changes after six months

Variable	Total group (n=41)	Super-responders (n=23)	Others (n=18)	P-value
Age (years)	67 ± 9	65 ± 9	69 ± 8	p=0.184
Gender (n, % male)	25 (61%)	12 (52%)	13 (72%)	p=0.192
Etiology (n, % ICMP)	8 (20%)	7 (30%)	1 (6%)	p=0.046
NYHA class (n, %)				
Class II	29 (71%)	16 (70%)	13 (72%)	
Class III	12 (29%)	7 (30%)	5 (28%)	p=0.853
Medical history (n, %)				
Diabetes	5 (12%)	1 (4%)	4 (22%)	p=0.083
Hypertension	15 (37%)	7 (30%)	8 (44%)	p=0.355
Atrial fibrillation	4 (10%)	2 (9%)	2 (11%)	p=0.796
Medication (n, %)				
Beta-blocker	31 (76%)	18 (78%)	13 (72%)	p=0.655
Diuretics	29 (71%)	16 (70%)	13 (72%)	p=0.853
ACE / ATII inhibitors	40 (98%)	23 (100%)	17 (94%)	p=0.252
Aldosterone antagonist	26 (63%)	17 (74%)	9 (50%)	p=0.115
Lab – eGFR (ml/min/1.73m^2)	69 ± 15	73 ± 14	64 ± 16	p=0.069
Lab – NT-pro BNP (pmol/L)	57 (28 – 134)	51 (28 – 101)	62 (28 – 307)	p=0.511
ECG – PR duration (ms)	179 ± 30	170 ± 20	190 ± 37	p=0.029
ECG – QRS width (ms)	167 ± 14	169 ± 15	164 ± 13	p=0.244
EP – intrinsic AV interval (ms)*	271 ± 53	254 ± 36	293 ± 64	p=0.020
CMR – LVEDV (ml)	286 ± 83	303 ± 75	265 ± 90	p=0.148
CMR – LVESV (ml)	216 ± 80	231 ± 66	197 ± 94	p=0.179
CMR – LVEF (%)	25 ± 8	24 ± 6	28 ± 10	p=0.141
CMR – Scar on LGE images (n, %)	7 (18%)	2 (9%)	5 (31%)	p=0.082
CMR – Scar size (% LV mass)**	5 (3 – 16)	2 (1-2)	12 (5-19)	p=0.095
Follow-up				
Echo – Change in LVEF after six months (%)***	+10 ± 9	+16 ± 6	+2 ± 2	p<0.001
Echo – Change in LVESV after six months (%)	-33 ± 18	-41 ± 16	-23 ± 15	p<0.001

ICMP, ischemic cardiomyopathy; NYHA class, New York Heart Association functional class; ACE, angiotensin converter enzyme; ATII, angiotensin receptor II; eGFR, estimated glomerular filtration rate; NT-pro BNP, N-terminal prohormone brain natriuretic peptide; AV, atrioventricular; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LGE, late gadolinium enhancement; * intrinsic AV interval measured as right atrial pacing to right ventricular sensing interval **scar size in patients with presence of scar; ***absolute changes in % LVEF

was very unbalanced with E_A/E_{ES} ranging between 4.6 and 4.9. Improvement in E_A/E_{ES} was most pronounced for SW optimization (45±39% vs. 32±32%; p<0.001). Mechanical efficiency was depressed at baseline (SW/PVA: 0.31) with SW optimization resulting in highest mechanical efficiency (39±23% vs. 26±23%; p<0.001) compared to dP/dt_{max} optimization.

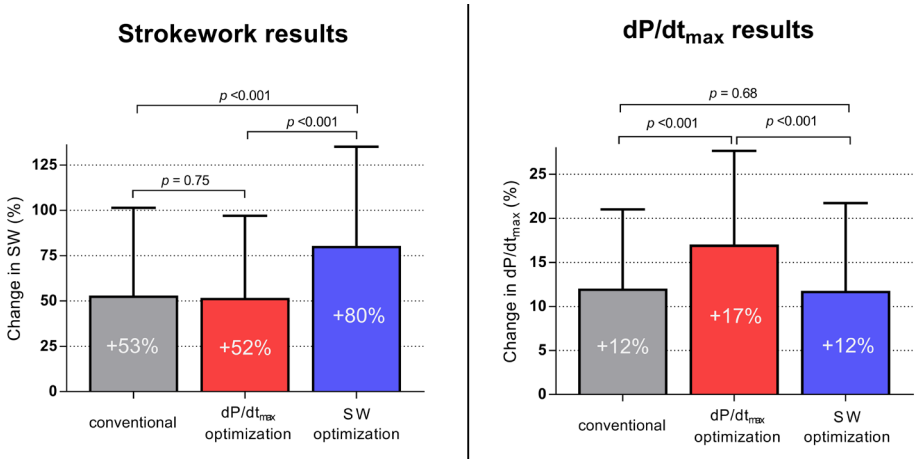

Figure 2. The effect of hemodynamic optimization on acute CRT response. The effect of hemodynamic optimization is illustrated for SW results (left diagram) and dP/dt_{max} results (right diagram). SW guided optimization resulted in one-third additional SW increase compared to conventional CRT without additional dP/dt_{max} changes. dP/dt_{max} guided optimization resulted in one-third additional dP/dt_{max} increase without additional SW benefit.

Table 2. Acute hemodynamic changes during conventional CRT and after hemodynamic optimization by dP/dtmax and strokework

Variable	Conventional CRT	dP/dt_{max} optimization	SW optimization	P-value conventional vs. dP/dt_{max}	P-value conventional vs. SW	P-value dP/dt_{max} vs. SW
Δ dP/dt_{max} (%)	+12 ± 9	+17 ± 11	+12 ± 10	p<0.001	p=0.679	p<0.001
Δ P_{max} (%)	+1 ± 4	+4 ± 4	+1 ± 4	p<0.001	p=0.913	p<0.001
Δ P_{min} (%)	-25 ± 15	-26 ± 38	-25 ± 15	p=0.901	p=0.949	p=0.930
Δ $dP_{max-min}$ (%)	+3 ± 5	+6 ± 4	+3 ± 5	p<0.001	p=0.993	p<0.001
Δ EDV (%)	+3 ± 10	+4 ± 9	+5 ± 9	p=0.079	p=0.017	p=0.159
Δ ESV (%)	-10 ± 9	-7 ± 9	-12 ± 10	p=0.013	p=0.017	p<0.001
Δ SV (%)	+52 ± 61	+51 ± 56	+85 ± 70	p=0.961	p<0.001	p<0.001
Δ EF (%)*	+9 ± 8	+8 ± 8	+13 ± 8	p=0.330	p<0.001	p<0.001
Δ SW (%)	+53 ± 48	+52 ± 45	+80 ± 55	p=0.754	p<0.001	p<0.001

dP/dt_{max}, maximum rate of pressure rise; P_{max}, maximal pressure; P_{min}, minimal pressure; $dP_{max-min}$, pressure rise; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction; SW, stroke work; *absolute changes in % EF

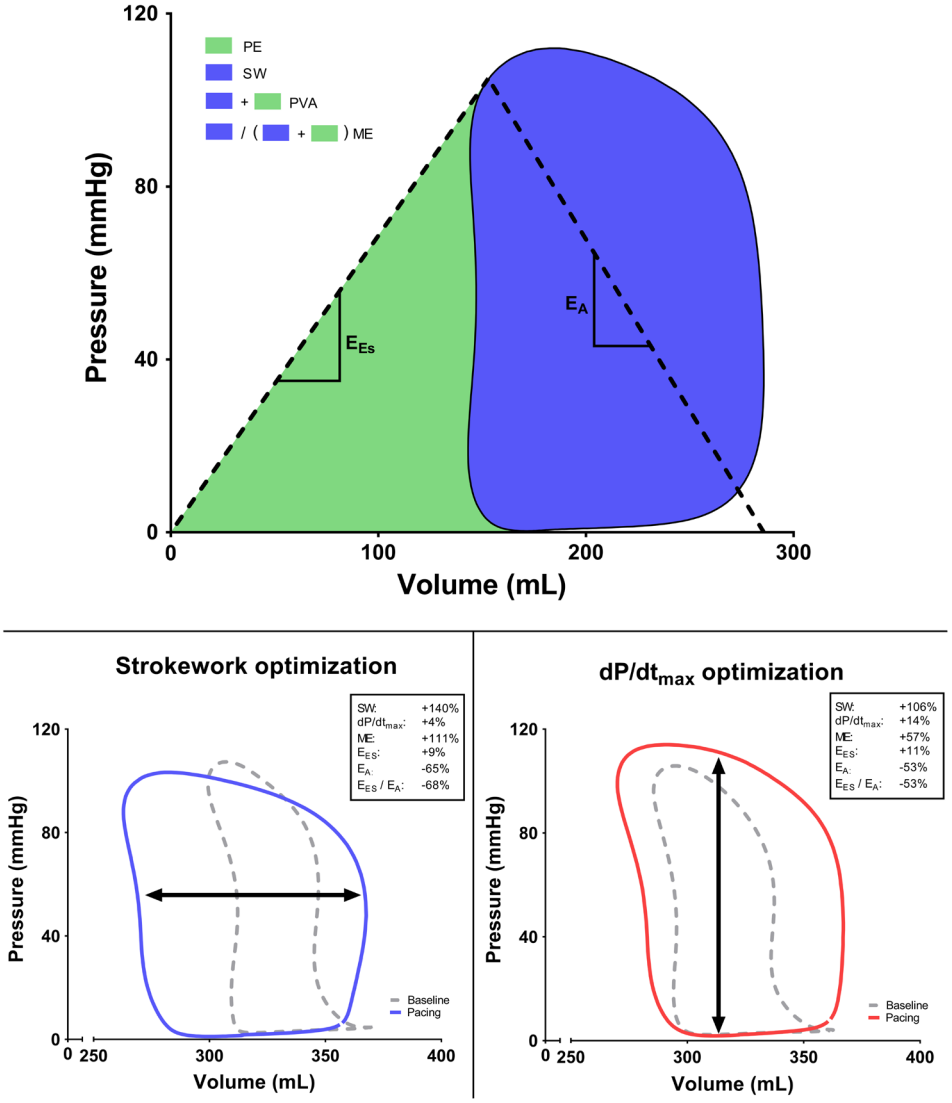

Figure 3. Ventricular-arterial coupling between optimization strategies. Schematic illustration of a PV-loop (top diagram). Typical example of PV-loops in a CRT patient illustrating the effects of SW guided optimization (bottom left diagram) and dP/dt$_{max}$ guided optimization (bottom right diagram). SW optimization results in widening of the PV loop (i.e. SV augmentation) whereas dP/dt$_{max}$ guided optimization results in lengthening of the PV loop (i.e. LV pressure rise increase). The optimal dP/dt$_{max}$ configuration demonstrates highest contractility whereas optimal SW is achieved at lowered arterial load, resulting in improved VA coupling and higher mechanical efficiency.

Table 3. Acute changes in VA coupling during conventional CRT and after hemodynamic optimization by dP/dtmax and strokework

	Baseline	Pacing	Δ (%)	
Arterial load (E_A)				
Conventional CRT	2.6 ± 2.0	1.9 ± 1.2	-26 ± 42	
dP/dt_{max} optimization	2.6 ± 1.9	1.9 ± 1.3	-26 ± 35	
SW optimization	2.7 ± 2.1	1.6 ± 1.1	-44 ± 44	*
Contractility (E_{ES})				
Conventional CRT	0.60 ± 0.25	0.62 ± 0.27	+5 ± 12	
dP/dt_{max} optimization	0.60 ± 0.25	0.65 ± 0.28	+8 ± 12	*
SW optimization	0.60 ± 0.25	0.63 ± 0.26	+5 ± 10	*
VA coupling (E_A/E_{ES})				
Conventional CRT	4.6 ± 2.4	3.3 ± 1.9	-28 ± 37	
dP/dt_{max} optimization	4.7 ± 2.4	3.2 ± 1.6	-32 ± 32	
SW optimization	4.9 ± 2.7	2.7 ± 1.3	-45 ± 39	*
Mechanical efficiency (SW/PVA)				
Conventional CRT	0.31 ± 0.10	0.40 ± 0.13	+29 ± 26	
dP/dt_{max} optimization	0.31 ± 0.10	0.39 ± 0.13	+26 ± 23	*
SW optimization	0.31 ± 0.10	0.42 ± 0.12	+39 ± 23	*

E_A, arterial elastance; dP/dt_{max}, maximum rate of pressure rise; SW, stroke work; E_{ES}, end-systolic elastance; VA, ventricular-arterial; PVA, pressure-volume area. Statistical differences between optimization strategies are marked with an asterisk

Acute changes in hemodynamic parameters in relation to long-term CRT response

Echocardiographic measurements showed high reproducibility with intra-class correlations (ICC) values of 0.95 (EDV); 0.96 (ESV) and 0.93 (EF) for intra-observer variability and ICC values of 0.92 (EDV); 0.95 (ESV) and 0.91 (EF) for inter-observer variability. Absolute LVEF change after six months was 10±9%, with 23 (56%) patients showing ≥10% increase in LVEF (CRT super-responders). For prediction of long-term CRT (super)response, change in SW showed an AUC of 0.78 (p=0.002) as demonstrated in **Table 4** and **Figure S3**, whereas change in dP/dt_{max} revealed a non-significant AUC of 0.65 (p=0.112). To predict long-term CRT (super)response, an optimal cut-off value of 40% increase in SW change yielded a sensitivity of 96%, specificity of 50%, and positive and negative predictive values of 71% and 90%, respectively. Using this cut-off value, thirty-one (76%) patients were categorized having ≥40% increase in SW and ten (24%) patients with <40% increase, or an decrease in SW. Patients with ≥40% SW increase showed larger improvement in absolute LVEF (13±8% vs. 2±7%; p<0.001) and larger reduction in LVESV (-36±17% vs. -23±16%; p=0.041) at follow-up compared to patients without, illustrated in **Figure 4**. The optimal cut-off value to predict long-term CRT response by change in dP/dt_{max} was 9%. Twenty-one (51%) patients with

Table 4. Predictive value of hemodynamic parameters for long-term CRT response

Variable	AUC	P-value	Cut-off (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Δ dP/dt_{max}	0.65	p=0.112	≥ +9	65	67	71	60
Δ P_{max}	0.60	p=0.297	≤ +1	63	44	64	50
Δ P_{min}	0.69	p=0.035	≤ -26	54	72	72	54
Δ $dP_{max-min}$	0.58	p=0.374	≤ +3	58	56	64	50
Δ EDV	0.51	p=0.916	≥ +4	63	44	60	47
Δ ESV	0.70	p=0.031	≤ -12	58	78	78	58
Δ SV	0.72	p=0.015	≥ +45	83	61	74	73
Δ EF	0.73	p=0.010	≥ +9*	71	61	71	61
Δ SW	0.78	p=0.002	≥ +40	96	50	71	90

For abbreviations, see table 2; *absolute changes in % E

≥9% dP/dt_{max} change were compared with twenty (49%) patients without, but no differences in absolute LVEF change (10±10% vs. 10±8%; p=0.939) or LVESV change (-32±21% vs. -34±14%; p=0.704) were found between groups.

DISCUSSION

The present study demonstrates that PV guided hemodynamic optimization of the LV pacing electrode and AV delay in CRT with quadripolar leads results in approximately one-third additional SW improvement on top of conventional CRT. Hemodynamic optimization by the pressure derivate dP/dt_{max} also showed one-third additional dP/dt_{max} improvement compared to conventional CRT. Improvement in one parameter, however, did not coincide with the other indicating two different mechanisms. Whereas dP/dt_{max} optimization favored LV contractility (expressed as E_{ES}), SW optimization improved ventricular-arterial coupling leading to higher stroke volume and ejection. Acute changes in SW showed higher predictive value for long-term CRT response compared to change in dP/dt_{max}s.

