# Prediction of (super) response to cardiac resynchronization therapy

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# Prediction of (super) response to cardiac resynchronization therapy

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# Abbreviations

| | |
|---|---|
| A/AS-posterior delay | difference between time to peak global radial strain of anterior or anteroseptal and posterior segments. |
| AS/MS-BL delay | difference between time to peak global longitudinal strain of apicoseptal or midseptal to basallateral segments. |
| Max delay 4C | maximal difference in time to peak global longitudinal strain between six segments in 4-chamber view. |

| | |
|---|---|
| AS-P delay | anteroseptal-posterior delay |
| ATP | anti-tachy pacing |
| AUC | area under the curve |
| BS-BL delay | basal septal-basal lateral delay |
| BI-BA | basal inferior-basal anterior |
| CRT | cardiac resynchronization therapy |
| CRT-D | cardiac resynchronization therapy with defibrillator |
| HF | heart failure |
| HR | hazard ratio |
| ICD | implantable cardioverter defibrillator |
| IVCD | intra-ventricular conduction delay |
| LBBB | left bundle branch block |
| LS | longitudinal strain |
| LV | left ventricular |
| LVEF | left ventricular ejection fraction |
| LVEDD | left ventricular end-diastolic diameter |
| LVESD | left ventricular end-systolic diameter |
| LVEDV | left ventricular end-diastolic volume |
| LVESV | left ventricular end-systolic volume |
| MACE | major cardiac adverse event |
| PSAX | parasternal short axis view |
| RBBB | right bundle branch block |
| RS | radial strain |
| SPWMD | septal to posterior wall motion delay |

*Voor mijn ouders*

*en*

*mijn vrouw*

CHAPTER 1

# Introduction and Outline of the thesis

## INTRODUCTION

Heart failure is a leading cause of cardiovascular morbidity and mortality worldwide and it is estimated that in developed countries 1–2% of all healthcare expenditure is devoted to heart failure [1]. Chronic heart failure is a condition in which a patient has varying symptoms of heart failure over a period of time [2]. Heart failure with reduced systolic left ventricular ejection fraction (LVEF) is the most common type of heart failure and also the best understood type of heart failure in terms of pathophysiology and treatment.
Approximately 1–2% of the adult population in developed countries has heart failure, with increasing prevalence with age (Figure 1) [3]. The combination of increasing survival after acute myocardial infarction and increased longevity in Western developed nations leads to an increase in the overall prevalence of heart failure.

### Pathophysiologic mechanism and treatment of heart failure

After myocardial injury, the changes in surviving myocytes and extracellular matrix lead to pathological 'remodelling' of the ventricle. Ventricular remodelling leads to dilatation and impaired contractility which results in reduced LVEF [4,5]. Ventricular remodelling and neurohumoral (renin-angiotensin-aldosterone and sympathetic nervous system) activation cause heart failure symptoms and signs, episodes of heart failure hospitalization and premature death. In some patient, the onset of conduction disorder with wide QRS contributes to worsening of ventricular remodelling. Interruption of this neurohumoral pathway is the basis of pharmacological treatment of heart failure [5].

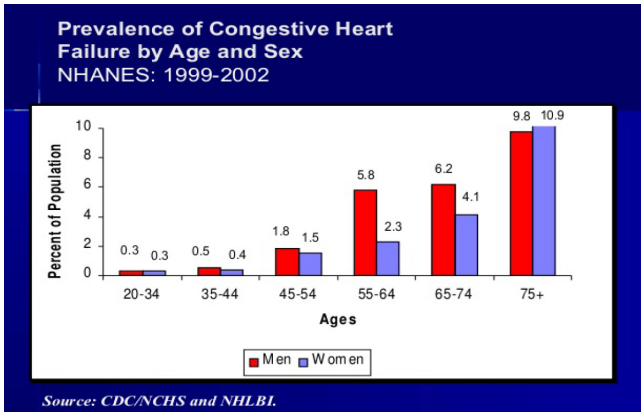


**Figure 1**. Prevalence of heart failure increases with age.

There is a clear relationship between severity of heart failure symptoms and survival. However, also patients with mild symptoms still have a relatively high absolute risk of hospitalization and (sudden) death [5,6]. The most important goals in the treatment of heart failure patients are to relieve the symptoms and signs, prevent hospital admission, and improve survival. There are three groups of medications (ACE inhibitors/AT2 antagonists, beta-blockers and aldosterone antagonists) which block the neurohumoral pathway. All these drugs have significantly improved the survival of patients with heart failure. Although remarkable progresses have been achieved in medical treatment, the mortality rate remains unsatisfactorily high. Besides this pharmacological therapy, an implantable cardioverter defibrillator (ICD) can be added, which is designed to detect and correct high-risk arrhythmias [7–9]. Figure 2 shows the additional effects of medication and ICD on survival.

Almost 50% of the deaths in heart failure patients, especially in those with milder symptoms, occurs suddenly and unexpectedly, and many of those are related to ventricular arrhythmias (Figure 3).

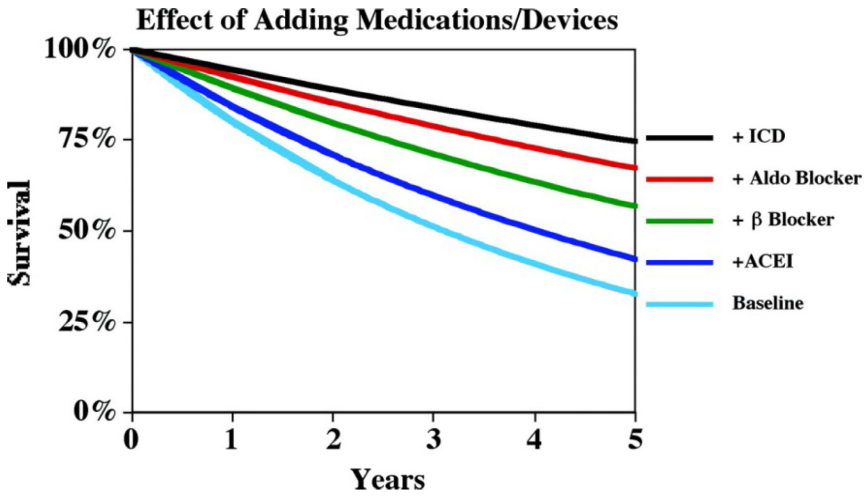


**Figure 2**. The predicted effects on survival of sequentially adding medications and an ICD for a heart failure patient with an annual mortality of 20% and a mean survival of 4.1 years at baseline. Adding an ACE inhibitor (ACEI), a β-blocker, an aldosterone (Aldo) blocker, and an ICD decreases the annual mortality by 70% (20% to 6%) and increases the mean survival by 5.6 years (mean survival 4.1, 5.0, 6.6, 8.2 and 9.7 years, respectively). Circulation 2006;113:1424−1433.

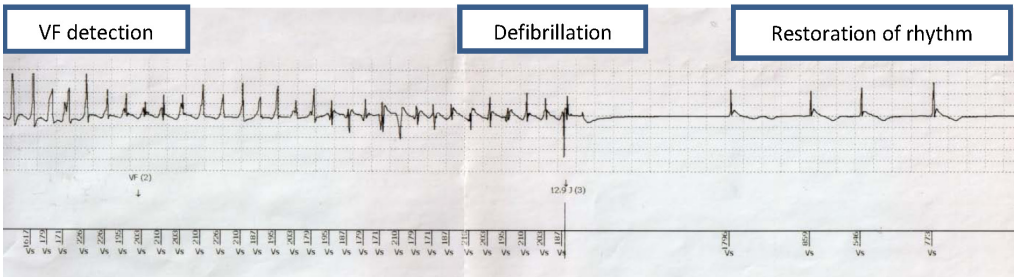


**Figure 3.** One of our patients with heart failure and LVEF 25% developed ventricular arrhythmia with almost 320 bpm and converted to normal rhythm after ICD-shock.

Therefore, prevention of sudden death is an important goal. The role of antiarrhythmic drugs such as amiodarone or sotalol on overall survival was investigated in AVID trial [10] and was inferior to ICD. Two important randomized controlled trials (MADIT II [11] and SCD-HeFT [12]) demonstrated relative risk reduction of ICD of 23–31% in mortality in heart failure patients with LVEF ≤30–35% when added to optimal medical therapy (Figure 4). These two trials changed the treatment of heart failure patients worldwide.

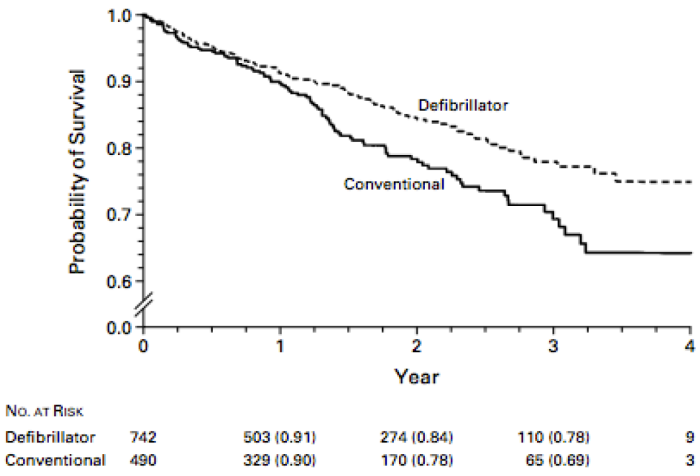


**Figure 4**. Survival curves of patients with or without ICD of the land-mark MADIT 2 trial. The difference in survival between the two groups was significant (p=0.007), the relative risk reduction was 31%.