Hemodynamic optimization strategies

Previous studies showed that invasive hemodynamic optimization in CRT can be used to guide LV lead placement,[3,7-12] find the optimal AV- and VV-delay,[4,13,14] and evaluate benefit from multi-site stimulation.[12,15-17] A standardized approach for invasive optimization, however, is lacking as part of these studies used dP/dt_{max},[4,7,10-14,16] while others used SW as optimization parameter.[3,8,9,14-17] Although the two strategies have been used interchangeably in literature, previous work from

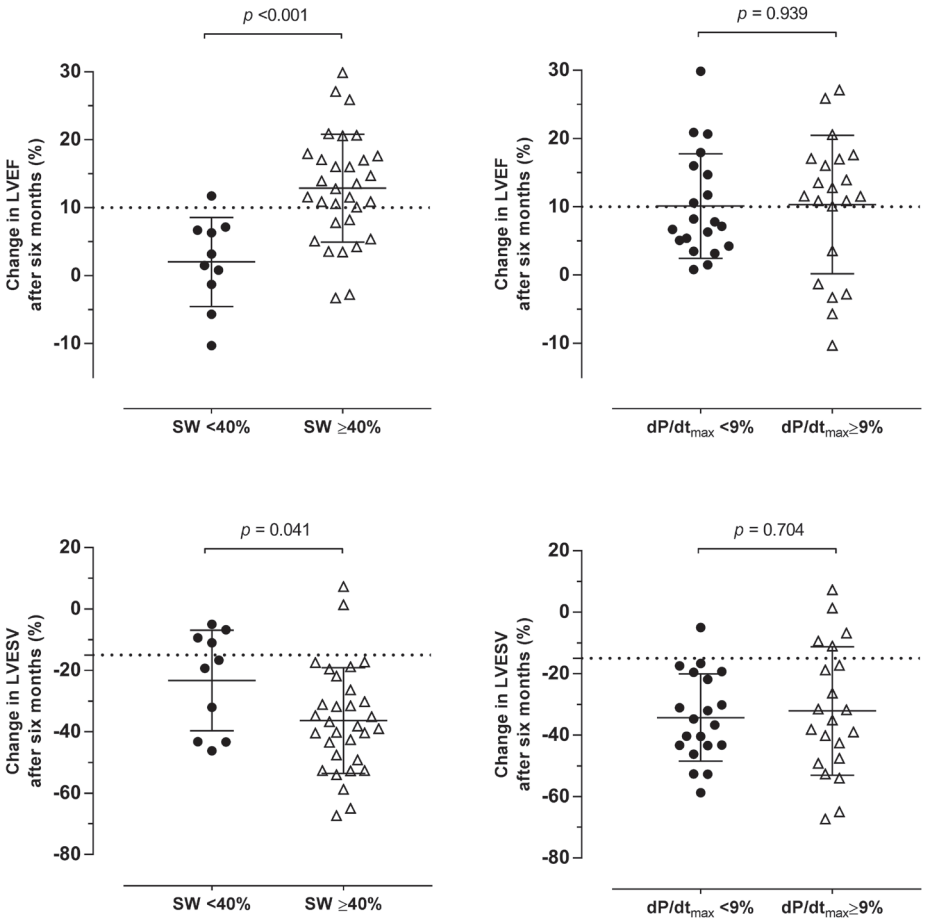

Figure 4. Acute CRT response and echocardiographic changes after six months.
Scatter plots illustrating long-term echocardiographic absolute changes in LVEF (upper panel) and LVESV (lower panel) for patient stratification by SW changes (left diagrams) and dP/dt_{max} changes (right diagrams).

our group showed a discordant relationship between dP/dt_{max} and SW improvement among CRT candidates.[18] Pappone et al. found that even within an individual patient, changes in the two parameters were often poorly correlated.[16] The present study confirms previous findings, and extends these by evaluating the effect of invasive hemodynamic optimization by dP/dt_{max} versus SW on cardiac performance in CRT with quadripolar LV leads. Each optimization strategy resulted in approximately 1/3 additional improvement in the parameter used for optimization. Improvement in one parameter, however, did not coincide with the other (**Figure 2**). These findings indicate that although CRT with quadripolar LV leads provides substantial room for hemodynamic optimization, results differ significantly between optimization strategies.

Interestingly, dP/dt_{max} guided optimization resulted in longer AV-delays (165ms, 63% of intrinsic AV interval) compared to SW guided optimization (132ms, 49% of intrinsic AV interval). Possibly, these longer AV-delays allow for fusion of the intrinsic AV conduction and LV capture (i.e. fusion pacing) which has been shown to favor dP/dtmax.[19] Comparing hemodynamic effects, marked differences were observed in LV pressure rise and stroke volume between optimization strategies. Whereas dP/dt_{max} optimization favored LV pressure rise (i.e. height increase of the PV loop), SW optimization rather showed SV augmentation (i.e. widening of the PV loop), see **Figure 3**. Increases in SV involved small changes in EDV and large ESV reduction. These changes can be explained by different interactions between the LV and the arterial system influencing ventricular performance by alterations in cardiac afterload (i.e. VA coupling). Under normal conditions, the VA system is closely coupled with an E_A/E_{ES} ratio of 0.6-1.2 to achieve optimal work and mechanical efficiency.[20] In chronic HF, however, depressed systolic function (low E_{ES}) coupled to a high arterial impedance (high E_A) will result in a state of afterload mismatch with severely elevated E_A/E_{ES}.[21] Previous studies showed that CRT directly improves VA coupling by enhancing LV systolic performance (E_{ES}) and reducing net arterial load (E_A).[22,23] The immediate reduction in afterload has been ascribed to acute effects of CRT on the sympathetic nerve activity.[24,25] Our results are in line with previous findings, demonstrating enhanced VA coupling during biventricular pacing as a result of beneficial changes in both determinants (i.e. E_{ES} increase and E_A reduction). When comparing VA coupling between optimization strategies, dP/dt_{max} optimization resulted in highest E_{ES} rise whereas SW optimization showed most reduction in E_A. Net changes in VA coupling were most pronounced for SW optimization with 45% reduction in E_A/E_{ES}.

One must consider that LV systolic function is affected by changes in preload, afterload and contractility. Since additional increases in SW are achieved under conditions of equal contractility (defined as E_{ES}) and comparable preload (defined as EDV), enhanced VA coupling may be considered an important mechanism of CRT response (i.e. SW optimization ≈ VA optimization). Interestingly, it has been described that improvements in cardiac function during CRT are obtained at diminished energy cost indicating enhanced mechanical efficiency.[26] Mechanical efficiency can be calculated from the PV loop by the ratio of SW (i.e. external work) to the pressure-volume area (PVA). The latter reflects the total mechanical energy that is generated by the LV.[27] SW optimization demonstrated highest improvement in mechanical efficiency (39%) relative to dP/dt_{max} optimization (26%) and conventional CRT (29%). These differences may be important since therapeutic interventions that enhance mechanical efficiency have proven to be beneficial with respect to outcome.[28]

Acute hemodynamic changes and long-term CRT response

Previous studies that examined the predictive value of dP/dt_{max} changes for long-term CRT response yielded conflicting results. Duckett et al. showed that the rise in dP/dt_{max} accurately predicted reverse remodeling after CRT at a cut-off value of 10%.[29] However, their results are not supported by several other studies. Two studies (one of our group in a different population) found dP/dt_{max} changes to be unrelated to reverse remodeling after CRT.[30,31] In addition, two more studies found no relationship between acute change in dP/dt_{max} and cardiac morbidity or survival.[32,33] Results of the present study add to the accumulating evidence opposing a relationship between acute changes in dP/dt_{max} and long-term CRT outcome. Although the optimal cut-off value that we found is similar to the one found by Duckett et al., patients with acute dP/dt_{max} increase ≥9% lacked favorable long-term CRT response compared to patient with <9% (**Figure 4**).

Acute changes in SW, on the other hand, accurately predicted long-term CRT response with an optimal cut-off value of 40%. Recently, our group was the first to demonstrate a clear association between acute SW increase and reverse remodeling after six months of CRT.[30] Acute SW response accurately predicted ≥15% reduction in LV end-systolic volume (LVESV) at an optimal cut-off value of 20% in a mixed population of wide- and narrow QRS complex patients. The present study, however, included only patients with strict LBBB (Strauss definition). The presence of favorable patient characteristics associated with large CRT benefit, combined with the PV-guided hemodynamic optimization protocol resulted in almost every patient becoming a CRT responder following the ≥15% LVESV reduction definition (6 non-responders). Therefore, we used the alternative definition of ≥10% absolute LVEF increase to identify "super-responders" resulting in a lower response rate (18 non-responders). The stricter definition of CRT response explains the higher cut-off value of 40% SW change that we found in the present study. Still, acute changes in SW showed high sensitivity for prediction of long-term CRT response, similar to previous findings.[30] In other words, patients lacking acute SW response are unlikely to become responders at the long-term. This was underlined by ten SW non-responders, of which only one became a long-term responder (**Figure 4**).

Limitations

Some limitations need to be taken into consideration. Due to the invasive nature of the study protocol, the sample size may be considered relatively small. Furthermore, we only included patients with strict LBBB (Strauss criterion) resulting in a homogenous population with a low number of ischemic cardiomyopathy and transmural scar. Moreover, a relatively large part of patients was excluded from the present analysis because of unreliable baseline PV loops. These patients demonstrated severe LV dilation with low ejection fractions on CMR. As a result, electrical conductance is measured in a large blood-pool with minimal volume changes throughout the

cardiac cycle, resulting in a low signal-to-noise ratio. Baseline PV-loops showed large volume changes during the isovolumic phases, resulting in a hourglass-shaped loop. Underestimation of the baseline loop results in excessive SW changes during biventricular pacing, overestimating LV pump function changes. Although these measurements can still be used to determine the optimal pacing configuration (the patient serves as its own control), absolute changes in SW do not adequately reflect benefit from CRT. Lastly, the effect of hemodynamic optimization on long-term CRT response was not investigated in comparison with a control group. Since the optimal SW setting was typically used for programming, this may have introduced bias.

Clinical applications

The development of quadripolar leads offers new possibilities and challenges in the field of CRT. Multiple stimulation sites are now offered from a single lead, increasing opportunities for CRT optimization strategies.[34] Hemodynamic optimization showed to be highly rewarding with an additional one-third increase in acute CRT response. Although non-invasive methods are searched to optimize settings, previous findings of the OPTICARE-QLV demonstrated that (i) electrical (QLV) parameters were unable to identify the most beneficial pacing electrode of a quadripolar lead,[3] (ii) optimal AV-delays varied substantially between patients,[35] and (iii) benefit from multipoint pacing was hard to predict from baseline parameters.[17] The use of other non-invasive methods such as echocardiography or electrocardiographic markers also remain to be proven. For now, invasive hemodynamic optimization strategies may therefore be considered the gold standard approach to optimize benefit from CRT.[1] However, the conductance technique is invasive, limited available in clinical practice, and not suitable for all patients. The additional time duration of the stimulation protocol was about 60 minutes but because the protocol was performed after wound closure (using the programmer), there was no additional risk of device infection. There was one complication of ventricular fibrillation (on entering the LV with the guidewire) that was successfully treated by cardiac defibrillation. No perforation, stroke or bleeding was observed. Although invasive hemodynamic optimization is unfeasible in clinical practice, the concept of volume-based optimization may guide future implementation of non-invasive surrogates of LV volume changes such as changes in intra-cardiac impedance, or stimulation in the CMR environment. It should be noted, however, that non-invasive surrogates do not always translate to direct hemodynamic measurements.

CONCLUSIONS

Pressure-volume guided hemodynamic optimization in CRT results in approximately one-third additional SW improvement on top of conventional CRT. Hemodynamic optimization by the pressure derivate dP/dt_{max} showed a similar one-third additional dP/dt_{max} improvement compared to conventional CRT. Improvement in one parameter, however, did not coincide with the other indicating different mechanisms. Whereas dP/dt_{max} optimization favored LV contractility (expressed as Ees), SW optimization improved ventricular-arterial coupling leading to higher stroke volume and ejection. Ultimately, acute changes in SW showed larger predictive value for long-term CRT response compared to dP/dt_{max}. Pressure-volume guided hemodynamic optimization may therefore be considered a potential strategy to use the full potential of CRT with quadripolar leads.

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SUPPLEMENTAL MATERIAL

Table S1. Device programming during conventional CRT and after hemodynamic optimization by dP/dt_{max} and strokework

Variable	Conventional CRT	dP/dt_{max} optimization	SW optimization	Kappa / P-value conventional vs. dP/dt_{max}	Kappa / P-value conventional vs. SW	Kappa / P-value dP/dt_{max} vs. SW
Electrode (n, %)				0.0	0.0	-0.3
D1	41 (100%)	12 (29%)	22 (54%)	(0.0 – 0.0)	(0.0 – 0.0)	(-0.2 – 0.2)
M2	0	12 (29%)	5 (12%)			
M3	0	8 (20%)	5 (12%)			
P4	0	9 (22%)	9 (22%)			
Circumferential position (n, %)						
Anterior	0	0	0			
Anterolateral	4 (10%)	7 (17%)	7 (17%)	κ 0.5	κ 0.5	κ 0.5
Lateral	23 (56%)	26 (63%)	26 (63%)	(0.2 – 0.7)	(0.3 – 0.8)	(0.3 – 0.8)
Posterolateral	14 (34%)	8 (20%)	8 (20%)			
Posterior	0	0	0			
Longitudinal position (n, %)						
Basal	0	13 (32%)	11 (27%)	κ 0.3	κ 0.5	κ 0.2
Mid	29 (71%)	21 (51%)	19 (46%)	(0.0 – 0.5)	(0.3 – 0.7)	(-0.1 – 0.4)
Apical	12 (29%)	7 (17%)	11 (27%)			
Paced AV delay (ms)	119 ± 13	165 ± 41	132 ± 58	p <0.001	p = 0.191	p = 0.001
Paced AV delay (% intrinsic AV interval)*	45 ± 9	63 ± 14	49 ± 19	p <0.001	p = 0.352	p <0.001

*intrinsic AV interval measured as right atrial pacing to right ventricular sensing interval

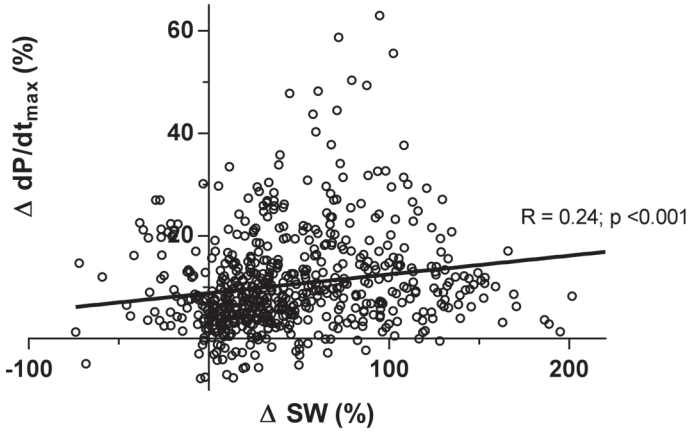


Figure S1. Relation between changes in SW and dP/dt$_{max}$ for the total group. The relation between change in SW (x-axis) and change in dP/dt$_{max}$ (y-axis) per pacing configuration is illustrated for the total group.

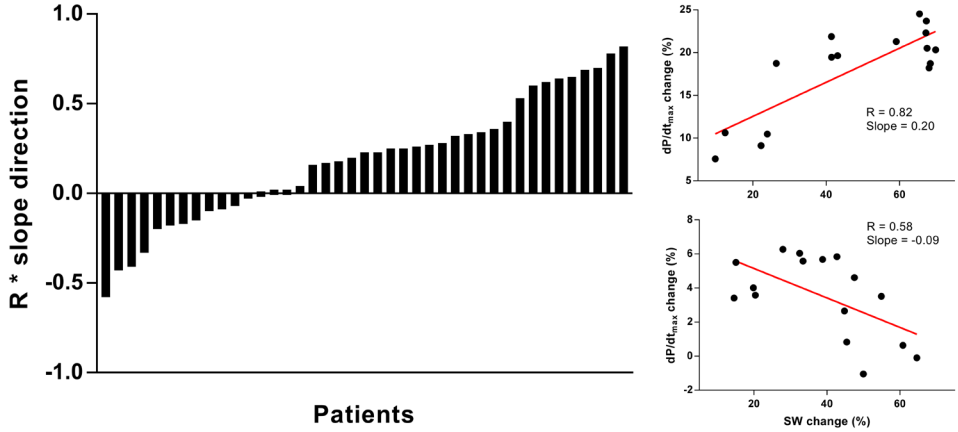


Figure S2. Relation between changes in SW and dP/dt$_{max}$ per patient analysis. The relation between changes in SW and dP/dt$_{max}$ per individual is illustrated by the slope direction multiplied by the correlation coefficient (R) of the trend line. Twenty-nine patients demonstrated a positive slope (patient example in upper right corner) whereas twelve patients demonstrated a negative slope (patient example in lower right corner). Only nine patients demonstrated a positive correlation with R ≥0.5.

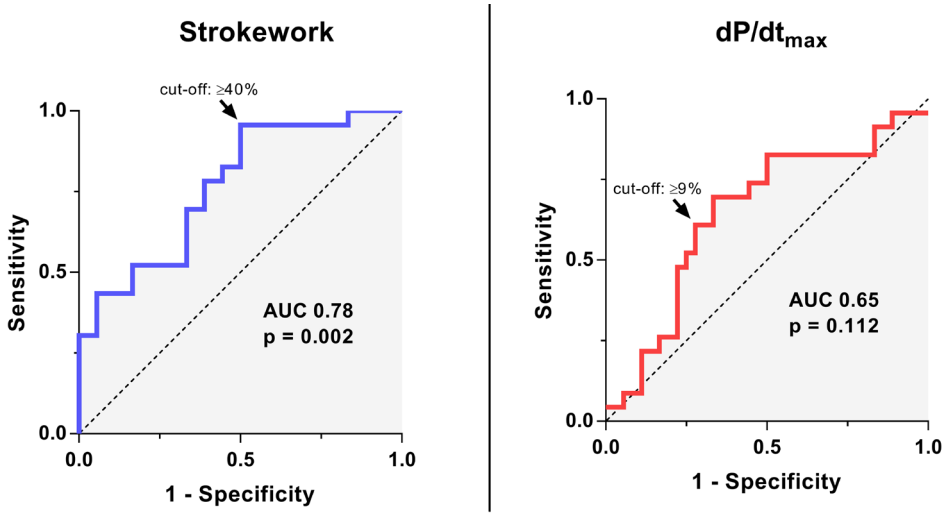
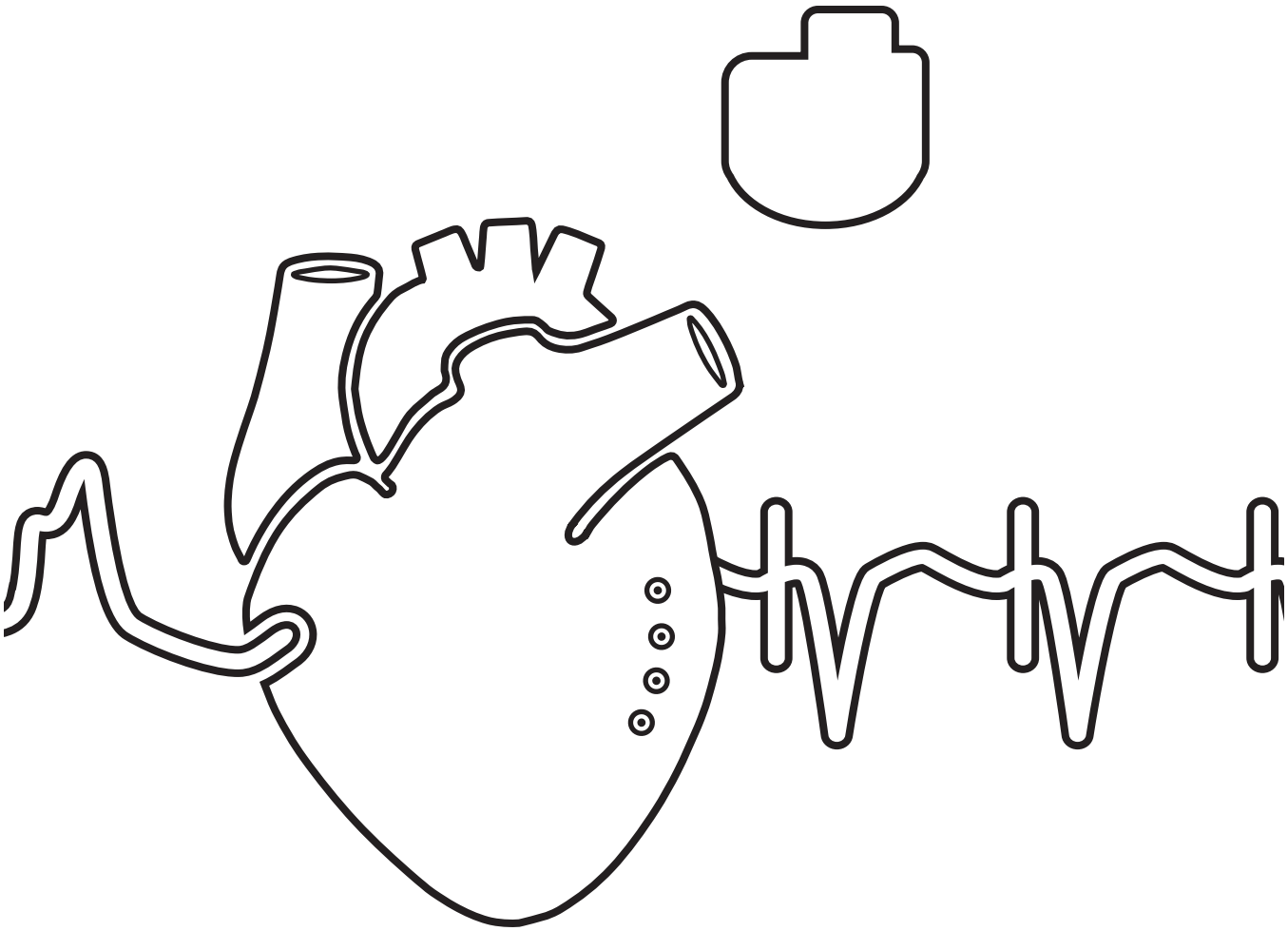


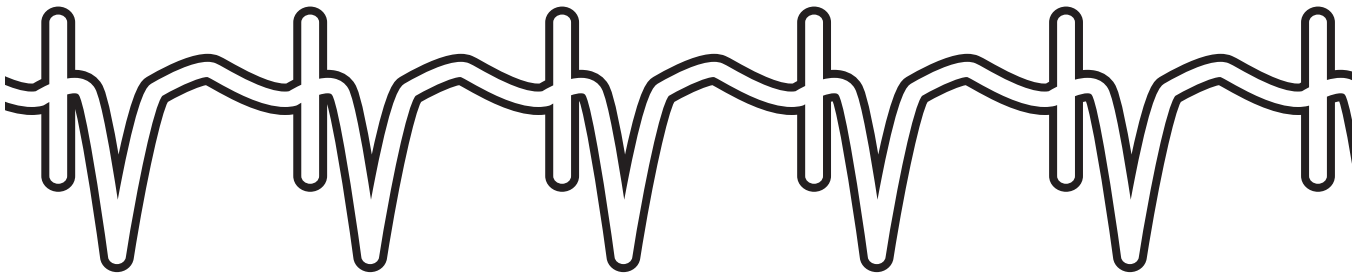
Figure S3. Predictive value of SW and dP/dt_{max} for long-term CRT response. ROC curve analysis for predicting long-term CRT response by changes in SW (left diagram) and by changes in dP/dt_{max} (right diagram).



Chapter 8

Pressure-volume loop analysis of Multi Point Pacing with a quadripolar left ventricular lead in Cardiac Resynchronization Therapy

JACC: Clinical Electrophysiogy 2018;4:881-889.



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ABSTRACT

Background

Multi-point pacing (MPP) with a quadripolar left ventricular (LV) lead may increase response to cardiac resynchronization therapy (CRT).

Objectives

This study aimed to compare MPP to optimal biventricular pacing with a quadripolar LV lead and find factors associated with hemodynamic response to MPP.

Methods

Heart failure patients with a left bundle branch block underwent CRT implantation. Q to local LV sensing interval (QLV), corrected for QRS-duration (QLV/QRSd) was measured. Invasive pressure-volume loops were assessed during four biventricular pacing settings and three MPP settings, using four atrioventricular delays. Hemodynamic response was defined as change in stroke work (Δ%SW) compared to baseline measurements during intrinsic conduction. Δ%SW of MPP was compared to conventional biventricular using the distal electrode (BIV-CONV) and the electrode with highest change in Δ%SW (BIV-OPT).

Results

Forty-three patients were analyzed (66±10 years, 63% males, 30% ischemic cardiomyopathy (ICM), LV ejection fraction (LVEF) 29±8%, and QRS-duration 175±13ms. QLV/QRSd was 84±8% and variation between LV electrodes 9±5%. Compared to BIV-CONV, MPP showed a significant higher increase of SW (Δ%SW +15±35%, $p<0.05$) with a large interindividual variation. There was no significant difference in Δ%SW with MPP compared to BIV-OPT (-5±24%, $p=0.19$). Male gender and low LVEF were associated with increase in Δ%SW due to MPP vs. BIV-OPT in multivariate analysis, while ICM was only associated in univariate analysis.

Conclusion

Optimization of the pacing site of a quadripolar LV lead is more important than to program MPP. However, specific subgroups (i.e. especially males) do benefit substantially from MPP.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is an established therapy for patients with heart failure and left ventricular (LV) conduction delay.[1] CRT aims to improve LV hemodynamic function by electromechanical resynchronization of LV contraction. Unfortunately, a considerable (30-40%) proportion of patients are considered non-responders to CRT.[2] Non-response has several causes, of which a suboptimal LV lead position is an important contributor.[3] A suboptimal placed LV lead may reduce the effect of biventricular pacing on efficient electromechanical resynchronization.[4] Several strategies have been suggested to optimize LV lead position, such as guided LV lead positioning, endocardial pacing, and multi-site pacing (i.e. LV pacing in more than one vein) or multi-point pacing.[5,6] Multi-point pacing (MPP) implies pacing the LV free wall with two pacing stimuli, delivered by a single quadripolar LV lead. MPP might lead to a more homogeneous electromechanical activation and subsequently an additional improvement in LV function.[4,7] MPP is proven to be beneficial compared to conventional biventricular pacing in terms of acute hemodynamic response, functional improvement and reverse remodeling.[5,8] Although these results are promising, most studies did not compare MPP to the most optimal setting of biventricular pacing, as obtained with a quadripolar LV lead. Moreover, hemodynamic response of MPP varies among patients,[9] suggesting that patient specific differences (e.g. presence of ischemic cardiomyopathy or a low myocardial conduction velocity between electrodes) and/or therapy delivery (e.g. lead position) are factors contributing to the effect of MPP.

The aim of this study was to compare the acute hemodynamic response of MPP, measured by invasive pressure-volume (PV) loops, to biventricular pacing using the electrode of quadripolar LV lead with highest increase in hemodynamic function. Patient characteristics, electrocardiographic and electro-anatomical parameters are correlated with MPP response. The hypothesis of this study is that patients with ischemic cardiomyopathy or those with an low myocardial conduction velocity between electrodes of a quadripolar LV lead will benefit to MPP, as the additional pacing site may cause a faster and/or more homogeneous depolarization of the LV.

METHODS AND MATERIALS

Patient cohort

The OPTICARE-QLV trial is a multicenter observational study, which was performed in three university medical centers (University Medical Center Utrecht; VU University Medical Center, Amsterdam; and Maastricht University Medical Center, Maastricht; all in the Netherlands). Fifty-one patients planned for CRT implantation were prospectively enrolled. Inclusion criteria were

moderate to severe heart failure (i.e. NYHA class II or III), LV ejection fraction ≤35%, optimal pharmacological therapy, sinus rhythm, and a left bundle branch block (LBBB) according to Strauss criteria.[10] Exclusion criteria were presence of LV thrombus, severe aortic valve stenosis, or a mechanical aortic valve replacement. The study was performed according to the Declaration of Helsinki and in agreement with the local medical ethics committees. All subjects gave written informed consent.

Baseline characteristics

Prior to implantation baseline characteristics were collected, among which laboratory tests (creatinine and BNP-levels), age, gender, NYHA functional class, PR-interval, QRS-duration, and QRS morphology. All patients underwent an echocardiographic examination and cardiac magnetic resonance imaging (CMR) before CRT implantation. Derived LV volumes were used to calibrate the conductance catheter-derived volumes. Type of cardiomyopathy was classified as dilated (DCM) or ischemic (ICM) using the definition of Felker et al.[11] Patients with history of myocardial infarction or revascularization (CABG or PCI), with ≥75% stenosis of left main or proximal LAD, or with ≥75% stenosis of two or more epicardial vessels were categorized as ICM.

CRT implantation

CRT implantation was performed under local anesthesia. The right atrial (RA) and right ventricular (RV) leads were placed transvenously at conventional positions. The quadripolar LV lead (Quartet 1458Q, St. Jude Medical, St. Paul, Minnesota, United States) was placed transvenously in one of the coronary veins overlying the LV free wall. An anterolateral, lateral, or posterolateral position was preferred. After electrophysiological measurements, the three leads were connected to a St. Jude Medical CRT-device.

Electrophysiological measurements

Electrophysiological (EP) measurements were performed using an on-site dedicated EP system. EP system settings (i.e. filter settings, gain, sampling frequency) of the three participating centers were matched to study protocols. Using the EP system, simultaneous registrations of the twelve-lead surface ECG and the three implanted leads were recorded. Temporary pacing was used to measure delays of specific pacing settings between electrodes, among which the Q on the surface ECG to LV sensing delay (QLV) and the ratio between QLV, QRS duration (QLV/QRSd) and local myocardial conduction velocity. Conduction time was measured as the pacing to sensing intervals between the four electrodes during LV only pacing with the separate electrodes (**Supplemental figure 1**). The distances between the electrodes were used to obtain the conduction velocity. Conduction velocity below 0.70 m/s was considered 'slow', while all other values were considered normal.[12]

Hemodynamic measurements and pacing protocol

A dedicated PV-loop conductance catheter (CD Leycom, Zoetermeer, The Netherlands) was placed in the LV cavity after right femoral artery access. For all pacing settings, including MPP, the RV coil was used as anode and the interventricular delay between first LV pacing site and RV was kept constant at 40ms LV first (**Table 1**). Biventricular pacing was performed with each quadripolar electrode separately as LV pacing site. MPP was programmed in three settings: 1) distal and proximal simultaneously (i.e. 5ms delay), 2) distal followed by proximal with a 35ms delay and 3) proximal followed by distal with a 35ms delay. The observed conduction delay between the two electrodes used for MPP was above 35ms in all cases. MPP was conducted with the electrodes with the largest anatomical distance (e.g. usually D1 and P4) or any other combination with acceptable pacing thresholds and without phrenic nerve stimulation.