**Cardiac resynchronization therapy (CRT) in heart failure with intraventricular conduction delay**

Although single-lead shock-only ICD implantation may be very effective in preventing sudden death in heart failure patients with intraventricular conduction delay, it will not improve the symptoms and signs of heart failure.

The primary and immediate aim of CRT (Figure 5) is to reduce the timing differences in electrical and mechanical activation as compared with the situation during the conduction abnormality. Since 2002, it has been demonstrated that CRT improves left ventricular function (reduction of LVESV, Figure 6), NYHA functional class and quality of life [13,14].

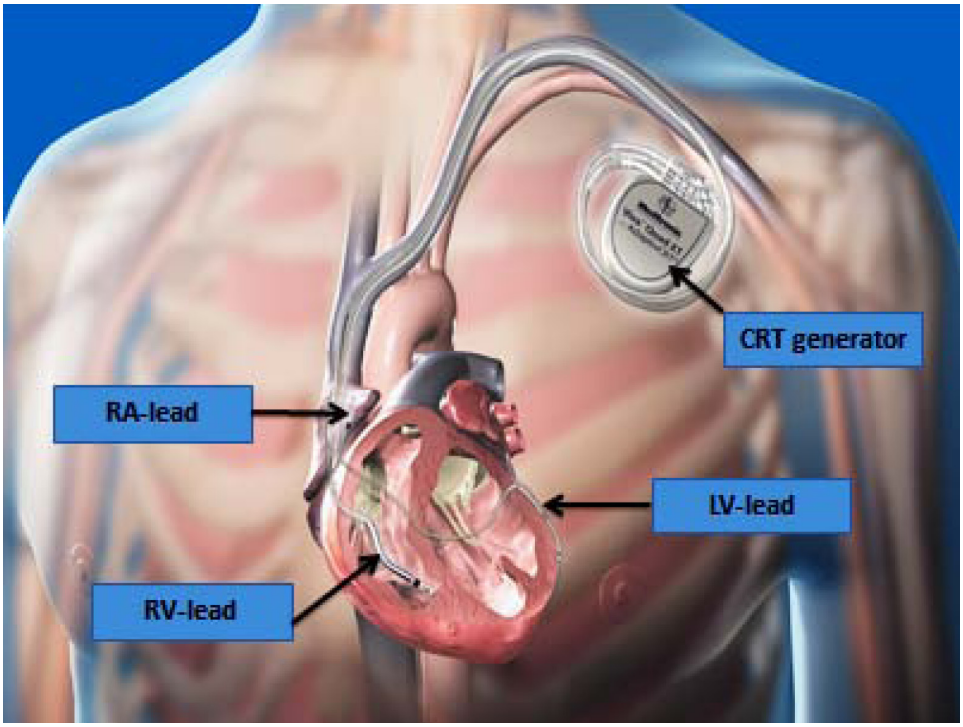


**Figure 5.** CRT-device works by simultaneously pacing both the right and the left ventricle 'bypassing' the intrinsic conduction system.

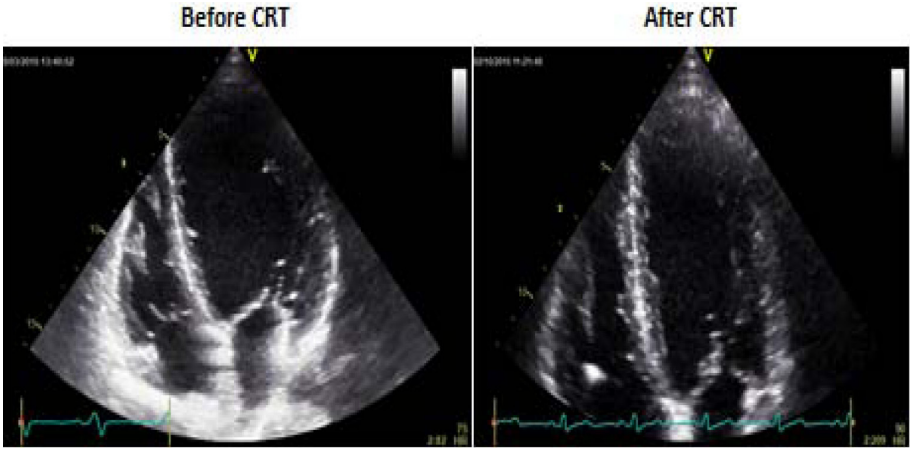


**Figure 6.** Echocardiography of a patient from Zwolle, before CRT implantation and during follow-up, showing reduction of the left ventricular end-systolic diameter.

Although initially CRT was seen as beneficial for the symptoms of heart failure [14,15], more recent trials investigated whether CRT can also improve survival. The Care-HF trial [16] as one of the first trials demonstrated the beneficial impact of cardiac resynchronization therapy with a pacemaker (CRT-P) on all-cause mortality when added to pharmacological therapy (Figure 7). A pooled analysis of five randomized trials with addition of CRT-P to pharmacological therapy showed 24% reduction in all-cause mortality [17].

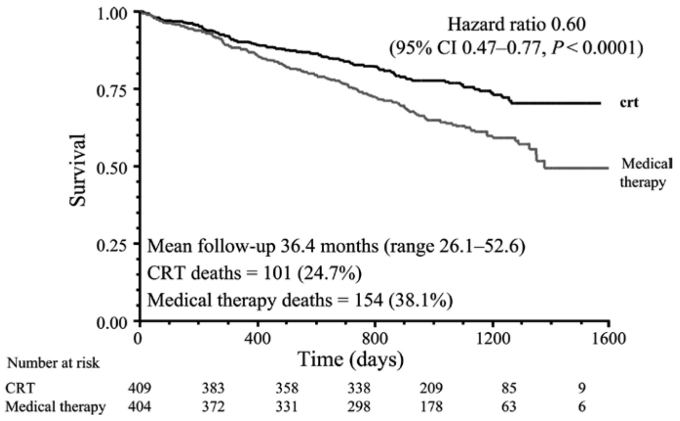


**Figure 7.** Kaplan–Meier estimates of the time to all-cause mortality (Care-HF Trial).

**Cardiac resynchronization therapy with defibrillator (CRT-D) in heart failure**

Whether the combination of CRT and ICD would create a synergistic effect has been an object of debate for many years. The beneficial effects of CRT-D to ICD alone on mortality and prevention of heart failure hospitalization in patients with intraventricular conduction delay were investigated in several landmark trials [14,15,18–21]. These trials demonstrated 30–40% reduction in mortality or heart failure hospitalization (Figure 8). A pooled analysis of six randomized trials [17] that compared the additional value of CRT-D above ICD alone demonstrated a significant reduction of 17% in all-cause mortality. The general conclusion of these trials is that CRT-D can slow down the progression of heart failure and provide additional benefits in reducing morbidity and mortality among these patients. The evidence from these landmark CRT trials has led to formation of guidelines which were updated in 2013 for the last time based on new evidence on QRS duration and left bundle-branch block (LBBB) (Figure 9). The comparison between CRT-D and CRT-P regarding all-cause mortality in Companion Trial [15] showed an additional 20% risk reduction in CRT-D patients. Comparing the characteristics of heart failure patients in early CRT trials [15,16] with a more recent trial [19] shows that early trials included heart failure patients with NYHA class III or IV; however, a more recent trial included patients with NYHA class II or even class I.