Table 1. Pacing configurations

Biventricular pacing (BIV)	Multi-point pacing (MPP)
LV-D1 – 40ms – RV (BIV-CONV)	LV-D1 – 5ms – LV-P4 – 35ms – RV (MPP1)
LV-M2 – 40ms – RV	LV-D1 – 35ms – LV-P4 – 5ms – RV (MPP2)
LV-M3 – 40ms – RV	LV-P4 – 35ms – LV-D1 – 5ms – RV (MPP3)
LV-P4 – 40ms – RV	

All pacing configurations were tested with four atrioventricular delays. In case of non-capture or phrenic nerve stimulation, a different electrode pair with largest inter-electrode distance was used for MPP. LV: left ventricular, LV-D1: LV pacing with electrode D1, LV-M2: LV pacing with electrode M2, LV-M3: LV pacing with electrode M3, LV-P4: LV pacing with electrode P4, RV: right ventricular

For each pacing mode, atrioventricular (AV) delays of 80%, 60%, 40% and 20% of the patient's intrinsic atrioventricular conduction (i.e. RA pacing to RV sensing delay) were used. PV-loops were recorded during pacing 5 to 10 bpm above intrinsic rhythm, for 60 beats during pacing settings and for 30 beats during baseline references of RA pacing. Stroke work (SW) was calculated as the surface of the recorded PV-loops. The change in SW (Δ%SW) of each pacing setting was calculated compared to the adjacent baseline references. The Δ%SW of the four different AV-delays of a single pacing configuration was plotted and a 2nd order polynomial line was fitted. The peak of the parabola was used as maximal increase in Δ%SW of the specific pacing setting (**Figure 1**). The same method was used for the maximal value of the first derivative of LV pressure (dP/dt_{max}). This methods reduces measurement variability and allows for reliable estimation of the maximal achievable increase in SW.[13] Patients were excluded from the final analysis if the PV-loop during baseline measurements showed crossing sections and large end-diastolic tails. These loops are the result of poor measurement of volume changes and lead to underestimation of SW during

intrinsic LBBB. Underestimation of baseline values leads to unreliable high increases in Δ%SW, as the PV-loops often increase to normal shape during biventricular pacing.

Response to MPP was defined as the change in Δ%SW compared to either conventional biventricular pacing using the most distal electrode (BIV-CONV), or as change in Δ%SW compared to biventricular pacing with the electrode of the quadripolar lead with highest change in Δ%SW (BIV-OPT).

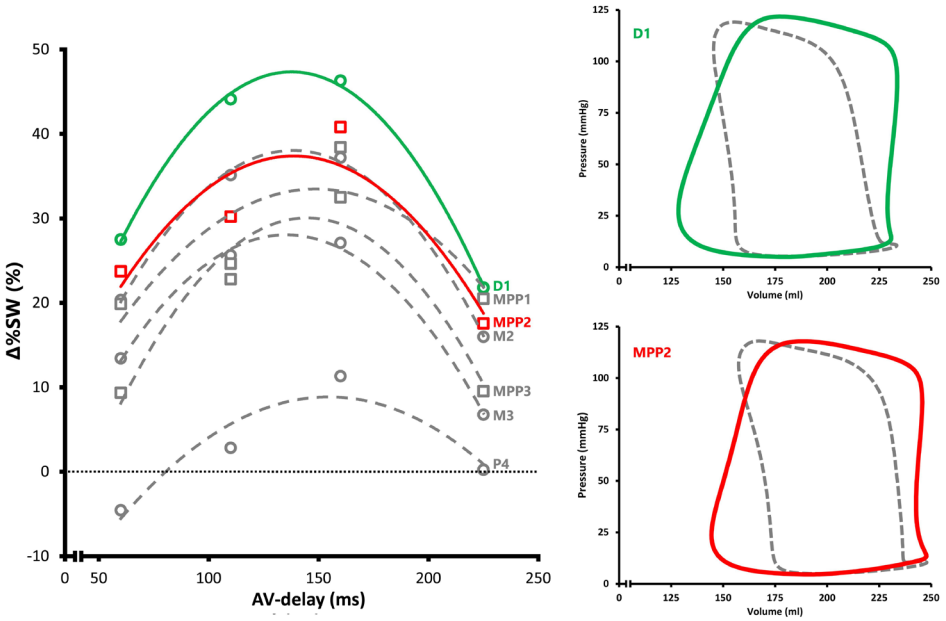

Figure 1. Optimization method based on pressure-volume loops.
Left panel: Optimization curves during all pacing modes in one patient. Broken lines represent parabolic curves fitted through the measured changes in stroke work compared to intrinsic conduction during four atrioventricular (AV) delays. In this patient biventricular pacing (circles) with D1 (green) was the optimal biventricular configuration and multi-point pacing (MPP) (squares) with D1-P4 with 35ms delay between both pacing stimuli (MPP2, red) the best MPP configuration. The corresponding pressure-volume loops are displayed in the right panels, with loops of broken lines representing intrinsic conduction (right atrial pacing).

Lead position

After lead placement, fluoroscopy images were made in the left anterior oblique (LAO) 40° and in the in the right anterior oblique (RAO) 30° angle to determine the specific position of each quadripolar LV lead electrode. The LV was divided in six segments in the circumferential direction (septal, anterior, anterolateral, lateral, posterolateral, and posterior) on the LAO view and in three segments (basal, mid, and apical) on the RAO view.[14]

Statistical analysis

Statistical analysis was performed using SPSS (SPSS statistics 23.0, IBM, New York, USA). Patients were classified with a benefit of MPP if Δ%SW of MPP was higher than Δ%SW of BIV-OPT, the remaining patients were classified as those without benefit of MPP. The univariate relation of predictors for change in Δ%SW due to MPP were analyzed using linear regression, both for change compared to BIV and compared to BIV-OPT. Univariate predictors with a p-value <0.10 were tested in a multivariate analysis. The relation of variables with response to MPP was analyzed using a T-test or Mann-Whitney U-test, dependent on normality of data, or a Chi-Square test in case of categorical variables. The optimal AV-delays and hemodynamic effect of pacing strategies analyzed with a paired T-test or Wilcoxon signed rank test, depending on normality of data. Mean ± standard deviation or median and interquartile range are given, depending on normality of data. A p-value below 0.05 was considered significant for all tests.

RESULTS

Fifty-one patients were included in the study, of whom eight were excluded from this analysis. Three of the excluded patients had considerable underestimation of the PV-loop during intrinsic rhythm. Two patients did not receive MPP due to a technical error during the pacing protocol. Three more patients were excluded due to large baseline drift of SW measurements between biventricular pacing and the MPP pacing configurations.

In the remaining 43 patients there were 63% male (n=27) and 30% (n=13) with an ischemic etiology of heart failure (**Table 2**). PR-duration was 183±32ms, QRS-duration was 175±13ms. QLV of the electrode with highest value was 147±16ms, with a QLV/QRSd ratio of 84±8%. LV dimensions were enlarged (end-diastolic volume 208±62ml, LV end-systolic volume 154±56ml), and systolic function was impaired (LV ejection fraction 29±8%). CMR images were available in 40 patients, of whom 8 had evidence of delayed enhancement. There was no statistical significant difference in the amount of patients with scar, nor in scar size, between patients with and without a positive effect of MPP compared to BIV-OPT.

During biventricular pacing, the largest Δ%SW was achieved with electrode D1 in fifteen (35%), M2 in eight (19%), M3 in five (12%) and P4 in fifteen (35%) patients. MPP was applied using electrode D1 and M3 in three patients (7%) and with D1 and P4 in all other patients. There was no statistical difference between MPP vectors regarding the change in Δ%SW (MPP1: 66±59%, MPP2: 66±57%, MPP3: 61±56, p=ns). Thirty-one (72%) patients showed a larger Δ%SW during MPP then during BIV-CONV pacing and seventeen (40%) showed a larger Δ%SW during MPP then during BIV-OPT (**Table 3** and **Figure 2**). MPP increased Δ%SW significantly (+15±35%, p<0.05) as

Table 2. Baseline characteristics

Parameter	Analyzed patients (n=43)	Patients without benefit of MPP (n=26)	Patients with benefit of MPP (n=17)	p-value
Age	66±10	66±10	65±9	0.750
Sex (n, % of male)	27 (63%)	13 (50%)	14 (82%)	0.032
Cardiomyopathy (n, % of ICM)	11 (26%)	6 (23%)	5 (29%)	0.642
Scar (n, %)	8 (19%)	6 (24%)	2 (13%)	0.414
Scar size* (%)	9 (2-19)	9 (4-16)	11 (1-20)	1.000
NYHA-class (n, %)				
II	29 (67%)	18 (69%)	12 (71%)	0.722
III	14 (33%)	8 (31%)	5 (29%)	
PR-duration (ms)	183±32	181±24	185±41	0.717
QRS-duration (ms)	175±13	173±14	177±12	0.280
Max QLV (ms)	147±16	146±17	148±15	0.691
Max QLV/QRSd (%)	84±8	85±9	84±5	0.624
QLV/QRSd variation (%)	9±5	10±5	8±4	0.187
Conduction time (ms)	75±21	69±20	84±21	0.034
Conduction velocity (m/s)	0.60±0.20	0.67±0.28	0.51±0.12	0.014
LVEDV (ml)	209±62	191±43	235±77	0.044
LVESV (ml)	151±57	134±39	178±70	0.029
LVEF (%)	29±8	31±9	26±6	0.031
Creatinine (µmol/L)	87±21	84±24	92±15	0.218
Log BNP	1.85±0.49	1.8±0.41	1.99±0.60	0.212
Medication (n, %)				
ACE-inhibitor or ATII-antagonist	42 (98%)	26 (100%)	16 (94%)	0.211
Beta-blocker	36 (84%)	20 (77%)	15 (88%)	0.351
Diuretics	30 (70%)	16 (62%)	13 (76%)	0.307
Aldosterone-antagonists	25 (58%)	16 (62%)	11 (65%)	0.834
Anti-coagulants	27 (43%)	13 (50%)	13 (76%)	0.083
Comorbidities (n, %)				
Hypertension	15 (35%)	12 (46%)	3 (18%)	0.055
Renal dysfunction	3 (7%)	1 (4%)	2 (12%)	0.820
Circumferential electrode position (n, %)				
Anterior	0	0	0	0.152
Anterolateral	31 (19%)	22 (22%)	9 (14%)	
Lateral	96 (58%)	52 (51%)	44 (67%)	
Posterolateral	37 (22%)	24 (24%)	13 (20%)	
Posterior	3 (2%)	3 (3%)	0	

Table 2. Continued

Parameter	Analyzed patients (n=43)	Patients without benefit of MPP (n=26)	Patients with benefit of MPP (n=17)	p-value
Longitudinal electrode position (n, %)				
Basal	55 (33%)	34 (34%)	21 (32%)	0.124
Mid	89 (53%)	49 (49%)	50 (76%)	
Apical	23 (14%)	18 (18%)	5 (8%)	

Multi-point pacing (MPP) responders and non-responders are defined by a positive or negative change in stroke work (Δ%SW) between biventricular pacing with the electrode with highest change in Δ%SW and highest increase in Δ%SW with MPP. The p-value of the comparison of patients with a benefit and those without a benefit of MPP compared to BIV-OPT is depicted in the last column. ACE: angiotensin converter enzyme, ATII: angiotensin receptor II, BIV-OPT: optimal change in Δ%SW with biventricular pacing, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, LVEF: left ventricular ejection fraction, ICM: ischemic cardiomyopathy, Log-BNP: 10th logarithmic conversion of Brain Natriuretic Peptide, LV: left ventricular, NYHA-class: New York Heart Association functional class, SW: stroke work, QLV: Q to LV sensing delay. QLV/QRSd: ratio between QLV and intrinsic QRS-duration. *: scar size in patients with scar on late gadolinium enhanced images.

compared to BIV-CONV pacing, but there was no significant change between MPP and BIV-OPT (-5±24%, p=0.19). The Δ%SW due to MPP compared to BIV-OPT was heterogeneous, being larger than 10% in sixteen patients, larger than 10% in nine patients and eighteen patients showing a decrease in Δ%SW larger than 10%. A heterogeneous effect was also seen for changes in %dP/dt$_{max}$ (**Figure 3**). There was a large variation in response to MPP compared to BIV-OPT (**Figure 4**). Δ%dP/dt$_{max}$ of MPP was not significantly different from BIV-CONV (-0.2±4.0%, p=0.71), whereas it was significantly lower for MPP compared to BIV-OPT (-1.8±3.8, p<0.01). There were no significant differences in the AV-delay with highest change in Δ%SW between pacing configurations. The optimal AV-delay for BIV-CONV was: 133±43ms, BIV-OPT: 120±37ms, MPP: 129±36ms (BIV-CONV vs. BIV-OPT: p=0.15, BIV-CONV vs. MPP: p=0.17, BIV-OPT vs. MPP p=0.65).

Multi-point pacing (MPP) responders and non-responders are defined by a positive or negative change in stroke work (Δ%SW) between biventricular pacing with the electrode with highest change in Δ%SW and highest increase in Δ%SW with MPP. In the last column, the p-value is depicted for the comparison of MPP responders and non-responders. Δ%SW: percentage change in stroke work. BIV: biventricular pacing with the distal electrode (D1) of the quadripolar left ventricular lead, BIV-OPT: biventricular pacing with the electrode with highest change in Δ%SW, MPP: multi-point pacing. Effects between groups were compared with a Mann-Whitney U test and corresponding p-values are shown in the rightmost column. Effects within a group were compared with a Wilcoxon signed rank test, with: *: p<0.05 between two strategies. †: p<0.001 between two strategies.

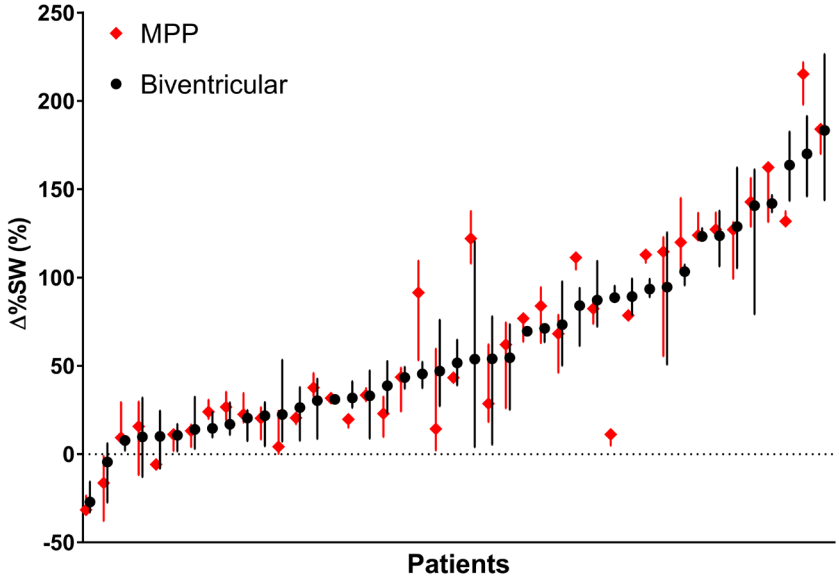

Figure 2. Acute hemodynamic effect of four optimization strategies. Acute hemodynamic effect in percentage change of stroke work (Δ%SW) of biventricular pacing with the distal electrode (BIV-CONV), with the optimal electrode (BIV-OPT), multi-point pacing (MPP) or the optimal setting (OPT). The optimal setting is either MPP or BIV-OPT. *: p<0.01 compared to all other strategies.

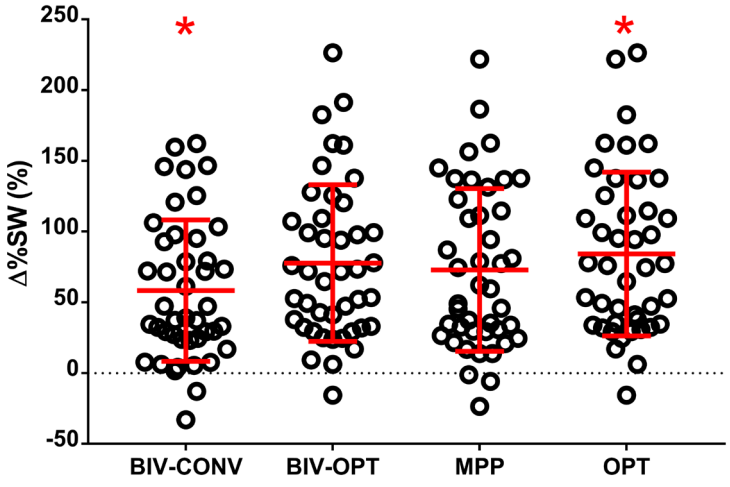

Figure 3. Acute hemodynamic effect of biventricular pacing and multi-point pacing per patient. Change in stroke work (Δ%SW) of biventricular pacing (black circles) and multi-point pacing (MPP) (red diamonds). The symbols depicts the median value of the four BIV settings and of the three MPP settings, while lowest and highest values of BIV and MPP are displayed by bars.

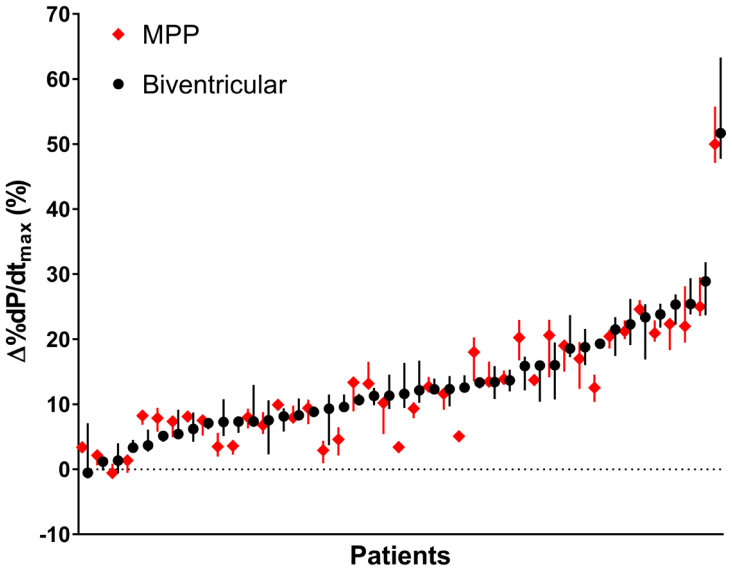

Figure 4. Change in dP/dt_{max} of biventricular site pacing and multi-point pacing per patient. Change in $\%dP/dt_{max}$ of biventricular pacing (black circles) and multi-point pacing (MPP) (red diamonds) is given. The medians of four BIV settings and three MPP settings are displayed by the symbol, while lowest and highest value are displayed by bars. $\%dP/dt_{max}$: percentage change in maximal rate of LV pressure rise.

Patients with a positive effect of MPP compared to BIV-OPT were more often male, had larger LV end-diastolic and end-systolic volume, a lower LV ejection fraction, and lower myocardial conduction velocity (**Table 2**). Male patients and those with ICM also had a larger Δ%SW of MPP vs. BIV-OPT (**Figure 5**). Increase in Δ%SW tended to be higher for those with low conduction velocity (p=0.055). Patients with a positive response to MPP vs. BIV-OPT tended to have distal electrodes (D1) in a mid-position (15 mid and 2 apical), while patients with a negative response had a more evenly distributed D1 position (16 mid and 10 apical, p=0.056). Univariate analysis of linear regression showed significant association of LV ejection fraction, type of cardiomyopathy and sex with change in Δ%SW of MPP vs. BIV-OPT (**Table 4**). End-diastolic volume, QRS duration, QLV/QRSd, scar size and conduction velocity were not associated with change in Δ%SW of MPP vs. BIV-OPT. Multivariate analysis confirmed that LV ejection fraction and male sex were independent predictors for hemodynamic response of MPP compared to BIV-OPT, while type of cardiomyopathy was not included in the model.

Table 3. Effect of pacing strategies on acute hemodynamic response

Strategy	All patients (n=43)	Patients without benefit of MPP (n=26)	Patients with benefit of MPP (n=17)	p-value
BIV-CONV (Δ%SW)	58±50	55±53	64±46	0.568
BIV-OPT (Δ%SW)	78±55	78±59	78±50	0.960
MPP (Δ%SW)	73±58	59±56	94±56	0.035
Differences				
BIV-OPT vs. BIV-CONV (Δ%SW)	19±27†	25±5†	14±29*	0.170
MPP vs. BIV-CONV (Δ%SW)	15±35*	5±32	30±34†	0.012
MPP vs. BIV-OPT (Δ%SW)	-5±24	-19±18†	16±15†	<0.001

Table 4. Univariate and multivariate models for predictors of response to MPP vs. BIV-OPT

Univariate analysis				
	B	**SE**	**R**	**p-value**
Sex (male)	19.16	6.95	0.40	0.009
Cardiomyopathy (ICM)	17.05	7.95	0.32	0.038
Scar size (%)	0.03	0.71	0.01	0.970
LV EDV (ml)	0.06	0.06	0.16	0.306
LV EF (%)	-0.95	0.42	0.33	0.030
Conduction velocity (m/s)	-0.17	0.16	0.17	0.293
QLV/QRSd (%)	3.12	47.1	0.01	0.948
QRS-duration (ms)	-0.07	0.28	0.04	0.793
Multivariate analysis				
	B	**SE**	**R**	**p-value**
Sex (male)	17.59	6.72	0.40	0.012
LVEF (%)	-0.83	0.40	0.49	0.042
Cardiomyopathy (ICM)	.	.	.	0.184

Univariate analysis depicts the values of linear regression of the specific parameter and change in Δ%SW between MPP and biventricular pacing with the electrode with highest change in Δ%SW (BIV-OPT). Multivariate forward analysis incorporates the parameters with a p<0.10 in the univariate analyses. R value of the multivariate analysis indicates the R value of the model with incorporation of that parameter. Sex was incorporated first, LVEF second. B: beta-coefficient, SE: standard error, R: correlation coefficient. For other abbreviations, see table 2.

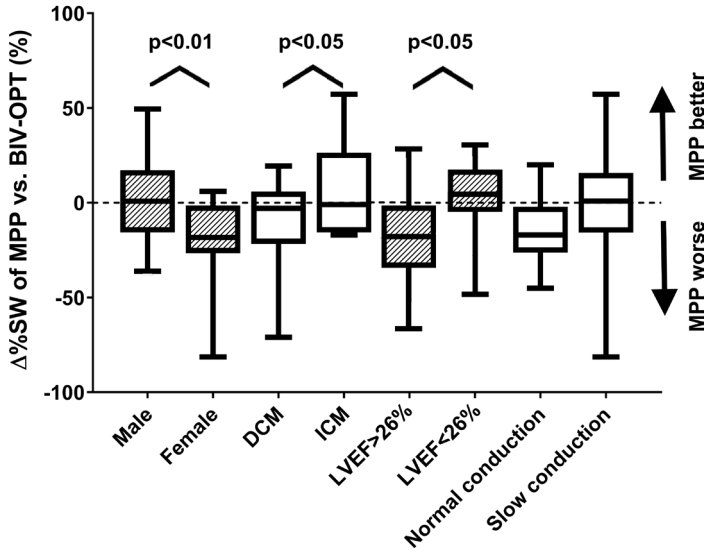

Figure 5. Response to MPP vs. BIV-OPT for four categorical variables. %-Change in stroke work (Δ%SW) of multi-point pacing (MPP) vs. optimal biventricular pacing with one of the electrodes of the quadripolar lead (BIV-OPT). Conduction velocity is categorized in fast (≥0.7m/s) and slow (<0.7m/s) myocardial conduction. DCM: dilated cardiomyopathy. For other abbreviations, see table 2. *: p<0.05 between indicated categories, †: p<0.01 between indicated categories.

DISCUSSION

The acute hemodynamic response of MPP compared to biventricular pacing with the distal electrode (BIV-CONV) showed a significant improvement. The effect of MPP compared to the optimal configuration of a quadripolar LV lead (BIV-OPT) showed no overall benefit. These findings indicate that optimization of the LV site for biventricular pacing with a quadripolar lead is of primary importance. MPP may have additional benefit in a sub-selection of patients, specifically males and those having a low LV ejection fraction.

The effect of multi-point pacing

While MPP was beneficial compared to conventional CRT, we found a heterogeneous and non-significant hemodynamic effect of MPP compared to CRT with the optimal configuration of a quadripolar LV lead. As we optimized the atrioventricular delay and tested each pacing site of a quadripolar LV lead for biventricular pacing, the additional effect of MPP compared to BIV-OPT was low in our study. Our results are however comparable to a study in which atrioventricular delay optimization was used and all biventricular pacing sites were compared to MPP.[15] While some studies also indicate that response to MPP is heterogeneous among patients,[9,15] Zanon et

al. found a small but significant increase in acute hemodynamic response (i.e. dP/dt_{max}) with MPP compared to unifocal LV paced sites in all patients.[5] We used both SW and dP/dt_{max} and found a variation in the effect of MPP with both indices (**Figure 2 and 3**). Pappone et al. also used SW derived from PV-loops and showed that the best of seven MPP settings improved hemodynamic function more than biventricular pacing with only the distal or proximal electrode of a quadripolar LV lead.[8] These findings are in line with our results, as we found that MPP resulted in higher Δ%SW benefit than BIV-CONV. As we found no benefit of three MPP settings compared to four BIV settings, a single optimized pacing site may be ideal for CRT. The presence of an ideal location for biventricular pacing which cannot be improved by multiple LV pacing sites has been put forward by Ploux et al.[4] Finding the optimal biventricular pacing configuration is of primary importance. Although we still need tools to select the optimal biventricular pacing configuration, one well-placed lead is potentially better than adding extra pacing sites to a suboptimal placed lead. Generally, patients benefit most from an optimized single LV pacing site, but some benefit from MPP. The effect of LV pacing site optimization is therefore heterogeneous and requires a patient tailored approach.

Predicting MPP response

Specific subsets of patients might benefit of MPP, as we observed that especially male patients and those with lower ejection fraction benefited from MPP. Gender was the strongest predictor in the multivariate analysis, possibly because males more often had ICM (50% vs. 13%, p=0.17) and larger hearts (LVEDV: 223±68 vs. 184±42ml, $p<0.05$). The additional electrical wave front of MPP may lead to a more homogeneous and/or faster depolarization of the enlarged LV free wall. Also, differences in cardiac size have shown to modify the effect of QRS duration on CRT response.[16,17] Although LVEDV was higher in MPP responders, LVEDV did not have an association with the percentage change in Δ%SW of MPP vs. BIV-OPT in our study. MPP could also beneficial in ventricles with heterogeneous conduction, potentially caused by myocardial fibrosis. The direct effect of scar burden on the hemodynamic benefit of MPP was shown in computer simulations.[18] These results were confirmed in a patient study with posterolateral scar,[19] and in patients with ICM in general in other studies.[15,20] Sohal et al. observed that only non-LBBB patients converted from hemodynamic non-responders with conventional CRT to multi-site pacing responders.[20] This may partly be explained by the prevalence of ICM, which is higher in non-LBBB patients resulting in a more heterogeneous conduction of the left ventricle.[21] As we only included patients with a 'strict' LBBB using Strauss criteria,[10] the prevalence of patients with substantial myocardial scar in our study was relatively low. Implementation of our methods in CRT candidates without strict LBBB is of interest, as the scar burden is potentially larger in these patients.[18]

We used the electrodes with largest inter-electrode distance for MPP, which were the most valuable electrodes for MPP in prior studies.[9,22] The results of Niazi et al. confirm that the MPP vector with largest anatomical separation has favorable effects on long-term clinical response, compared to other MPP vectors.[22] As the effect of MPP with a quadripolar LV lead may be dependent on the electrode spacing, the effect of inter-electrode distance and the number of electrodes on an LV lead are also of interest for future work. Several manufacturers, including the one used in this study, have developed quadripolar leads with varying electrode spacing. Larger electrode spacing may facilitate a better distribution of electrodes over the LV wall. Nonetheless, the effective electrode spacing is limited by the coronary venous anatomy. Large electrode spacing may result in non-capture in case of short tributary branches. We already observed non-capture on the proximal electrode in three patients with the electrode spacing (i.e. 47mm) of the current quadripolar lead.

MPP might be used to further optimize hemodynamic response in subgroups of patients. However, in the current patient population (i.e. strict LBBB), only one patient converted from non-responder with BIV-OPT to a responder with MPP using the 20% increase in Δ%SW cut-off value defined by De Roest et al. (Δ%SW of BIV-OPT: 9%, MPP: 29%).[23] However, three patients became a non-responder with MPP, while they were classified as responder to BIV-OPT. Although translation of acute response to long-term effects is difficult, other studies show that MPP may improve CRT response in individual patients.[22] Physicians should therefore first test the acute effect of biventricular pacing with each separate electrode of the quadripolar lead. MPP may then be implemented if the benefit of biventricular pacing is lower than desired, especially in patients with an ischemic etiology of heart failure, male patients and those with very low LV ejection fraction. Nevertheless, MPP should not be programmed blindly, as it can have a detrimental effect on hemodynamic response. The hemodynamic effect of MPP should therefore always be tested, moreover as it increases battery drainage. As PV-loop recordings are not standard clinical practice, testing of the hemodynamic effect of MPP should be performed by, preferably non-invasive, assessment of cardiac function such as the plethysmographic method of Kyriacou et al.[24]

Limitations

There are some limitations to take into account. Owing to the use of invasive measurements the sample size of this study is relatively small and the time period of inclusion relatively long. Due to the strict LBBB criteria, patients with ICM and pronounced areas of scar were prone to be excluded, while they might benefit more from MPP. The results regarding patients with ICM should therefore be interpreted with caution. Although patients with ICM often had only small areas of myocardial scar, the etiology of heart failure in these patients is different from DCM. PV-loop analysis with various AV-delays and pacing modes was time-consuming. The study protocol was

therefore shortened by the use of a fixed offset of 40ms LV first, as it is preferable in most CRT patients.[25] The fixed offset might have influenced results, as it has not been specifically tested for MPP. Due to the implantation protocol, most LV leads were placed in a favorable segment (i.e. anterolateral, lateral or posterolateral). The intra- and inter-individual differences between studied parameters was therefore relatively small, although it also reflects clinical practice. Although randomization is preferred to reduce bias by baseline drift of the catheter, pacing configurations were performed in a fixed order to reduce programming errors. PV-loop recording of MPP was therefore always performed after biventricular pacing modes. The effect of baseline drift was compensated by the repeated reference measurements before and after each pacing configuration. Furthermore, to minimize the effect that excessive baseline drift might have on the results, three patients with considerable drift between BIV modes and MPP were excluded from the analysis. Lastly, ECG recordings were not systematically collected during PV-loop measurements, therefore no comment can be made on the applicability of ECG parameters for optimization of CRT.

CONCLUSION

In patients with typical LBBB, the acute hemodynamic response of MPP compared to biventricular pacing with the distal electrode showed a significant improvement. The effect of MPP compared to the optimal configuration of a quadripolar LV lead showed no overall benefit. Therefore, optimization of the LV site for biventricular pacing with a quadripolar lead is of primary importance. Nevertheless, MPP may have additional benefit in a specific sub-selection of patients.