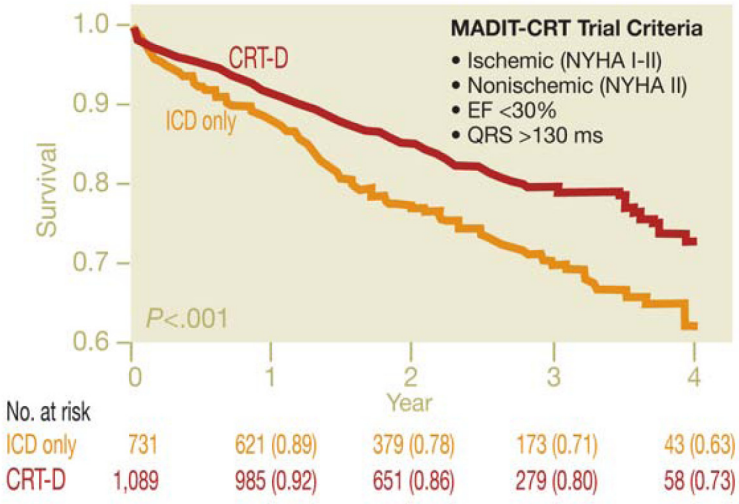


**Figure 8.** MADIT-CRT study compared CRT-D with ICD only in patients with heart failure, EF<30% and QRS-duration >130 ms. The hazard ratio in the CRT–ICD group was 0.66; 95% confidence interval 0.52−0.84; p=0.001). The superiority of CRT was driven by a 41% reduction in the risk of heart failure events.

| Recommendations | Class | Level |
|---|---|---|
| **1) LBBB with QRS duration >150 ms** is recommended in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II, and ambulatory IV despite adequate medical treatment. (*) | I | A |
| **2) LBBB with QRS duration 120-150 ms** should be considered in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II, and ambulatory IV despite adequate medical treatment. (*) | I | B |
| **3) Non-LBBB with QRS duration >150 ms** should be considered in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II, and ambulatory IV despite adequate medical treatment. (*) | IIa | B |
| **4) Non-LBBB with QRS duration 120-150 ms** may be considered in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II, and ambulatory IV despite adequate medical treatment. (*) | IIb | B |
| **5) QRS duration <120 ms** CRT in patients with chronic HF with QRS duration <120 ms is not recommended. | III | B |

**Figure 9**. Current guidelines for implanting CRT published in 2013. EHJ 2013;34:2281−2329.

**Response to cardiac resynchronization therapy:** Approximately one-third of patients with heart failure have intraventricular conduction delay presented by a QRS duration of ≥120 ms, most commonly as LBBB pattern. This wide QRS induces alterations in cardiac structure and function that result in regions of early and late contraction, known as 'mechanical dyssynchrony' [22]. CRT helps to restore dyssynchrony, improving LV function, reducing functional mitral regurgitation, decreasing end-systolic volume and diameter of LV. Although response to CRT is multifactorial, resynchronization of mechanical dyssynchrony is considered to be the primary mechanism behind the response. Response to CRT is divided in echocardiographic and clinical response. The most common definition for 'echocardiographic response' is a reduction of LVESV ≥15% compared to baseline. 'Clinical response' is most commonly defined as a clinical composite score (CCS) combining all-cause mortality, heart failure hospitalization, and NYHA class improvement [23]. The rate of CRT response varied between different studies, and depends in part on the used definitions. The majority of studies reported a rate of echocardiographic response between 60–70%. However, as many as 30–40% of patients did not benefit from this invasive and expensive therapy. These patients are called 'non-responders'. It is important to discriminate between potential responders and non-responders so as to avoid unnecessary CRT in those with high-risk of non-response and to (advice to) implant CRT in those with a high probability of response.

**Prediction of response to cardiac resynchronization therapy**

In the last decade, several potential predictors of CRT response have been introduced. The predictors of CRT response predictors are classified in (1) patient's characteristics, (2) electrocardiographic features, and (3) echocardiographic parameters that assess the mechanical dyssynchrony.

***(1) Patient's characteristics:*** A number of potentially important clinical, echocardiographic and neurohormonal factors were investigated to predict whether a patient will or will not respond to CRT. These studies demonstrated that ischemic aetiology, more severe mitral regurgitation and increased levels of N-terminal pro-brain natriuretic peptide were associated with an increased risk of death or unplanned cardiovascular hospitalization. Female gender and younger age were associated with better CRT response [24,25].

***(2) Electrocardiography*:** Electrocardiography is the corner stone for the indication for CRT and it is overly clear that patients with QRS <120 ms will not benefit from CRT. However, in those with QRS >120 ms, electrocardiography has several major limitations in identifying patients suitable for CRT. The threshold criteria of a QRS duration of $\geq$120 ms is not derived from prospective evaluation but rather from inclusion criteria of landmark clinical trials [14–16,18–21]. In fact, the mean values of QRS durations in these trials were 155 to 160 ms. In current guidelines patients with LBBB and QRS >150 ms have class 1A indication for CRT, whereas patients with LBBB and QRS 120–150 ms have class 1B indication. Furthermore, echocardiographic studies have revealed a significant discordance between electrical and mechanical delay, with up to 30% of patients with QRS durations >150 ms and 50% of those with QRS durations >120 ms demonstrating no evidence of septal to lateral dyssynchrony [26]. The QRS morphology is also an important issue in patient selection. Only 70–75% of included patients in CRT trials had LBBB. Whether patients with RBBB or non-specific intraventricular conduction delay (IVCD) would derive the same benefit from CRT is still unclear. Although prospective and randomized data concerning the CRT response in patients with RBBB are not available, these patients are currently excluded from receiving a CRT. However, in patients with a QRS >120 ms predictions of CRT response based only on the ECG remains difficult.

***(3) Mechanical dyssynchrony*:** Over the past decade, echocardiography has emerged as a potentially useful tool to assess mechanical dyssynchrony. There are numerous advantages of echocardiography, including non-invasiveness, portability and widespread availability. The rationale behind CRT is that CRT candidates have some degree of LV mechanical dyssynchrony coinciding with their prolonged depolarization, which if optimally targeted by biventricular pacing should result in better synchronous LV function, reflected by higher stroke volume and cardiac output, improving morbidity and mortality. Therefore,

echocardiography has been used to assess the presence or lack of 'mechanical dyssynchrony' in order to predict response to CRT.

## ECHOCARDIOGRAPHIC ASSESSMENT OF 'MECHANICAL DYSSYNCHRONY'

The methods used to assess mechanical dyssynchrony are based on (1) time-based dyssynchrony: peak strain/speckle tracking, (2) global dyssynchrony: LV filling (Tei index) and interventricular mechanical delay (IVMD), and (3) pattern-based dyssynchrony: septal dyssynchrony and apical rocking.

**(1) Time-based dyssynchrony**

Time-based dyssynchrony dentifying segmental LV dyssynchrony focused mostly on the time difference between peak shortening/deformation/velocity of segments. SPWMD (septal-to-posterior-wall-motion delay) by M-mode is one of the first LV dyssynchrony parameters and a cut-off value of $\geq$130 ms has been proposed as predictor of CRT. However, given the conflicting results between the studies in predictive value of SPWMD and numerous limitations of M-mode, it is not recommended for routine use in the prediction of CRT [27–29].

Tissue Doppler imaging (TDI) was used to assess tissue velocity or strain by myocardial deformation. TDI by pulsed-wave Doppler allows the assessment of longitudinal myocardial tissue velocity and has been the most investigated echo-technique for the evaluation of dyssynchrony. Septal-to-lateral delay (S-L) (Figure 10) and time-to-peak systolic velocity standard deviation (Ts-SD) were the wo parameters used to assess dyssynchrony, with good predictive value in single-center trials [30,31]. However, these parameters failed to predict CRT response in multicenter trial [23]. Color-coded Tissue Velocity Imaging is another technique that allows the simultaneous interrogation of time-to-peak velocity for multiple myocardial segments in 1 view and was therefore used to assess mechanical dyssynchrony. Although some studies demonstrated an association between these parameters and improvement of LVEF [32], the reproducibility of this method has been proven to be poor [23]. One of the major limitations for time-based dyssynchrony indices is that time differences for peak shortening or velocity relate only poorly to true dyssynchrony.

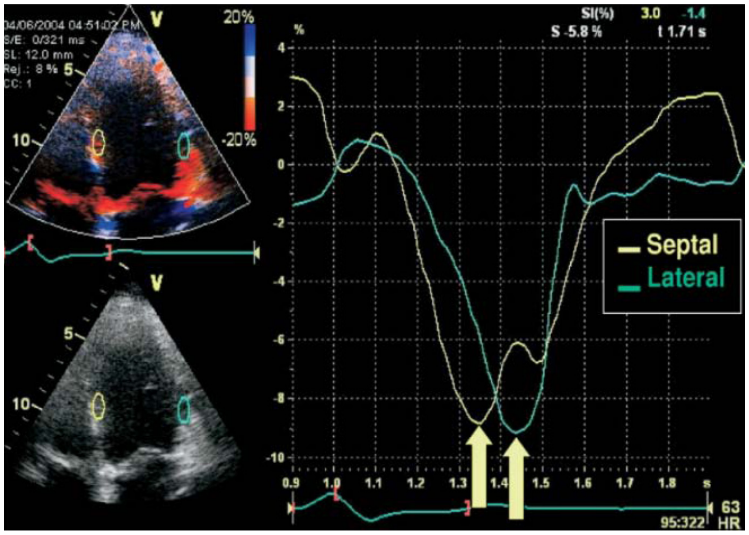


**Figure 10.** S-L delay. There is delay in the peak sustained systolic contraction in the septal (yellow curve) compared with the lateral wall (green curve).

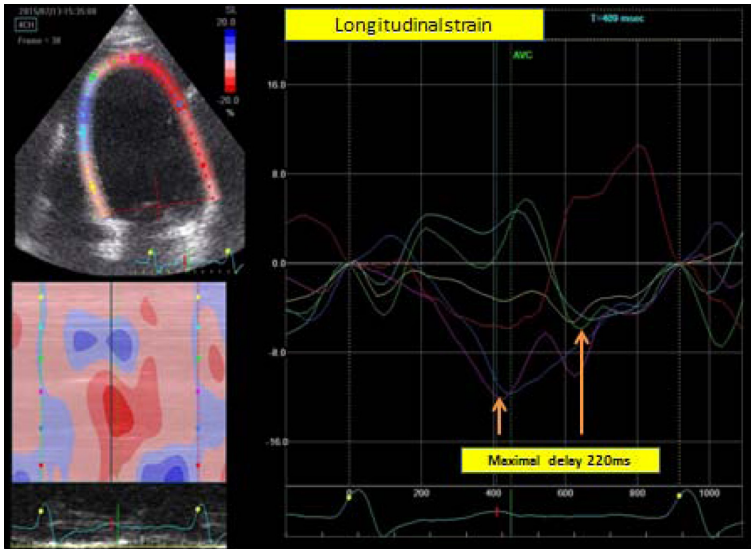


**Figure 11.** An example of time-based speckle tracking analysis in one of our patients as a marker of mechanical dyssynchrony. In this patient the maximal delay between earliest and latest activated segments is 220 ms.