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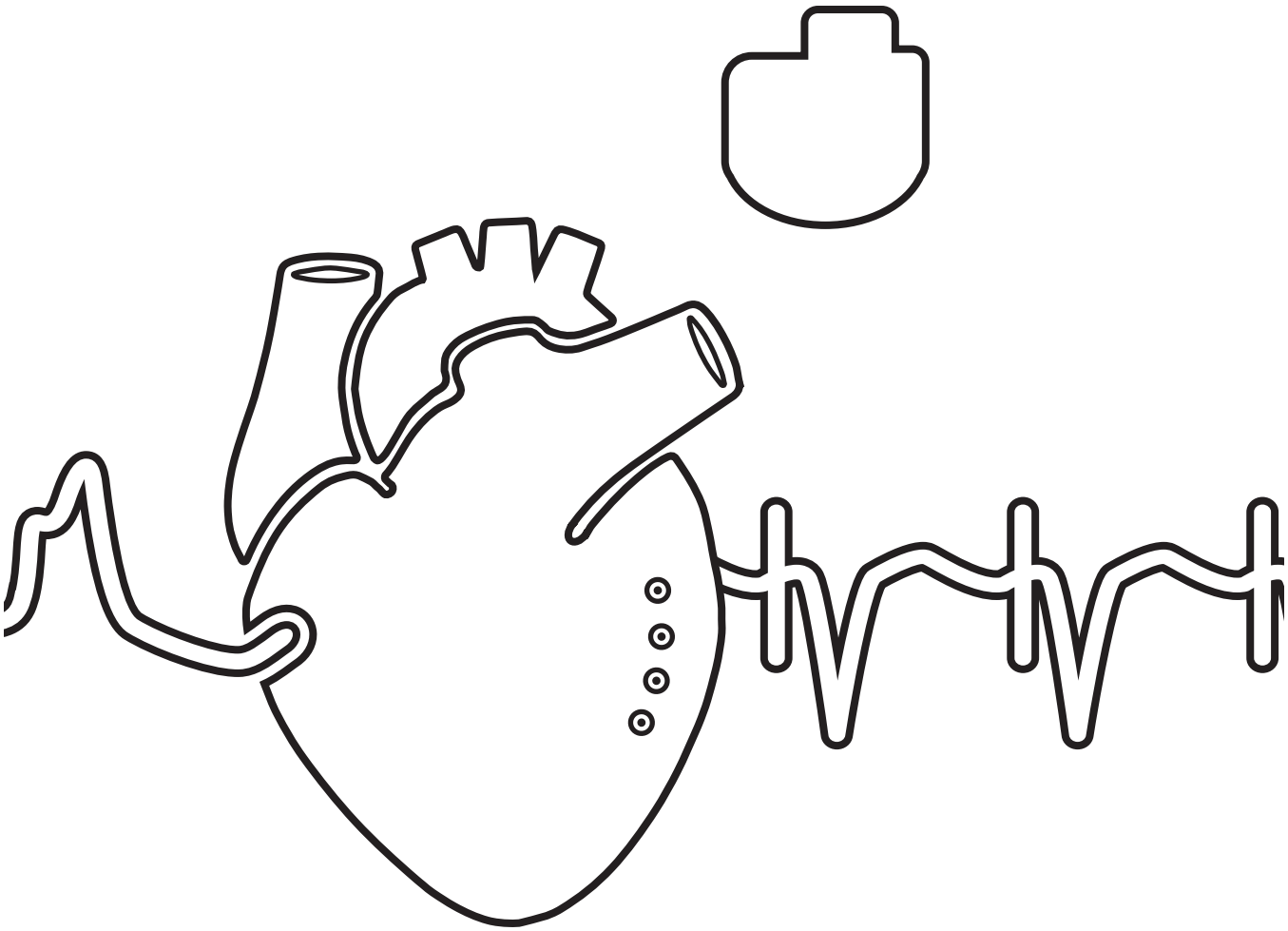
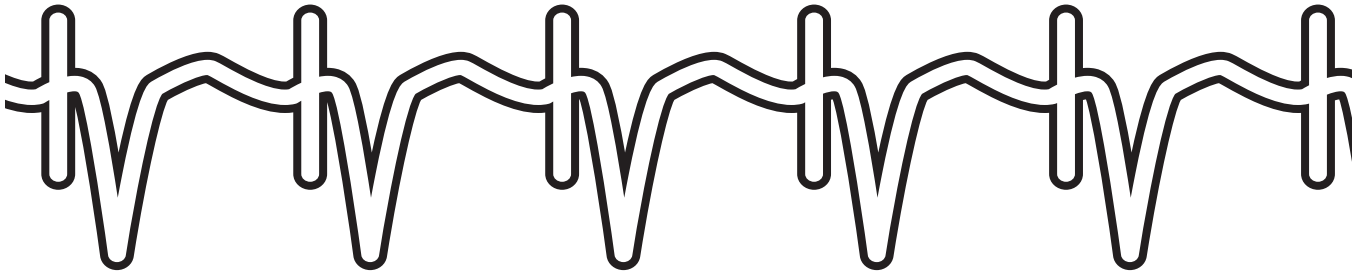


Chapter 9

General discussion and future prospectives



In this thesis, several refined strategies are proposed to better diagnose and treat patients with cardiac resynchronization therapy (CRT). Roughly these can be divided into strategies to improve patient selection, improve CRT delivery, and to optimize CRT configurations. From the first trials of CRT some twenty years ago, researchers hypothesized that patients with severe heart failure in sinus rhythm with a markedly reduced left ventricular (LV) ejection fraction and a prolonged QRS duration might benefit from CRT.[1,2] In principle and on average, these investigators were right, but a considerable number of patients (~30-40%) showed disappointing results. The determination to increase CRT response rates has led to refinements in the technology and in patient selection. Nowadays, CRT is more precise and personalized, taking advantage of the latest developments in device technologies, cardiac imaging, and electrophysiology. With all the progress made over the past years, tailor-made personalized medicine is the next step for CRT. Still, there are many challenges to overcome. Some of these issues are discussed below.

THE PATHOPHYSIOLOGY OF CRT RESPONSE

The assumed substrate for CRT is the existence of intrinsic left ventricular electrical dyssynchrony, in which the interplay between early septal contraction and delayed lateral wall activation results in myocardial stretching of the opposing wall during systole.[3,4]This paradoxical systolic LV stretching makes no contribution to LV ejection and, hence, causes a waste of energy during systole.[5,6] Biventricular pacing administered by a CRT device may convert systolic stretching into shortening and, hence, reduce myocardial wasted work. Still, (bi)ventricular pacing -by itself- induces a stage of dyssynchronous electrical activation, especially at the level of the LV.[7] Conventional biventricular pacing can, therefore, only be of benefit to patients with sufficient baseline electrical dyssynchrony. In patients with little or no electrical dyssynchrony, biventricular pacing may cause iatrogenic electrical dyssynchrony which will subsequently lead to worsening of cardiac function and will have a deleterious effect on patient outcomes. Accordingly, being able to distinguish between patients that may or may not benefit from CRT currently depends on establishing the existence of sufficient baseline dyssynchrony, for which several methods may be used. Yet, like many other treatments for heart failure, a single mode of action for CRT seems unlikely and, therefore, it would be surprising if any single measurement predicted CRT-response very accurately.

CHALLENGES IN PATIENT SELECTION

Novel treatment options are usually tested on broad populations and in daily clinical practice they are prescribed in patients using statistical averages. This is also the case for CRT, since guideline selection criteria favor LBBB patients, in whom statistically the best response to CRT is obtained.[8,9] Yet, other factors are known to impact response to CRT which are not incorporated by guideline recommendations, such as, sex and the cause of heart failure (e.g. ischemic).[10–12] Remarkable is the paradox that women are more responsive to CRT (double the effect size compared to men) but less likely to receive it (only 30% of CRT devices are implanted in women).[13] Of special interest is that women display response to CRT at shorter QRS duration than men do.[14] Because current CRT guideline recommendations are based on clinical trials which included approximately 75% men, they are biased to reflect CRT outcomes in men.[13,15] Consequently, the use of a QRS duration threshold of ≥150ms for recommending CRT, although appropriate in men, may deny a potentially very beneficial therapy to many women with a QRSd of <150ms, but likely to benefit from CRT. This has raised discussion for the introduction of more lenient QRS duration selection criteria in women (shorter QRS duration).[14,15] To enhance our understanding of the better CRT outcomes in women, in **chapter 4** we investigated sex-specific differences in the underlying electrical substrate responsive to CRT. In this chapter, we provide data to support the notion that female CRT recipients -despite an overall shorter QRS duration- experience greater LV dyssynchrony compared to their male counterparts, which contributes in part to their greater volumetric response to CRT. Whether the greater dyssynchrony in women is the result of current guideline-based selection criteria and whether sex-specific modifications to current guideline recommendations should be incorporated, is of interest for future research.

Another concern in modern-day patient selection are the shortcomings of using the 12-lead ECG for the assessment of a sufficiently large electrical substrate amenable to CRT. Although the definition of LBBB has evolved markedly since its' discovery in 1909, there are still substantial limitations of which operator-dependence (1:5 ECG classified differently by different observers) and the existence of multiple criteria to define LBBB are probably the most important.[16,17] As a consequence, a considerable part of patients will be classified differently, depending on the observer and LBBB criteria used. This severely impacts patient selection. In **chapter 2** we aimed to create awareness among cardiologists for the aforementioned shortcomings. Today, this is especially relevant, given that CRT is becoming increasingly controversial in patients without a typical LBBB. To improve CRT patient selection, physicians should be encouraged to look further than QRS duration and morphology on the ECG. Several tools that could be helpful for patient selection are proposed in **chapter 2 and 3**. In these chapters, we provide the current evidence of how more sophisticated markers of echocardiographic discoordination -taking

into account the underlying electrical substrate responsive to CRT- and parameters derived with vectorcardiography may aid in the selection of patients who may benefit from CRT. Although both strategies are very promising, they are yet to be validated in large prospective clinical trials.

The role of echocardiography for refining patient selection

The discovery that mechanical resynchronization paralleled with benefit from CRT formed the basis for using markers of mechanical dyssynchrony for patient selection.[18] However, after the disappointing results of the EchoCRT and the Predictors of Response to CRT (PROSPECT) trial, many cardiologists abandoned the use of echocardiographic measures of dyssynchrony for patient selection.[19,20] Computer models (such as CircAdapt: www.circapapt.org) have, however, in the meantime provided us with a deeper understanding of how different myocardial substrates exist in patients with heart failure that all may lead to some degree of LV mechanical dyssynchrony.[4,21,22] In essence, these computer simulations differentiated patterns of LV *mechanical discoordination* (caused by electromechanical substrates and responsive to CRT) from patterns of *timing-based mechanical dyssynchrony* (related to regional hypocontractility or scar and unresponsive to CRT). By assessing mechanical discoordination, rather than mechanical dyssynchrony, potential CRT responders may, thus, be identified.[21,23] Strain patterns of mechanical discoordination are meant to quantify opposing wall motions within the LV. Systolic stretching the myocardium does not contribute to LV ejection and, therefore, represents a waste of energy (wasted work) which can be recruited by a CRT device by converting systolic stretching into shortening.[3,5,6] Because the septum is positioned between the two ventricles it is particularly susceptible to discoordination and wasted work caused by an LBBB.[3,24,25]Therefore, in **chapter 3** we used the systolic rebound stretch of the septum (SRSsept) for quantification of mechanical discoordination and the prediction of volumetric CRT response. Interesting and important is that SRSsept is assumed not only to be affected by electrical dyssynchrony (increasing SRSsept) but also by myocardial stiffness and scarring (reducing SRSsept), given that early septal shortening happens in viable, early activated septal segments and rebound stretch is affected by the contractility of the late activated lateral wall.[24] This likely explains why in **chapter 3** we found that -the more complex to acquire- SRSsept held additional predictive power over ECG-based patient selection and over the -more simple- visual assessment of mechanical dyssynchrony (by apical rocking). An advantage of using SRSsept, rather than total LV systolic stretching, for mechanical discoordination assessment is that acquiring high-quality images of the septum is comparatively easier to high-quality image acquisition of the LV lateral wall. In addition, in **chapter 3** we displayed that the association between SRSsept and volumetric CRT response was strongest for SRSsept derived from a focused septal single wall image, suggesting that high quality focused

images of the septum may especially be suited for improvement of echocardiography-based patient selection. Unfortunately, STE has shortcomings that should be overcome before STE-derived markers can get implemented in international guideline recommendations. Besides being dependent on image quality, an important limitation of STE is that the strain amplitude identified is dependent on the specific echocardiographic view chosen, and the imaging system/vendor used.[26,27] Furthermore, STE software is constantly under development, and new versions may lead to different strain values. Strain-based cut-offs identified in previous studies -like our own- therefore currently cannot be transferred 1:1 to daily clinical practice. Accordingly, strain-based CRT patient selection is still challenging.Only after validation and standardization of the technique in large patient studies, we can expect mechanical discoordination parameters to make an impact on CRT patient selection.

CHALLENGES IN DEVICE IMPLANTATION

The effectiveness of CRT is, not only, influenced by the underlying electromechanical substrate at baseline, but also, by the position of the LV lead. Yet, there is compelling inter-patient variation as to the optimal LV lead position. Given this inter-patient variation, it is unlikely that a single, empirical location for LV lead placement will adequately resynchronize all patients with an indication for CRT. Tailored LV lead delivery, guided towards a pre-procedurally defined patient-specific 'optimal LV lead position', therefore, is a promising strategy for improving CRT implantation. In this respect, **chapters 5 and 6** of this thesis explore how pre-implantation derived information from more sophisticated cardiac imaging modalities (e.g. CMR and computed tomography) may be used to identify the optimal LV lead position and guide LV lead delivery in the individual patient. For this, we used the CARTBox software toolbox (CART-Tech B.V. The Netherlands). With this toolbox, pre-procedurally defined 'optimal pacing sites' can be visualized intra-procedurally by merging of cardiac imaging datasets (e.g. CMR) with live fluoroscopy. This allows users to directly interact with more sophisticated imaging data during the CRT implantation procedure. In **chapter 6** we demonstrate the feasibility of this toolbox to guide LV lead placement 1) away from the left phrenic nerve (identified with computed tomography) and scarred myocardium, and 2) towards the area of latest mechanical activation (the latter two identified with CMR). Myocardial scar is not excitable and there is an abundance of evidence showing that myocardial scar in the proximity of the LV lead results in a suboptimal response to CRT in terms of both pump failure and sudden cardiac death.[28–30] Late gadolinium enhancement CMR imaging is considered the gold standard to identify LV scar tissue. Accordingly, fusing of CMR data with live fluoroscopy to avoid pacing in myocardial scar is a rational approach for improving CRT delivery, and is likely

to enhance patient outcomes. Yet, the concept that the latest activated region should be targeted is debated. Furthermore, no method is universally advised for the identification of the LV region of latest activation.

Should we aim LV lead delivery towards the latest site of activation?

Given the abundance of studies identifying electromechanical dyssynchrony as the substrate for CRT, one would imagine an abundance of studies with evidence advocating the targeting of the part of the LV myocardium that displays the most electromechanical delay. There are in fact only a few. The TARGET and STARTER trial, both randomized controlled trials, showed similar results, indicating that image-guided LV lead delivery towards the area of latest mechanical activation (timing based time-to-peak delay) probably is a reasonable strategy.[31,32] However, it should be born in mind that both trials excluded areas of scar as LV target on the basis of wall thickness and/or low amplitude strain curves. Therefore, it is possible that their findings are at least partially attributed to the avoidance of scar and not to the targeting of the latest mechanical contraction. As a consequence, it remains uncertain whether the site of latest activation should indeed be targeted for achieving the best CRT repsonse.[33] Another challenge in the identification of the 'region of latest activation' is that there is, as yet, no agreement on whether it is electrical or mechanical delay that should be targeted for acquiring the most optimal response to CRT. Zanon et al. found a strong correlation between the LV electric delay (Q-LV interval: the interval from the onset of the intrinsic QRS on the surface ECG to the first large peak of the LV electrogram) and acute hemodynamic improvement by biventricular pacing ($dPdt_{max}$).[34] Still, these results may be primarily driven by the shorter QLV values (<95ms) included in the analysis, which are below the cut-off value for CRT response defined by Gold et al.[35] In previous work from our group, van Everdingen et al. showed that pacing from the LV lead electrode with the largest QLV value did not always produce the highest hemodynamic improvement (as measured by stroke work).[36] The question whether it is electrical or mechanical dyssynchrony that should be targeted is especially relevant because important disparities exist between electrical and mechanical dyssynchrony.[37] The physiology behind these disparities is complex but, in essence, encompasses that electrical dyssynchrony can induce a variable degree of mechanical dyssynchrony due to differences in LV wall stress, workload and contractility.[37] Consequently, further research is required to determine whether we should aim for the area of latest activation, how we should identify this area, and before real-time guided LV lead implantation towards the region of latest LV activation may be implemented in daily clinical practice.