Regional myocardial strain or deformation has been evaluated mostly by speckle tracking in order to assess mechanical dyssynchrony. Speckle tracking applies specific acoustic markers, 'speckles', to the myocardium (Figure 11). Movements of these markers are tracked during the cardiac cycle to determine regional myocardial deformation or strain. Assessment of mechanical dyssynchrony with speckle tracking has advantages over TDI because it measures myocardial deformation instead of TDI which assesses the motion. Therefore, it can differentiate between passive translational motion of the myocardium and active systolic contraction. Another advantage of speckle tracking is its ability to assess circumferential and radial strain in addition to longitudinal strain. Most studies using speckle tracking were single center and reported associations between the parameters and CRT response [33–35]. However, a large prospective multicenter trial on this issue is yet to come. The general limitation of these parameters is high-quality imaging which is required to determine segmental differences. This is not always feasible, especially in patients with dilated ventricles due to heart failure. Moreover, this technique is limited by high inter-observer and intra-observer variability and poor reproducibility. Time-based dyssynchrony assessment might also be influenced by myocardial scar tissue. It is very difficult to determine the peak strain of scar segment/region because the strain curve is rather flat. How to deal with scar tissue in assessment of mechanical dyssynchrony by time-based markers is not clear yet.

**(2) Global dyssynchrony**

***LV filling and Tei index*:** the segmental function assessment of mechanical dyssynchrony might not be an optimal way to determine the extent of dyssynchrony that contributes to reduced LV function and the patient's symptoms. For this reason, recognition of the importance of using LV filling and ejection velocities has been proposed as a potential tool for assessing the impact of the sum of the segmental dyssynchrony on cavity filling and ejection [36]. This is based on the use of two isovolumic time analyses. Early systolic dyssynchrony results in delayed onset of LV ejection and early diastolic dyssynchrony which starts already during the isovolumic relaxation period causes delayed onset of LV filling. The sum of isovolumic contraction and relaxation time intervals in relation to ejection time (Tei index) predicts clinical response to CRT [37,38]. The sum of isovolumic contraction and relaxation time intervals 'total isovolumic time' (T-IVT) represents the global wasted time in the cardiac cycle when the LV cavity is neither filling nor ejecting and has been shown to be a better predictor of clinical response [39]. In general, the overall experience and the amount of evidence with global marker of dyssynchrony are limited and the impact of myocardial scar tissue on the evaluation of global dyssynchrony is not clear.

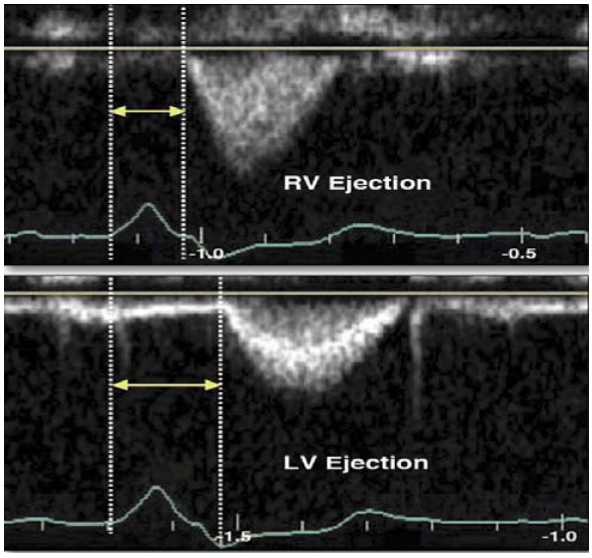


**Figure 12**. Interventricular Mechanical Delay (IVMD) by Pulsed Doppler. (Top) Time from onset of right ventricular (RV) ejection (arrows), obtained from the parasternal short-axis window. (Bottom) Time from onset of left ventricular (LV) ejection (arrows), obtained from the apical 5-chamber echo-cardiographic view.

***Interventriclur mechanical delay (IVMD)*:** correction of interventricular dyssynchrony is one of the targets of CRT. Therefore, identifying interventricular dyssynchrony may help to predict the CRT response. IVMD (Figure 12) reflects the interventricular dyssynchrony and can be measured as the difference in pre-systolic period measured from the onset of the QRS complex on the ECG to the initiation of Doppler flow in the pulmonary artery and the aorta. A cut-off value of 40 ms has been used to determine dyssynchrony and has been shown to be associated with better survival [16]. However, IVMD has a linear relationship with response and a specific cut-off for response is unsuitable [40,41]. It is therefore not applicable for patient selection.

**(3) Pattern-based dyssynchrony**

***Septal dyssynchrony*:** the septum provides information on interventricular interaction as well as intraventricular properties. The dyssynchronous electrical activation of the left ventricle causes the early activated septum to contract against a reduced load, which leads to pre-stretch of a not activated LV free wall. This pre-stretch increases the contractile force of LV free wall

which, in turn, paradoxically stretches the septum in systole. This 'wasted' work expresses the poorly coordinated contraction, which also results in poorer pump function. The concept of shortening and stretching of the septum was studied by MRI tagging images [42] in which the internal stretch fraction (ISF) was defined as the ratio of stretch to shortening during ejection. ISF was a better predictor of reverse remodelling after CRT. The special contraction and stretching of the septum during systole has been proposed to assess mechanical dyssynchrony [43,44]. Septal rebound stretch (SRSsept) defined as the cumulative amount of systolic rebound stretch after initial shortening of the septum (Figure 13). SRSsept assesses the amount of wasted work for the septum that can be recruited by CRT and has been shown to predict the long-term outcome of CRT response [45]. However, the sensitivity and specificity of SRSsept has not been clearly reported yet. There are several advantages of dyssynchrony parameters using septum as region of interest. Echocardiographic imaging of the septum is almost always feasible and reproducible and its central position in the ultrasound window guarantees adequate imaging quality.

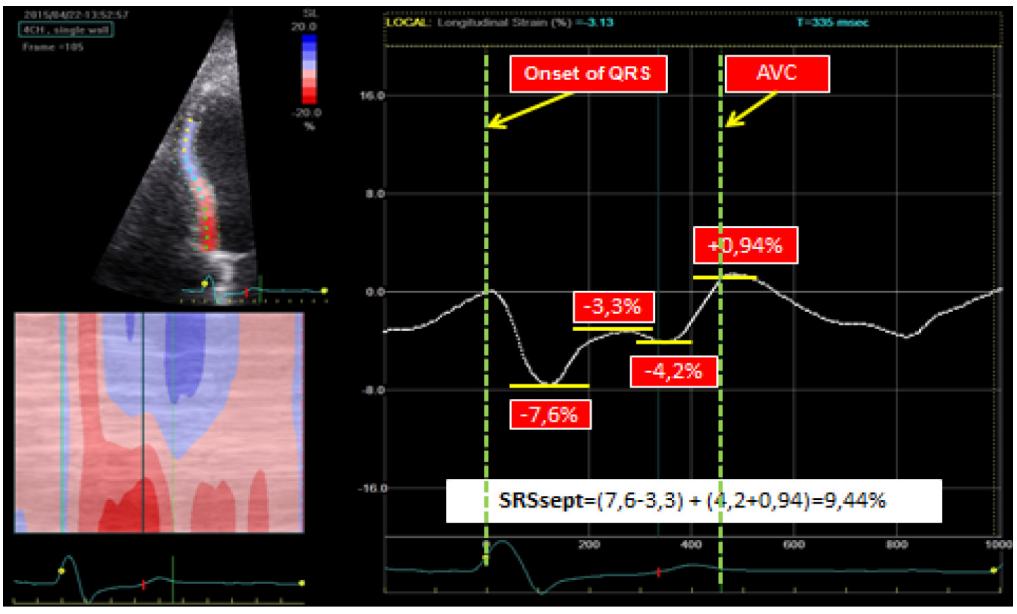


**Figure 13.** An example of septal rebound stretch as a marker of mechanical dyssynchronyin one of our patients. The cumulative amount of stretch after initial shortening of septum is 9.44%.

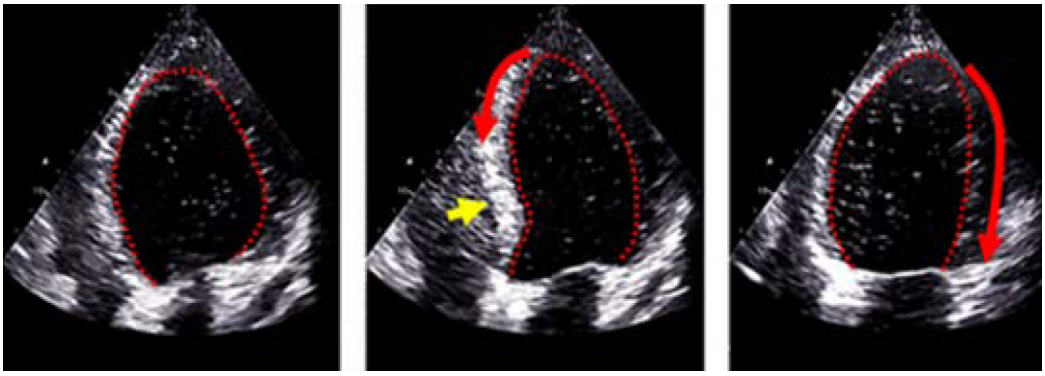

**Figure 14**. An early electrical activation of the septum results in a short initial septal contraction and causes the apex to move septally while the septum moves leftward (yellow arrow in the middle panel). The delayed activation of the lateral wall pulls then the apex laterally during the ejection phase while stretching the septum. This typical sequence of the septal-to-lateral apex motion is described as 'Apical Rocking'.

***Apical rocking*:** Apical rocking as visual assessment of mechanical dyssynchrony may be the most feasible method for routine clinical application. Apical rocking (Figure 14) is a relatively new dyssynchrony parameter. It is defined as a short initial septal contraction which results in a short inward motion of the septum and pulls the apex to the septum, and then the delayed activation of the lateral wall which pulls the apex laterally during the ejection time while stretching of the septum takes place. The predictive value of apical rocking on echocardiographic response to CRT is investigated in small numbers of patients [46]. The predictive value of apical rocking on long-term outcome has yet to be demonstrated.

**Super-response to cardiac resynchronization therapy**

Recent studies have shown that in certain patients there is an exceptional improvement of LV function after CRT, up to EF>50%. These patients are called 'super-responders'. Super-response is not only associated with short-term reduced heart failure deaths, ICD shocks and hospitalization, but also with an excellent long-term prognosis [47,48]. Because of this excellent prognosis it is important to be able to predict this super-response. Theoretically this could be of influence on the choice of device at the first implant or during replacement when elective replacement is indicated. Previous studies have tried to find easily identifiable clinical factors to predict super-response to CRT. Female gender, body mass index <30 kg/m$^2$, typical LBBB, QRS duration >150 ms, smaller LV and left atrial dimensions, shorter duration

of heart failure symptoms, and non-ischemic cardiomyopathy were among the factors associated with super-response to CRT [13,49−52]. However, to the best our knowledge, there is no information on echocardiographic predictors of super-response to CRT yet.

## OUTLINE OF THE THESIS

The main aim of this thesis was to improve the prediction of both response and super-response to CRT in a real-world everyday clinical setting. For this purpose we used data from a large cohort of patients who underwent CRT implantation at the Isala hospital, Zwolle.
The number of ICD implantations is growing fast due to expanding indications and aging of the population. Besides the greater advantages of ICD implantations there are also some small but important disadvantages connected to these devices. In **Chapter 2** the complications of ICD or pacemaker implantation in our hospital are reported.
Electrocardiography is one of the most important tools for the indication of pacemakers and/or CRT. Electrocardiographic, intrinsic LBBB is mimicked by right ventricular pacing (‘pacing-induced LBBB’). In C**hapter 3**, the differences in mechanical activations pattern between intrinsic LBBB and pacing-induced LBBB were studied. The predictive value of time-based speckle tracking imaging on prediction of CRT response has been a matter of debate. In **Chapter 4**, we focused on the prediction of CRT response by time-based speckle tracking. Little is known about the value of speckle tracking imaging during follow-up with regard to distinguishing the responders and non-responders to CRT. In **Chapters 5**, we studied changes in LV dyssynchrony as results of CRT during follow-up. Septal rebound stretch (SRSsept) reflects an inefficient deformation of the septum during systole and is a potential new echocardiographic tool to predict response to CRT. However, only limited data are available on the potential predictive value of SRSsept. In **Chapter 6**, we studied the predictive value of SRSsept on echocardiographic response to CRT with its sensitivity and specificity. Apical rocking” is frequently observed in asynchronously contracting ventricles and small studies suggested that it may predict CRT response. In **Chapter 7**, we studied prediction value of apical rocking on clinical and echocardiographic response to CRT. There are no data on the association of apical rocking with long-term outcome of CRT patients. **Chapter 8** describes the prognostic value of apical rocking as dyssynchrony parameter. About 20−25% of CRT patients shows almost normalization of LVEF as results of CRT, these patients are called ‘super-responders’. It seems that these patients have a good long-term prognosis. In **Chapter 9**, we described the long-term prognosis and patient characteristics of super-responders. There are no data on echocardiographic predictor of super-responder. In

**Chapter 10**, we studied the association of apical rocking as LV dyssynchrony with super-response to CRT. **Chapter 11** contains the summary of our studies, future perspectives and a general discussion with implication of our results on prediction of CRT response and super-response in daily practice.

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CHAPTER 2

# Incidence of lead dislodgement, malfunction and perforation during first year following device implantation

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## ABSTRACT

***Background*:** The number of cardiac rhythm device implantations has been growing fast due to expanding indications and aging of the population. Complications of implantation were rare in the trials. However, these involved small numbers and selected patients. Prospective real-life data are necessary to assess cardiac device implantation procedure-related risks.
***Objective*:** To determine the incidence and predictors of lead-related re-intervention in a Dutch high-volume teaching hospital.
***Methods:*** Data from all patients who underwent cardiac rhythm device implantation between January 2010 and December 2011 were collected in a prospective registry. At least 1 year of follow-up regarding re-intervention was available for all patients. Lead-related reasons for re-intervention were categorised into lead dislodgement, malfunctioning or perforation.
***Results*:** 1929 devices including 3909 leads were implanted. In 595 patients (30.8%) a CRT-D/P was implanted. Lead-related re-intervention was necessary in 86 (4.4%) patients, it was more common in younger and male patients, and due either to lead dislodgement (66%), malfunctioning (20%) or perforation (18%). Coronary sinus lead dislodgement or malfunctioning was 1.4%. Right atrial dislodgement (1.9%, $p<0.001$) or ICD lead dislodgement (1.8%, $p=0.002$) was more common than right ventricular dislodgement (0.3%). The incidence of lead malfunctioning was higher (0.8%) in ICD leads. Apical position of the right ventricular lead and lateral wall position of the right atrial lead were related to cardiac perforation.
***Conclusions*:** The incidence of lead-related re-intervention was comparable to the literature. The majority of re-interventions were due to lead dislodgements, particularly with right atrial and ICD leads. Re-intervention due to coronary sinus lead dislodgement was rare.


## INTRODUCTION

The number of cardiac rhythm device implantations, including implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT) devices, has increased fast in the past decade due to expanding indications and aging of the population. Although the benefits of these devices were demonstrated in randomized controlled trials, this concerned selected patients and real life data are necessary to assess cardiac device implantation-related risks. Several prospective and retrospective studies reported both short- and long-term complications related to device implantation and pacing system upgrade. However, the majority of these reports are derived from randomized clinical trials which reflect selected

patients and circumstances [1] whereas other studies concern relatively old reports, also including leads with passive fixation, which are nowadays less commonly used [2−8].
The objective of this prospectively registry study was to assess the real-life incidence of lead dislodgement, malfunctioning or perforation during the first year following implantation in a Dutch high-volume teaching hospital.

## METHODS

Data on all patients who underwent procedures of *de novo* cardiac rhythm device implantations and pacing system upgrades in our hospital between January 2010 and December 2011 were prospectively collected. The indications for the implantation of pacemakers, ICD and CRT devices were based on contemporary guidelines [9,10]. The procedures were performed by seven operators including two cardiac electrophysiology fellows under direct supervision of an attending cardiac electrophysiologist, in cardiac catheterization laboratories equipped according to the guidelines of the European Society of Cardiology [9]. The leads and devices were implanted according to the manufacturers' recommendations. The baseline characteristics of patients, included age, gender, left ventricular ejection fraction (LVEF), presence of conduction disorders and functional New York Heart Association (NYHA) class were recorded in the prospective database. To identify the lead-related complications, the database was searched on re-intervention procedures during the first year following the implantation. In all lead-related re-intervention cases, data on the clinical manifestation and course, results on chest X-ray, echocardiography and technical data on lead performance were collected.

## DEFINITION OF COMPLICATIONS

**Lead dislodgement** was defined if there was documentation of a change in the lead tip position on chest X-ray and changes in electrical lead parameters (rise in impedance, loss of sensing and pacing).
**Lead electrical malfunctioning** was defined if lead impedance, electrogram amplitude or threshold was changed abruptly, necessitating surgical revision without clear changes in position of the lead on chest X-ray.
**Lead perforation** was defined in case of high suspicion of cardiac perforation, e.g. an acute stabbing chest pain or dyspnoea, significant changes in electrical lead parameters and

significant amount of pericardial effusion requiring pericardiocentesis with or without extracardiac lead location on X-ray.
**Screw perforation** was defined if there were pericarditis-like symptoms without clear changes in electrical lead parameters and absence of significant amount of pericardial effusion.