CHALLENGES IN OPTIMIZING DEVICE CONFIGURATIONS

After LV lead placement, multiple device settings are programmable to increase the effect of CRT. These include individualized programming of the atrioventricular (AV) and interventricular (VV) delay, selection of the most beneficial LV pacing electrode, or stimulation of the LV by multiple electrodes (multipoint pacing [MPP]). Several optimization strategies are presently available to determine the optimal pacing setting, of which some are automated (e.g. QuickOpt [St. Jude Medical], SmartDelay [Boston Scientific], and Adaptive-CRT [Medtronic]).[38] Other non-automated optimization strategies include electrical methods (determining longest QLV interval, achieve largest decrease in paced QRS duration or paced QRS area) or echocardiographic methods (e.g. largest velocity-time integral through the LV outflow tract or maximal separation of A and E wave in mitral inflow patterns).[39–41] Yet, convincing large scale scientific evidence for these methods is still lacking. A valid approach to assess the acute hemodynamic effect of multiple pacing configurations directly after CRT implantation is invasive hemodynamic testing using a pressure-volume-loop conductance catheter. Because a standardized approach for invasive hemodynamic optimization is lacking, and because previous work suggested that changes in dP/dt_{max} and stroke work (SW) are often poorly correlated,[42] we tested both parameters for hemodynamic optimizing of device configurations in **chapter 7**. An important finding from this chapter is that each optimization strategy resulted in approximately 1/3 additional hemodynamic improvement of the parameter used for optimization. However, improvement in one parameter did not coincide with the other. Moreover, similar to previous studies, we expose that dP/dt_{max} changes were unrelated to reverse remodeling after CRT.[43,44] Acute changes in SW, on the other hand, accurately predicted long-term CRT response.

Subsequently, in **chapter 8**, we use invasive SW measurements to assess the effect of multipoint pacing (MPP) over conventional biventricular pacing. Like in previous work, we found that especially male patients, those with an ischemic cardiomyopathy, and those with low LV ejection fraction respond more favorably from MPP.[45] Yet, compared to other MPP studies, in our study, the overall effect of MPP over biventricular was relatively small.[42,46] This may be caused by a relatively high acute hemodynamic effect of biventricular pacing in our study participants given that we included only patients with strict LBBB, identified the optimal pacing electrode for conventional biventricular pacing, and optimized the AV delay for each pacing electrode (rather than comparing MPP with conventional biventricular pacing at the distal LV pacing electrode at a fixed AV delay). Previously, it has been demonstrated that MPP does not provide incremental hemodynamic benefit over biventricular pacing in patients already displaying acute hemodynamic response to CRT.[47] Similar to our findings are the data of the iSPOT study, which showed limited improvement in LV contractility with MPP over biventricular pacing at optimized AV delays in

patients with an LBBB.[48] These results should encourage clinicians to be reserved concerning the implementation of MPP in patients with a strict LBBB, who are already likely to become CRT responders. This is important, especially because MPP increases battery drainage and reduces device longevity. It will, however, be of particular interest to investigate the effect of MPP in patients without typical LBBB. These patients more frequently have myocardial scarring and display a larger heterogeneity in electrical conduction patterns. In these patients, MPP may lead to a more homogeneous electromechanical activation of the LV, and hence greater benefit over conventional biventricular pacing.[47] Invasive testing with MPP in non-LBBB patients is of interest for future research, given that positive effects of MPP may increase the number of CRTs being implanted in this subgroup. However, there are still challenges to overcome because there is, as yet, no agreement on the optimal setting of sequence and delays in MPP. This is likely the result of the relatively short clinical experience with MPP-capable devices and the high number of settings available. Consequently, some clinicians might prefer a 'wait and see' approach activating the MPP only in non-responders to conventional CRT rather than turning it on directly after CRT implantation. This strategy has recently been investigated by the randomized controlled MORE-CRT trial. However, the preliminary results (presented in a late-breaking clinical trial session at the EHRA 2018 congress) displayed that in these patients MPP did not result in a significant improvement in echocardiographic CRT response.

FUTURE PROSPECTIVES

CRT has been one of the biggest innovations for heart failure management of the last decades and has the potential to expand its impact in the coming years by refinements in technology and personalized medicine. The field of medicine is moving fast, from treating patient groups based on statistical averages, towards a more p*ersonalized medicine. Personalized medicine* has the potential to tailor therapy with the best response and highest safety margin to ensure the best possible patient care. A promising example of the implementation of personized medicine in CRT is the employment of multi-modality imaging to guide LV lead delivery in real-time towards pre-procedurally defined LV lead target areas, as discussed in the second part of this thesis. In cardiology, image-guided interventions have been applied for decades, starting with X-ray fluoroscopy to guide catheter placements in angiography. Recently, more sophisticated imaging modalities have migrated out of their traditional roles and into the operation room (e.g. the fusion of MRI with live X-ray or interventional MRI).[49] These technical advancements enable physicians to directly interact with images during procedures. Although there are still important challenges to overcome, real-time image-guidance might be a promising tool for the improvement of CRT delivery, especially owing to the ability to avoid pacing in scarred myocardium.[49–51]

The possibility to better tailor and refine CRT has emerged from an improved understanding of dyssynchronous heart failure and the way CRT works. Since the early 1990s, experimental and clinical research using electrical mapping and deformation imaging have enhanced our insights into the electromechanical consequences of conduction disturbances and biventricular pacing.[52–55] More recently, computer modeling has provided us with a better understanding of the mechanistic aspects of dyssynchrony and the electromechanical substrate which is amenable by CRT.[4,21,56] In this respect new predictors of response (e.g. echocardiographic discoordination) have emerged, which are to be validated in the coming years by prospective clinical trials.[24,57] Computer modeling is becoming increasingly popular in scientific research since it can help to provide a better understanding of disease mechanisms and treatment options. Interesting and important is that such computer models may not only be used to achieve an improved understanding of the mechanical consequences of dyssynchrony and CRT, but that they also should be able to provide predictions on the best way to apply CRT in the individual patient. Ultimately, the goal will be to create patient-specific models that can support clinical decision-making preprocedurally.[56] In this way, we may be able to accurately predict the effect of CRT for the individual patient. This would not only include whether a patient would respond positively to the therapy, but also planning of different pacing configurations and various LV lead locations.[56] In this respect, tech-companies are already working on a so-called 'digital twin' that can be used for real-life simulations and to tailor therapy to each patient specific needs.

Yet, as discussed previously, it is imperative to keep in mind that (epicardial) biventricular, by itself, induces a stage of electrical dyssynchrony as well as abnormal repolarization. As a consequence, the currently most common mode of CRT is imperfect.[7] Another limitation of contemporary CRT devices, is that it is not always feasible to place the LV lead at the preferred site for LV stimulation due to restrictions of the epicardial coronary venous system. Alternative pacing approaches that overcome these challenges may significantly impact the treatment of dyssynchronous heart failure in the coming years. These alternative pacing approaches include i) biventricular stimulation by endocardial LV pacing, ii) His bundle pacing, iii) left bundle branch (LBB) area pacing and iv) LV septal pacing.[58–62] These pacing strategies often provide a more physiologic depolarization of the ventricles, which in the healthy heart extends from the His bundle through the bundle branches, via the Purkinje fibers to the myocardium, and from the endocardium to the epicardium. Accordingly, these new alternatives to conventional CRT, induce less dyssynchrony and, hence, may yield a better response and higher safety margin for patients with dyssynchronous heart failure. Important in this respect is the recent discovery that approximately two-thirds of patients with an LBBB, have a conduction block at the level of the left-sided His fibers (left intrahesian block), which is located proximal to the left bundle branch.[63]

His bundle pacing and LBB area pacing may, as a consequence, engage the native His-Purkinje system and, hence, maintain physiological electromechanical synchrony. Importantly, these new pacing approaches may even extend pacing therapy to heart failure patients with narrow QRS and PR prolongation by providing AV synchrony without inducing ventricular dyssynchrony and associated pacing-induced cardiomypathy.[64] Due to the limited published data available for these strategies and scarce long-term follow-up data, further research is required before these strategies can become implemented into daily clinical practice. Still, these innovations of novel pacing approaches combined with advanced imaging technologies and computer modeling may eventually offer a refined CRT system uniquely tailored to each patient's needs.

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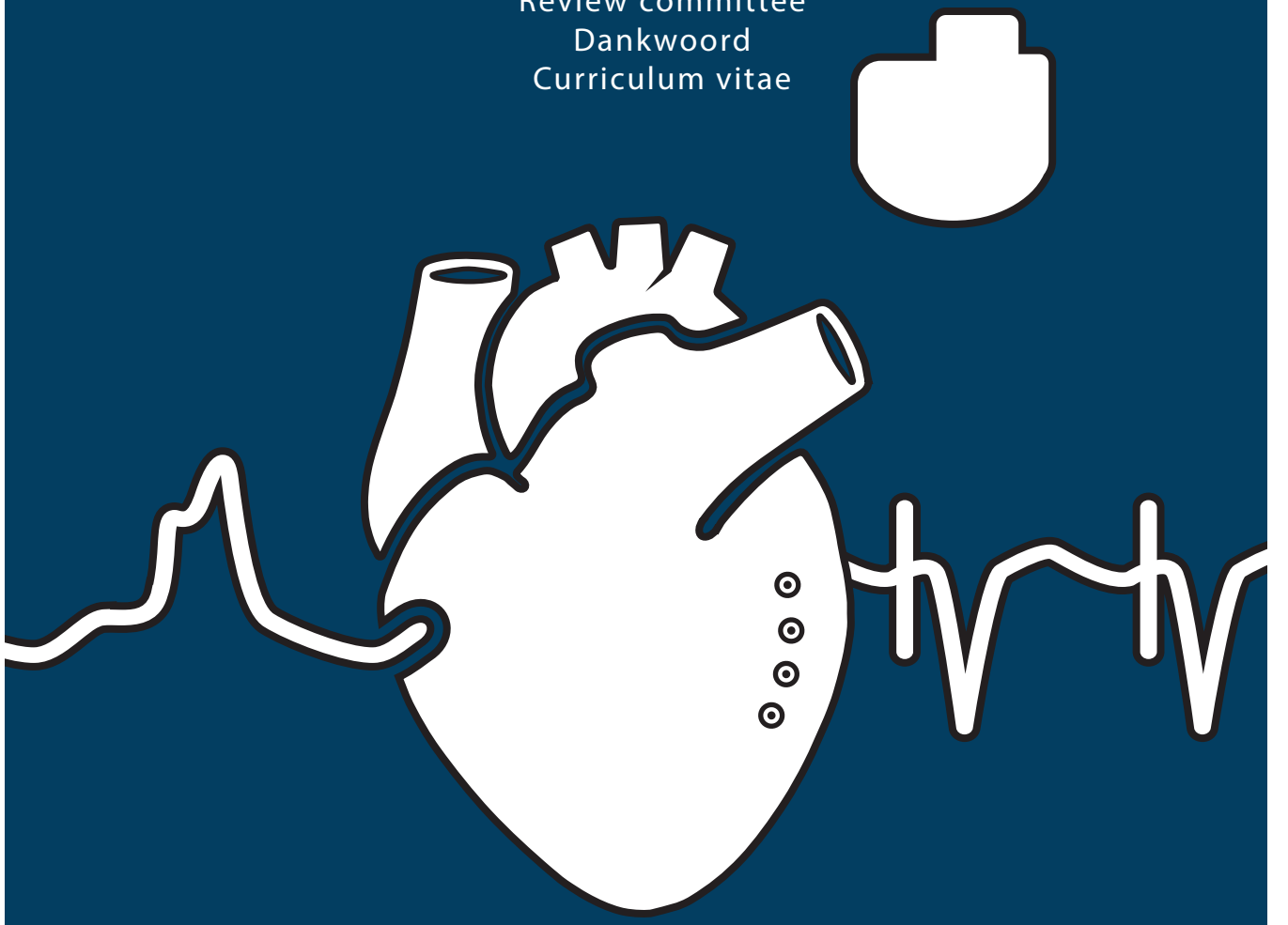
Appendix

Nederlandse samenvatting
List of publications
Review committee
Dankwoord
Curriculum vitae



NEDERLANDSE SAMENVATTING

In dit proefschrift worden verschillende strategieën besproken voor het verbeteren en verfijnen van de behandeling van patiënten met hartfalen door middel van cardiale resynchronisatie therapie. Van hartfalen is sprake wanneer de structuur en pompfunctie van het hart zijn aangetast. Patiënten met hartfalen hebben een sterk verminderde levensverwachting met slechts 50% overleving 5 jaar na het stellen van de diagnose en 10% overleving na 10 jaar. In Nederland komt hartfalen voor bij ongeveer 2-4% van de volwassen populatie, en bij 6-10% van de bevolking ouder dan 65 jaar. Bij een aanzienlijk deel van de patiënten met hartfalen is er een stoornis in de elektrische aansturing van het hart aanwezig. Zo'n elektrische stoornis kan veroorzaakt worden door hartfalen maar kan zelf ook aanleiding geven tot hartfalen. Een veel voorkomende stoornis in de elektrische geleiding van het hart is het linker bundel tak blok (LBTB). Bij een linker bundeltak blok is er een vertraging van het elektrische signaal naar de linker hartkamer. Het elektrisch signaal naar de rechterkamer is daarentegen normaal. Dit resulteert in een normale samentrekking van de rechterkamer, terwijl de samentrekking van de linkerkamer vertraagd is. Hierdoor ontstaat een niet harmonieuze samentrekking tussen de rechter- en linkerkamer, tussen de boezems en de kamers en van de linkerkamer zelf. Dit wordt asynchronie of dyssynchronie genoemd en leidt op den duur tot een verminderde pompfunctie van het hart, meer ziektelast en grotere sterfte onder patiënten met hartfalen.

Asynchronie van het hart (cardiale asynchronie) kan behandeld worden met cardiale *resynchronisatie* therapie (CRT). CRT is een geavanceerde pacemaker behandeling waarbij een speciale pacemaker met drie pacemaker draden (leads) wordt verbonden met het hart. Een lead wordt in de rechterboezem geplaatst, een lead in de rechterkamer, en een lead op de vrije wand van de linkerkamer. Door middel van deze drie draden kunnen de linker en rechter kamers tegelijkertijd (of vlak na elkaar) worden gestimuleerd met elektrische pulsen. Op deze manier kan asynchronie tussen de hartkamers worden verminderd en kan de harmonieuze samenwerking tussen de verschillende hartkamers worden hersteld. Dit leidt tot een verbetering van pompfunctie en zorgt ervoor dat de negatieve effecten (deels) worden doorbroken of teruggedraaid (zogenaamde reverse remodeling). Hierdoor nemen symptomen van hartfalen af, daalt het aantal ziekenhuisopnames en verbetert de overleving van patiënten met dyssynchroon hartfalen. Met de introductie van CRT, ruim 20 jaar geleden, hebben patiënten met mild-ernstig hartfalen een goede kans gekregen op significante verbetering van hun levenskwaliteit en prognose. CRT heeft daarmee een revolutie veroorzaakt in de behandeling van patiënten met hartfalen, wiens enige andere optie een harttransplantatie of steunhart was. Helaas heeft ongeveer 30-40% van de patiënten die behandeld worden met CRT onvoldoende effect van de behandeling (de

zogenaamde non-responders). De vastberadenheid om het aantal non-responders op de therapie te verminderen is de inspiratie van al het onderzoek dat wereldwijd wordt verricht naar het verfijnen en verbeteren van de techniek achter de therapie en het selecteren van de juiste patiënten voor de behandeling. Grofweg kunnen er drie verschillende strategieën worden gehanteerd om de kans op respons na CRT te verbeteren, dit zijn i) verbeteren van patiënt selectie, ii) verbeteren van de plaatsing van het CRT apparaat en iii) het verbeteren van de instellingen (configuraties) van het CRT apparaat. In de drie delen van dit proefschrift worden deze strategieën verder besproken.