**Statistical analysis**
Statistical analysis was performed using SPSS statistical software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0., Armonk, NY: IBM Corp.). Continuous variables were expressed as mean±SD and p value was calculated by using ANOVA test. Categorical variables were presented as number and percentages, and significance of differences was analyzed using $Chi^2$-test or Fisher exact test. The denoted p values were two-sided, and $p<0.05$ was considered significant.

## RESULTS

Over a period of 2 years, 1929 cardiac rhythm devices and 3909 leads were implanted in 1929 consecutive patients with commonly accepted indications for either pacemaker, ICD or CRT device implantation. The baseline characteristics of patients and type of device implantation are summarized in Table 1. Patients with a pacemaker indication were older than those with an ICD indication, and 66% of patients with cardiac rhythm device implantation were male.

**Table 1**. Clinical characteristics

| Baseline | Single-chamber PM (n=259) | Dual-chamber PM (n=426) | Single-chamber ICD (n=287) | Dual-chamber ICD (n=364) | CRT-P (n=91) | CRT-D (n=504) | p value |
|---|---|---|---|---|---|---|---|
| Age (year) | 78±11 | 74±11 | 61±13 | 65±11 | 72±12 | 69±9 | p<0.001 |
| Male (%) | 55 | 55 | 72.5 | 77 | 65 | 76 | p<0.001 |
| LVEF (%) | - | - | 30±9 | 31±12 | 40±13 | 26±11 | p<0.001 |
| NYHA class | - | - | 2.1±0.5 | 2.2±0.6 | 2.3±0.9 | 2.4±1 | p=0.1 |
| QRS duration (ms) | - | - | 112±33 | 112±40 | 143±60 | 161±59 | p<0.001 |

LVEF, left ventricular ejection fraction; NYHA class, New York Heart Association functional class.
p value is calculated by using ANOVA test.

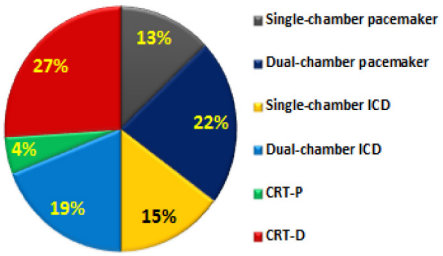


**Figure 1.** A total of 1929 cardiac rhythm devices implanted.

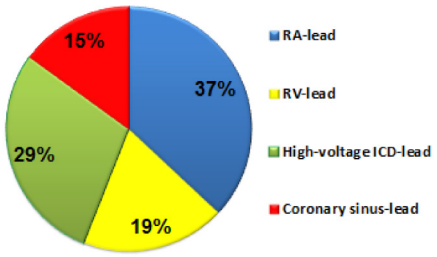


**Figure 2.** A total of 3909 leads implanted.

All leads were actively fixed, except the coronary sinus leads. Device and lead manufacturers included Medtronic, St. Jude Medical, Biotronik, Sorin Group and Boston Scientific. Of all implanted devices 1148 (60%) were ICDs, and of all implanted leads 1148 (29%) were ICD leads. Details regarding implanted devices and leads are summarized in Figures 1 and 2.

Thirty-one (1.5%) patients were re-admitted because of Cardiac Device Infection, and all had explantation of their device. One (3.2%) patient died within 30 days of hospitalization. Positive cultures were present in 27/31 (87%) cases. These consisted predominantly of micro-organisms part of the skin flora (84%).

**Re-intervention**

A total of 90 (2.3% of the leads) lead-related complications occurred in 86 (4.4%) patients for which re-intervention was needed. The cause of re-intervention was mainly lead dislodgement (66%), followed by malfunctioning (20%) and perforation (18%). Re-intervention was more common in men compared to women (70% vs 30% p=0.001). Re-interventions occurred more often in younger patients (mean age 65±13 vs 70±13 years, p=0.001).

**Lead dislodgement or malfunction, and time of occurrence**

A total of 3909 leads were implanted. During the first year of follow-up, a total of 74 (1.9%) lead dislodgements or malfunctions occurred in 71 (3.7%) patients: 57 (1.4%) dislodgements and 17 (0.5%) malfunctions. Regarding lead dislodgement, RA lead (1.9%) showed the most frequent lead dislodgement compared to RV pacemaker lead (0.3%) or ICD lead (1.8%) (p=0.0007 and p=0.002), Table 2. Only 6 (1%) coronary sinus (CS) leads dislocated, requiring re-intervention. Regarding lead malfunction, ICD lead (0.8%) showed the most frequent lead malfunction compare to RA lead (0.1%) (p=0.002), Table 2.

**Table 2.** Lead dislodgement, malfunctioning and perforation

| Type of lead | Number implanted | Dislodge-ment (%) | Malfunc-tioning (%) | Lead perforation (%) with pericardiocentesis | Screw perforation (%) without pericardiocentesis |
|---|---|---|---|---|---|
| Atrial leads | 1442 | 28 (1.9) [a] | 2 (0.1) | 5 (0.3) | 2 (0.1) |
| Right ventricular pacemaker leads | 724 | 2 (0.3) | 4 (0.5) | 1 (0.1) | 7 (0.9) |
| ICD leads | 1148 | 21 (1.8) [b] | 9 (0.8) | - | 1 (0.08) |
| Coronary sinus leads | 595 | 6 (1) [c] | 2(0.3) | - | - |
| **Total** | **3909** | **57 (1.5)** | **17 (0.4)** | **6 (0.15)** | **10 (0.25)** |

p value is calculated by using Fisher's exact test.
[a] p=0.0007 compared with RV pacemaker lead as reference.
[b] p=0.002 compared with RV pacemaker lead as reference.
[c] p=0.15 compared with RV pacemaker lead as reference.

The timing of occurrence of lead dislodgement/malfunction is summarized in Figure 3. The majority of RA and RV lead dislodgements occurred before discharge, whereas the majority of RA and RV lead malfunction occurred after 2nd month following implantation. All CS-lead dislodgements or malfunctions occurred after the 2nd month following implantation. In almost 1/3 of the cases the sleeves on the leads were not fixed adequately and in 2/3 of the cases the cause of dislodgement was unclear. All re-do interventions were conducted without further complications.

**Lead dislodgement per device type**

In this study 595 CRT-D/P devices were implanted. In the CRT-D group, significantly more lead dislodgments or malfunctions were observed compared to the single-chamber pacemaker (30 vs 3, p=0.006). The risk of any lead dislodgement or malfunctioning was higher in CRT-D (5%, p=0.006) and dual-chamber ICD (5.8%, p=0.002) as compared to single-chamber pacemaker (1.2%). Numbers of lead dislodgements per type of device are summarized in Table 3.

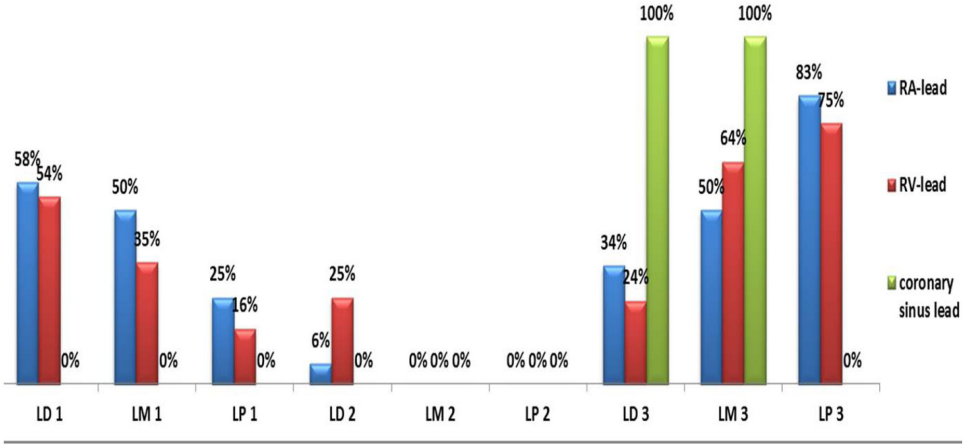


**Figure 3.** Timing of either lead dislodgement, malfunctioning or perforation. The majority of lead dislodgements occurred before discharge and all perforations occurred after 2e month of implantation. LD 1: lead dislodgement before discharge; LM 1: lead malfunctioning before discharge; LP 1: lead perforation before discharge. LD 2: lead dislodgement between discharge and 2 months; LM 2: lead malfunctioning between discharge and 2 months; LP 2: lead perforation between discharge and 2 months. LD 3: lead dislodgement between 2 months and 1 year; LM 3: lead malfunctioning between 2 months and 1 year; LP 3: lead perforation between 2 months and 1 year.

**Table 3.** Lead dislodgement and type of device

| Type of device | Number of lead dislodgement or malfunction | Risk of any leads lead dislodgement or malfunction | Number of lead/screw perforation with or without pericardiocentesis | Risk of lead/screw perforation with or without pericardiocentesis |
|---|---|---|---|---|
| Single-chamber PM | 3 | 1.2% | 3 [d] | 0.8% |
| Dual-chamber PM | 10 | 2.3% | 12 [e] | 3.0% |
| Single-chamber ICD | 10 [a] | 3.5% | 1 | 0.3% |
| Dual-chamber ICD | 21[b] | 5.8% | 0 | 0% |
| CRT-D/P | 30 [c] | 5.0% | 0 | 0% |

[a] p=0.09 compared with single-chamber pacemaker as reference.
[b] p=0.002 compared with single-chamber pacemaker as reference.
[c] p=0.006 compared with single-chamber pacemaker as reference.
[d] p=0.35 compare with single-chamber ICD as reference.
[e] p=0.02 compared with single-chamber ICD as reference.

**Lead or screw perforation**

During follow-up 16 (0.4% of the leads) leads showed screw/lead perforation in 15 (0.8%) patients. They were re-admitted to the hospital with pericarditis-like symptoms suspected for cardiac perforation. The clinical presentation of all suspected cardiac perforations was subacute (±21 days after implantation). Fourteen patients were implanted with single- or dual-chamber pacemaker and 1 patient with a single-chamber ICD. The majority of these patients were re-admitted after the first week of implantation, Figure 3. Ten patients were re-admitted with pericarditis-like symptoms with a slight amount (<0.5 cm) of pericardial effusion on the echocardiogram. In these patients only repositioning of the lead was sufficient without need for pericardiocentesis. The other five patients were re-admitted with symptoms of cardiac tamponade and a significant amount of pericardial effusion (>2 cm, with >25% respiratory mitral flow variation) on echocardiogram suspect of lead perforation without obvious extracardiac location of a lead on chest X-ray. In these five (0.26%) patients, with dual-chamber pacemakers, pericardiocentesis was necessary and performed. In all cases a repositioning or implantation of a new lead was performed without further complications and without the need for thoracic surgical intervention. In all patients, the pericarditis-like symptoms disappeared after repositioning of the suspected lead. From the 16 (0.4%) lead/screw perforations, 7 were RA leads, 8 were right ventricular pacemaker leads and 1 was an active fixation ICD lead. RV pacemaker leads caused significantly more lead/screw perforation compared to ICD leads (p=0.02; Table 3). All RV leads that caused perforations were located in the RV apex region and 4 of the 7 RA leads that caused perforation were located in lateral wall of right atrium.

**Lead or screw perforation per type of device**

Most (12 cases) lead/screw perforations occurred in dual-chamber pacemakers compared to single-chamber pacemakers (2 cases) or single-chamber ICD (1 case) (p=0.02). There were no lead/screw perforations in dual-chamber ICD or CRT-D/P devices. The rate for lead/screw perforation in dual-chamber pacemakers was 3%, whereas this did not occur in CRT-D/P patients. Numbers of leads/screw perforations per type of device are summarized in Table 3.

## DISCUSSION

In this prospective device complication registry of 1929 patients, 4.4% of patients suffered from a lead dislodgement, malfunctioning or perforation during the first year following the implantation. The overall rate of lead dislodgement, malfunctioning or perforation requiring

re-intervention was low (2.3% of 3909 leads) in our study. RA lead and ICD lead were the leads with the highest risk (1.9%) of dislodgement compared to RV-pacemaker and coronary sinus leads. The rate of lead malfunctioning was higher in ICD leads. The rate of coronary sinus lead dislodgement or malfunction within the first year following the implantation was very low in this study (1.4%). Dual-chamber ICD implantation was the procedure with the highest risk of lead dislodgement, and DDD pacemaker implantation had the highest risk of lead perforation. The overall lead dislodgement rate in our hospital is low and comparable (1.5− 3.3%) with published studies [2,6,10−14]. The CRT trials [2,13−15] reported any lead dislodgement rate varying from 2.9% to 10.6%. In our hospital, the rate of any lead dislodgement in CRT-D/P devices was 5%. In CRT devices the lead failure rate exceeds the rate of lead failure in one- or two-chamber devices. This is comprehensible since per device more leads are implanted. In our group, the low rate of 5% for any lead dislodgement could be explained by the low rate of coronary sinus lead dislodgements. The rate of coronary sinus lead dislodgement in the present study is low (1.4%) compared to previous reports (4.0−8.4%) [16,17]. There are several possible explanations. The coronary sinus leads are today more diverse with different shape and thickness. These properties enable the operators to choose the lead which fits best in the side branches of the coronary sinus. Also, the use of inner catheters and selective shackling of the side branches makes it easier to advance the lead inside the vessel and to achieve a stable position. A possible other explanation is the experience of the operator. Almost all coronary sinus leads were implanted by three very experienced operators in our hospital. Furthermore, since coronary sinus leads from a number of different manufactures are available in our hospital during implantation, and there is no preferred manufacturer assigned to a case, the most suitable lead can be chosen for implantation, according to the anatomy, enhancing the success rate. We tried to identify the causes of lead dislodgments. In almost 1/3 of the cases the sleeves on the leads were not fixed adequately and in 2/3 of the cases the cause of dislodgement was unclear. It means that in 1/3 of the cases a lead dislocation could be prevented by adequate fixation. In the present study all lead/screw perforations were subacute and the incidence was very low (0.8%) and comparable with (0.6−5.2%) published reports [1,5,7]. The DDD pacemakers caused the most perforations (12 cases) and the majority of perforated leads were RV leads. There are several possible explanations:

1. All perforated RV-leads were located in RVapex which is the thinnest part of the right ventricle. In our routine practice we try to avoid the apex if possible and position the RV leads in a septal region if sufficient sensing and pacing values are present.
2. The relatively small size of the lead, 6-7 French, which perforates the apex easier than the thick high-voltage ICD (8-9 French) lead and, according *to the Laplace Low* (p=F/A;

pressure is the amount of force acting per unit area), it is easy to understand that when the surface area is smaller, then the pressure will be higher on that surface area.

3. Also, the experience of operators plays an important role. In our teaching hospital, most of pacemakers were implanted by less experienced operators, cardiologists in training, and the ICDs and CRTs by very experienced operators. The majority of perforated RA leads were located in the lateral wall, which is not the preferred site, due to its unstable position or insufficient electrical signals, and therefore the operator has been forced to choose this site.

**Strength and limitations of study**

This study demonstrates the real-world common daily practice of implanting large numbers of devices in a teaching hospital. Meticulous longitudinal follow-up was performed, with documentation of complications in all patients. This study also has certain limitations. We identified the re-intervention due to lead-related complication when the patients were returned to cardiac catheterization laboratories within the first year of implantation. Patients with lead-related complication who did not return for re-intervention based on the opinion of their cardiologists could be missing in our registry. Furthermore, the follow-up period in the present study is no longer than 1 year. However, most lead dislocations and perforations are expected to occur within 1 year [1,7,11]. This is also supported by our own data. To obtain reliable information about the rate of complications, we used predefined definitions of complications. We focused on lead dislodgement, malfunctioning and perforations. Other device-related complications, including infection, were beyond the scope of this study. Our analysis did also not evaluate mortality and duration of hospitalization in the study population.

## CONCLUSIONS

In this large observational study, lead-related re-intervention was necessary in 4.4% of patients, more common in younger and male patients, and due to either lead dislodgement (66%), malfunctioning (20%) or perforation (18%). With a total of 3909 leads implanted, the incidence of lead dislodgement, malfunction or perforation was low (2.3%). Right atrial and ICD leads caused more dislodgement compared to RV-pacemaker leads. Lead perforation was more common with RV- leads, especially when placed in the apex. In the patients with lead perforation, in only 1/3 pericardiocentesis was necessary. With 1929 devices implanted, more lead complications were observed in dual-chamber ICD and CRT-D/P.

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CHAPTER 3

# Assessment of left ventricular dyssynchrony in pacing-induced LBBB compared to intrinsic LBBB

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## ABSTRACT

***Aim*:** Although electrocardiographic and echocardiographic findings with right ventricular (RV) pacing mimic intrinsic left bundle branch block (LBBB), LV mechanical activation pattern may differ. We compared mechanical activation pattern of the LV in RV-pacing-induced LBBB with intrinsic LBBB in symptomatic chronic heart failure patients.
***Methods*:** We studied 37 patients with chronic RV pacing and 37 with intrinsic LBBB who were referred for CRT. Echocardiographic study including 2D speckle tracking longitudinal strain and M-mode were performed at baseline.
***Results*:** Patients with intrinsic LBBB were younger, had higher prevalence of ischemic heart disease and had more severe depressed LV function. The basal-septal segments were the earliest activated sites in 11% of patients in RV-pacing-induced LBBB compared to 30% in intrinsic LBBB (p=0.04). The mid-and basallateral segments were the latest activated sites in 57% of patients in RV-pacing-induced LBBB compared to 30% in intrinsic LBBB (p=0.03). LV dyssynchrony, using longitudinal strain, time delay $\geq$130 ms between either mid-septal or apico-septal and either basal or mid-lateral segments was present in 71% of patients with RV-pacing-induced LBBB compared to 59% in intrinsic LBBB (p=0.03). Using M-mode, LV dyssynchrony was present in 11% of patients with RV-pacing-induced LBBB compared to 59% in intrinsic LBBB (p=0.02).
***Conclusion*:** RV pacing results in less early basal activation and more often early mid-septal and late lateral wall activation in comparison with intrinsic LBBB. Imaging techniques that only visualize the basal or mid part of the LV may result in a serious underestimation of dyssynchrony in patients with pacing-induced LBBB.