DEEL 1 VERBETEREN VAN PATIËNT SELECTIE

Patiënten die voor CRT in aanmerking komen worden gescreend op de aanwezigheid van dyssynchronie. Uit grootschalig onderzoek naar de effecten van CRT is gebleken dat patiënten met meer elektrische dyssynchronie op het hartfilmpje (ook wel het electrocardiogram: ECG) de grootste kans hebben om gunstig te reageren op CRT. In de huidige internationale cardiologische richtlijnen worden daarom voornamelijk elektrische parameters gebruikt afkomstig van het ECG (zoals QRS duur en aanwezigheid van een LBTB) voor het stellen van de indicatie voor CRT. Echter er zijn belangrijke tekortkomingen aan deze manier van indicatiestelling, welke in de dagelijkse praktijk leiden tot een suboptimale selectie van patiënten. Het eerste deel van dit proefschrift onderzoekt hoe de patiëntselectie voor CRT verbeterd kan worden. In **hoofdstuk 2** bediscussiëren we de tekortkomingen van de huidige manier van patiënt selectie en onderzoeken we, aan de hand van een uiteenzetting van bestaande literatuur, hoe meer geavanceerde maten van dyssynchronie kunnen worden gebruikt om de selectie van patiënten voor CRT te verbeteren. Daarbij ligt het focus op patiënten met op het ECG een niet typisch LBTB. Deze patiënten hebben een kleinere kans om gunstig te reageren op CRT, daarom is in de dagelijkse praktijk het stellen van de indicatie voor CRT juist in deze patiëntengroep bijzonder lastig. Een belangrijke bevinding uit hoofdstuk 2 is dat enkele mechanische en vectorcardiografische dyssynchronie parameters veelbelovend zijn om die patiënten te selecteren die ondanks een niet LBTB op het ECG wel baat hebben van de behandeling met CRT.

Mechanische dyssynchronie kan geëvalueerd worden met medische beeldvormende technieken zoals echocardiografie en magnetic resonance imaging (MRI). De mate van mechanische dyssynchrony kan op een hartecho in detail worden gekwantificeerd met een speciale software techniek, genaamd speckle tracking echocardiografie. Met speckle tracking kan de beweging van het hartweefsel nauwkeurig gevolgd worden gedurende de hartslag. De hoeveelheid

dyssynchronie per hartregio (uitgedrukt in percentages) kan zo in detail worden gemeten. Met name de hoeveelheid dyssynchronie van het interventriculaire septum (wand tussen de linker en rechter hartkamer) lijkt geassocieerd met de kans op herstel van pompfunctie na CRT. Dyssynchronie van het septum wordt daarbij gedefinieerd als paradoxiale stretch beweging van het interventriculaire septum tijdens de systole (passief oprekken van het septum tijdens de actieve samentrekkingsfase 'systole' van het hart). De hoeveelheid paradoxiale strech van het septum kan worden gebruikt als maat voor de te corrigeren afwijking: namelijk de hoeveelheid potentieel om te zetten passieve stretch naar actieve samentrekking (*Figuur 1, pagina 13*). In **hoofdstuk 3** gebruiken we een recent opgestelde database van 241 prospectief geïncludeerde patiënten behandeld met CRT uit zeven Nederlandse ziekenhuizen om de meerwaarde van mechanische dyssynchronie voor CRT patiëntselectie te onderzoeken. Daarmee laten we voor het eerst in multicenter verband zien dat patiënten met een hoge mate van paradoxiale stretch van het septum (*systolic rebound stretch of the septum*) een grotere kans hebben op baat van de behandeling met CRT. De resultaten van dit onderzoek impliceren daarmee dat de indicatiestelling voor CRT verbeterd kan worden door het toevoegen van mechanische dyssynchronie parameters aan de elektrische dyssynchronie parameters gebruikt in de huidige internationale richtlijn criteria.

Vectorcardiografie is een veelbelovende geavanceerde manier om elektrische dyssynchronie te kwantificeren. In tegenstelling tot het ECG, welk tweedimensionale informatie bevat, geeft vectorcardiografie driedimensionale informatie over de elektrische impulsgeleiding van het hart (*Figuur 2, pagina 14*). In **hoofdstuk 4** gebruiken we vectorcardiografie om geslachtsspeficieke verschillen te onderzoeken in de mate van elektrische dyssynchronie voorafgaand aan CRT. Hiervoor gebruiken we een grote database van patiënten die geïmplanteerd zijn met een CRT in drie Nederlandse academische centra (Utrecht, Maastricht, Groningen). Hoewel vrouwen meer baat hebben van CRT dan mannen wordt slecht een-derde deel van de CRT-apparaten geïmplanteerd in vrouwen. Deze tegenstrijdigheid is verontrustend omdat vrouwen mogelijk onderbehandeld worden. Om de behandeling van CRT in vrouwen te verbeteren is het belangrijk om meer inzicht te krijgen in mogelijke oorzaken van de betere uitkomsten in vrouwen na CRT. Een belangrijke bevinding uit ons onderzoek is dat een deel van de betere CRT uitkomsten in vrouwen verklaard kan worden doordat zij een gunstiger onderliggend elektrisch substraat hebben (meer vectorcardiografische dyssynchronie in kleinere harten). Met deze bevinding is een mogelijke eerste stap gezet in de richting van geslachtsspecifieke selectie criteria voor CRT.

DEEL 2 VERBETEREN VAN DE PLAATSING VAN HET CRT APPARAAT

Na het selecteren van de juiste patiënt voor CRT, is de volgende stap het verbeteren van de plaatsing van het CRT-apparaat op de voor de patiënt zo gunstig mogelijk plek in het hart. Uit meerdere onderzoeken naar de werking en effectiviteit van CRT is gebleken dat de locatie van de linkerkamer lead belangrijk is. Patiënten bij wie de linkerkamer lead in of dichtbij verlittekend hartweefsel geplaatst is, hebben minder kans op verbetering van pompfunctie en hebben een slechtere ziektevrije overleving na CRT ten opzichte van patiënten in wie de linkerkamer lead geplaatst is in vitaal (niet verlittekend) hartweefsel. Daarnaast hebben patiënten waarschijnlijk meer kans op verbetering van hartfalen en overleving als de linkerkamer lead geplaatst wordt op een locatie waar de samentrekking van het hart voldoende vertraagd is (meer dyssynchroon). Voor plaatsing van een CRT apparaat wordt standaard gebruik gemaakt van doorlichtingsbeelden. Met doorlichting kan de cardioloog met behulp van röntgenstraling zien in welk gebied van het hart (boezem/kamer) of in welk bloedvat hij/zij zich bevindt. Hoewel deze beelden zeer nuttig zijn voor ruimtelijke oriëntatie tijdens de CRT implantatie, bevatten ze geen informatie over het bestaan en de locatie van littekenweefsel in het hart of dyssynchronie. Dit maakt het moeilijk voor cardiologen om de linkerkamer lead op een zo optimaal mogelijke plek te plaatsen. Hoewel littekenweefsel en dyssynchronie niet zichtbaar worden met röntgenstraling, kunnen zij wel in detail worden afgebeeld met MRI scans. In **hoofdstuk 6 en 7** demonstreren we de toepasbaarheid en veiligheid van een nieuwe techniek die het mogelijk maakt om tijdens het plaatsen van de linkerkamer lead, littekenweefsel en dyssynchronie zichtbaar te maken voor de cardioloog. Hiervoor worden MRI beelden en computed tomografie (CT) beelden gefuseerd met doorlichtingsbeelden (*Figuur 3, pagina 15*). Deze techniek wordt voor het eerst toegepast in Nederland, en de eerste resultaten in 15 patiënten laten zien dat de plaatsing van het CRT apparaat en de uitkomsten van patiënten mogelijk verbeterd wordt.

DEEL 3 HET VERBETEREN VAN DE INSTELLINGEN VAN HET CRT APPARAAT

De laatste strategie voor het optimaliseren van patiënt uitkomsten na CRT is het verbeteren van de instellingen van het CRT apparaat. Omdat het CRT apparaat uit drie verschillende pacing leads bestaat zijn er verschillende instellingen te bedenken om het hart elektrisch te prikkelen (stimuleren). Er kan bijvoorbeeld gevarieerd worden in de vertraging van stimulatie (delay) tussen de boezems en de kamers (atrio-ventriculair delay) en tussen de rechter- en linkerkamer (ventriculo-ventriculair delay). Bovendien telt de linkerkamer lead vier elektrodes. Voor linkerkamer

stimulatie kan daarom gekozen worden voor stimulatie met één van deze vier elektrodes (standaard pacing) of door stimulatie met meerdere elektrodes tegelijk (multi-point pacing). Welke instelling de meest gunstige effecten geeft voor de individuele patiënt is echter onbekend. Er zijn verschillende manieren die gehanteerd kunnen worden om de effecten van verschillende CRT instellingen te meten in de individuele patiënt. Een nauwkeurige manier voor het direct meten van de effecten van verschillende instellingen op de pompfunctie van de linkerkamer zijn druk-volume metingen. Bij invasieve druk-volume metingen wordt er via de bloedvaten in de lies een tijdelijke katheter in de linkerkamer geplaatst die continue de pompfunctie van elke hartslag registreert. Met invasieve druk-volume metingen kan zo direct informatie worden verkregen over de hemodynamische effecten van verschillende CRT instellingen (o.a. verbetering van geleverde arbeid van de linkerkamer: 'stroke work' of druk verandering in de linkerkamer: '$dPdt_{max}$')(*Figuur 4, pagina 16*). In **hoofdstuk 7 en 8** staan de resultaten verkregen uit het OPTICARE-QLV onderzoek waarin de hemodynamische effecten van verschillende CRT instellingen zijn gemeten in 51 LBTB patiënten uit drie academische ziekenhuizen (Utrecht, VU Amsterdam, Maastricht). Belangrijke bevindingen uit **hoofdstuk 7** zijn onder andere dat, ten opzichte van conventionele CRT, optimalisatie van CRT instellingen leidde tot circa 33% verbetering van de hemodynamische respons. Daarnaast bleek dat optimalisatie aan de hand van stroke work niet leidde tot dezelfde instellingen vergeleken met optimalisatie aan de hand van $dPdt_{max}$, en was optimalisatie van stroke work beter gecorreleerd met 'reverse remodeling' op zes maanden na CRT dan $dPdt_{max}$ optimalisatie. Hoewel het, vanwege een relatief lange tijdsduur en groter risico op complicaties, niet mogelijk is om invasieve hemodynamische metingen te verrichten in alle patiënten die CRT ondergaan, zijn deze bevindingen voor onderzoeksdoeleinden van groot belang. In **hoofdstuk 8** gebruiken we invasieve druk-volume metingen om de meerwaarde van multipoint pacing (MPP) t.o.v. standaard pacing te onderzoeken. Het gemiddelde effect op groepsniveau van MPP t.o.v. standaard pacing was neutraal. Interessant genoeg hadden sommige patiënten (m.n. mannen, mensen met een ischemische oorzaak van hartfalen en mensen met slechte linkerkamer functie) meer baat van MPP, terwijl anderen meer baat hadden van standaard CRT pacing. Aangezien MPP een negatief effect heeft op de levensduur van de batterij van het CRT-apparaat is het belangrijk dat MPP een bewezen meerwaarde heeft. Aangezien de meerwaarde van MPP t.o.v. standaard CRT pacing niet is aangetoond in patiënten met een typisch LTBT, adviseren we clinici terughoudend zijn met het implementeren van MPP in deze patiëntengroep. Meer onderzoek is daarom nodig om die patiënten te identificeren in wie MPP wel een duidelijk gunstiger effect heeft voordat MPP kan worden toegepast in de dagelijkse praktijk.

CONCLUSIES

In de afgelopen drie jaar heb ik mij toegelegd op verschillende optimalisatie strategieën voor het verbeteren en verfijnen van de behandeling met een CRT. Hoewel ons begrip van hoe CRT werkt en welke patiënten het meeste baat hebben van de behandeling nog lang niet compleet is, is met dit proefschrift is een belangrijke bijdrage geleverd aan hoe de effecten van CRT in de individuele patiënt verbeterd kunnen worden. Daarmee zijn we een stap dichterbij 'therapie op maat' (personalized medicine) gekomen, waarbij het focus ligt op enerzijds het vergroten van de effectiviteit van de behandeling en anderzijds het voorkomen van ongewenste bijwerkingen in de individuele patiënt. Therapie op maat is van groot belang voor zowel het individu als voor de maatschappij en zal bijdragen aan een betere effectiviteit en doelmatigheid van CRT.

LIST OF PUBLICATIONS

Salden OAE, Zweerink A, Wouters P, Allaart CP, Geelhoed B, de Lange FJ, Maass AH, Rienstra M, Vernooy K, Vos MA, Meine M, Prinzen FW, Cramer M. The value of septal rebound stretch analysis for the prediction of volumetric response to cardiac resynchronization therapy. *European Heart Journal : cardiovascular imaging 2020 (in print)*

Salden OAE, *Vernooy K, van Stipdonk AMW, Cramer MJ, Prinzen FW, Meine M. Strategies to Improve Selection of Patients Without Typical Left Bundle Branch Block for Cardiac Resynchronization Therapy. JACC: Clinical Electrophysiology 2020*

Salden OAE*, *Gathier WA*, van Ginkel DJ, van Everdingen WM, Mohamed Hoesein FAA, Cramer M, Doevendans PA, Meine M, Chamuleau SAJ, van Slochteren FJ. Feasibility and potential benefit of pre-procedural CMR imaging in patients with ischaemic cardiomyopathy undergoing cardiac resynchronisation therapy. Netherlands Heart Journal 2020*

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Zweerink A, ***Salden OAE***, van Everdingen WM, de Roest GJ, van de Ven PM, Cramer M, Doevendans PA, van Rossum AC, Vernooy K, Prinzen FW, Meine M, Allaart CP. Hemodynamic Optimization in Cardiac Resynchronization Therapy: Should We Aim For Contractility by dP/dtmax or Left Ventricular Pump Function by Stroke Work? JACC: Clinical Electrophysiology 2019

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Zweerink A, van Everdingen WM, Nijveldt R, **Salden OAE**, Meine M, Maass AH, Vernooy K, de Lange FJ, Vos MA, Croisille P, Clarysse P, Geelhoed B, Rienstra M, van Gelder IC, van Rossum AC, Cramer M, Allaart CP. Strain imaging to predict response to cardiac resynchronization therapy: a systematic comparison of strain parameters using multiple imaging techniques. *ESC Heart Failure 2019*

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Salden OAE, Broekhuizen BDL, Rockmann H, Verheij TJM. Diagnosis of allergy against beta-lactams in primary care: prevalence and diagnostic criteria. *Family practice 2015*

*shared first authorship

MANUSCRIPTS IN PREPARATION

Salden OAE, van Stipdonk AMW, Ruijter HM, Cramer M, Kloosterman M, Rienstra M, Maass AH, Prinzen FW, Vernooy K, Meine M. Sex disparities in electrical dyssynchrony and response to cardiac resynchronization therapy. *Conditionally accepted at JACC: Circulation and arrhythmia*

Ghossein MA, van Stipdonk AMW, Plesinger F, Kloosterman M, Wouters P, **Salden OAE**, Meine M, Maass AH, Prinzen FW, Vernooy K. Change in QRS area after Cardiac Resynchronization Therapy is associated with clinical outcomes and echocardiographic response. *Submitted*

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DANKWOORD

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CURRICULUM VITAE

Odette Agnes Elisabeth Salden was born on the 2nd of March 1990 in Roermond, the Netherlands. She grew up in Deventer where she attended middle school which she completed Cum Laude. She participated in the national youth selection for fencing at the Royal Dutch Fencing Federation at Papendal for a brief period of time but finally decided to focus her time on medical school, for which she moved to Utrecht in 2008. After completion of her medical training in 2014 she decided to first obtain some clinical experience as a doctor (ANIOS) working in the emergency department of the 'St Antonius Hospital' (Nieuwegein), and in the cardiology department of the 'Gelre Hospitals' in Apeldoorn. Here she became fascinated into wonders of the electrocardiogram and decided to pursue a career in cardiology. In 2017, Odette started a PhD program at the cardiology department of the University Medical Center of Utrecht, which was inspired by the enthusiasm and support of her former mentor during medical school: Dr. M.J. Cramer. Under supervision of Prof. P.A.F Doevendans, Prof F.W. Prinzen, Dr M. Meine and Dr M.J. Cramer, Odette studied several strategies to optimize the efficacy of cardiac resynchronization therapy. During these three years as a PhD candidate, she had the opportunity to work with cardiologists, radiologist and researchers from other Dutch academic centers. These multidisciplinary efforts have provided the scientific basis for the work displayed in this thesis. In August 2020 Odette will start her formal Cardiology training at the University Medical Center of Utrecht under supervision of Dr. JF. van der Heijden and Dr. G.T. Sieswerda.