## INTRODUCTION

Cardiac resynchronization therapy (CRT) reduces mortality, improved symptoms and exercise tolerance in selected patients with left bundle branch block (LBBB) and severe chronic heart failure [1]. Right ventricular (RV) pacing has electrocardiographic and echocardiographic similarities with LBBB, but left ventricular (LV) activation pattern is probably different. Although it has been suggested that in patients with RV-pacing and heart failure the prevalence of dyssynchrony is comparable to patients with spontanous LBBB [2], the different left ventricular activation pattern may influence assessment of dyssynchrony and prediction whether patients have potential benefit of CRT. The aim of this study is to assess the mechanical activation pattern and LV dyssynchrony by 2D speckle tracking strain

imaging in patients with heart failure and pacing-induced LBBB, compared to patients with intrinsic LBBB and to investigate whether this influences assessment of dyssynchrony.

## METHODS

We retrospectively studied a total of 74 subjects, 37 patients with pacing-induced LBBB (RV apex pacing) and 37 patients with intrinsic LBBB. Patients with RV pacing-induced LBBB were candidates for an upgrading to a biventricular device and had been chronically paced in RV apex for more than 1 year with more than 90% RV apex pacing and the ECG showed LBBB pattern with a left axis deviation. The RV lead position was determined by X-ray (antero-posterior and in lateral views) and ECG. These patients were in heart failure NYHA functional class II or III and had a LV ejection fraction <35%. Patients with intrinsic LBBB had symptoms of heart failure and met the current guidelines for cardiac resynchronization therapy (symptomatic heart failure, NYHA class III-IV/IV despite optimal medical therapy (OPT), LV ejection fraction <35%, left ventricular end-diastolic diameter (LVEDD) >55 mm, QRS >120 ms and in sinus rhythm). All patients were on optimal medical regimen according to guidelines.

### Echocardiography and data acquisition

All patients underwent standard two-dimensional transthoracic echocardiography and Doppler imaging prior to implantation of the cardiac resynchronization device. The images were obtained using a 3.5 MHz transducer at a depth of 16cm in the parasternal (long axis) and apical (2- and 4-chamber) views. The images were stored in cineloop format by well-trained echocardiographists and reviewed by an independent cardiologist who was not involved in the study. Left ventricular end-diastolic diameter and volume (LVEDD and LVEDV), and left ventricular end- systolic diameter and volume (LVESD and LVESV) were obtained. The LV ejection fraction was calculated from the conventional apical 2- and 4-chamber imaging, using the Biplane Simpson's technique [3]. The M-mode was used to determine the intra-ventricular septal to posterior wall motion delay (SPWMD) in parasternal long-axis (PLAX) images. As reported by Pitzalis et al. [4], SPWMD $\geq$130 ms was used as a cut-off value for LV dyssynchrony.

### Strain analysis by 2D speckle tracking

*Longitudinal strain:* Longitudinal strain was assessed in an apical 4-chamber view with a frame rate of at least 40 frames/s to allow for reliable operation of software. The endocardial

border was manually traced and the region-of-interest width was manually adjusted to include the entire myocardium. The software then automatically traced and accepted segments of good tracking quality and rejected poorly tracked segments and allowed the user to manually over-ride its decisions at the same time using visual assessments. The time from QRS onset to peak global longitudinal strain was determined for 6 separate segments, i.e., basal-septal, mid-septal, apico-septal, apico-lateral, mid-lateral and basal-lateral. A total of 444 segments were analyzed on LV 4-chamber apical view images. Of these 444 segments, 10 segments (2.3%) were excluded from analysis because of poor tracking score. The location of the earliest and the latest activated segments and the maximal delay, defined as the time difference between the earliest and latest activated segments, were determined, Furthermore, the time delay between basal-septal to basal-lateral segments and the time delay between apico-septal or mid-septal to basal-lateral or mid-lateral segments were determined. LV dyssynchrony was defined as an interval $\geq$130 ms for the absolute difference in time-to-peak global longitudinal strain for basal-septal to basal-lateral segments [5]. Although no cut-off values are available for defining LV dyssynchrony in RV-pacing-induced LBBB, we defined an interval $\geq$130 ms for difference in time-to peak global longitudinal strain between apico-septal or mid-septal to basal-lateral or mid-lateral segments as cut-off value for LV dyssynchrony. The off-line analyses were performed on digitally stored images (EchoPac version 108.X.X) by one independent observer blinded to the clinical and other echocardiographic information.

**Statistical analysis**

Results are presented as mean±standard deviation and compared using two-tailed Student's *t*-test for paired and unpaired data. $p<0.05$ was considered significant for all tests.

## RESULTS

**Patients**

Baseline characteristics of the 74 patients are summarized in Table 1. Patients with intrinsic LBBB were younger, had higher prevalence of ischemic heart disease and had more pronounced impaired LV function than the patients with RV-pacing-induced LBBB.

**Mechanical activation pattern**

There were several differences in LV mechanical activation pattern between RV-pacing-induced LBBB and intrinsic LBBB. Differences in the earliest- and latest-activated segments between the two groups are depicted in Figures 1 and 2. The basal-septal segments were the

earliest activated sites in 11% of patients in pacing-induced LBBB compared to 30% in intrinsic LBBB (p=0.04). The mid- and basal-lateral segments were the latest activated sites in 57% of patients in pacing-induced LBBB compared to 30% in intrinsic LBBB (p=0.03).

**Left ventricular dyssynchrony**

The LV dyssynchrony parameters and assessment of LV dyssynchrony in both groups are summarized in Table 2. LV dyssynchrony, between either mid-septal or apico-septal and either basal or mid-lateral segments was present in 71% of patients with pacing-induced LBBB compared to 59% in intrinsic LBBB (p=0.03). Using M-mode in the basal segements alone, LV dyssynchrony was present in 11% of patients with pacing-induced LBBB compared to 59% in intrinsic LBBB (p=0.02).

**Table 1.** Baseline characteristics of patients with intrinsic and pacing-induced LBBB

| | Intrinsic LBBB (n=37) | Pacing-induced LBBB (n=37) | p value |
|---|---|---|---|
| Age (years±SD) | 63.2 ±9.5 | 70±10 | 0.004 |
| Male gender (%) | 62 | 70 | 0.461 |
| Sinus rhythm (%) | 100 | 45 | <0.001 |
| Ischemic (%) | 54 | 29 | 0.034 |
| NYHA class(mean±SD) | 2.65±0.42 | 2.77±0.61 | 0.063 |
| QRS (ms±SD) | 174±19 | 174±31 | 0.970 |
| LV end-diastolic diameter (mm±SD) | 64.4±7.7 | 57.1±7.1 | < 0.01 |
| LV end-systolic diameter (mm±SD) | 56.6±8.7 | 45.2±9.8 | < 0.01 |
| LV end-diastolic volume (ml±SD) | 208.1±76.6 | 127.1±47.9 | < 0.01 |
| LV end-systolic volume (ml±SD ) | 162.0±74.6 | 85.9±39.6 | < 0.01 |
| LV EF (%±SD ) | 23.7±8.6 | 31.2±9.3 | < 0.01 |

SD, standard deviation.

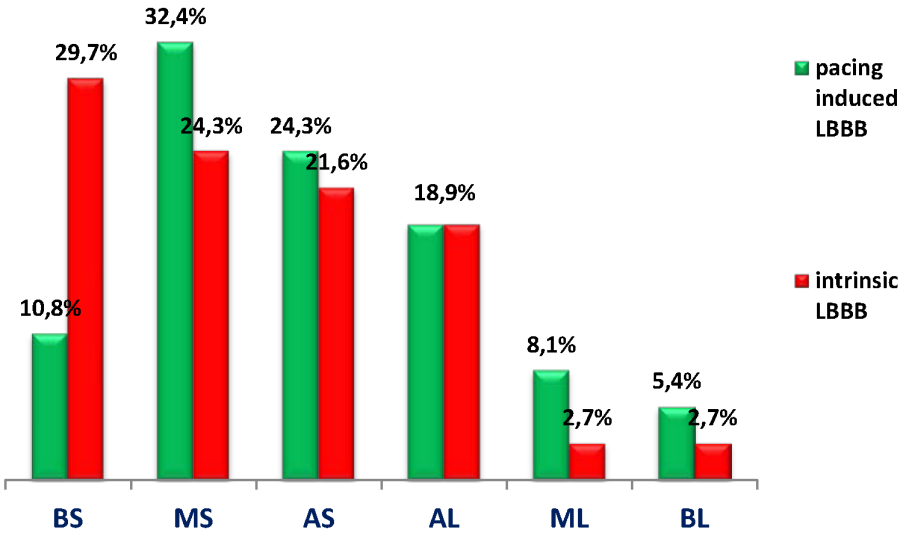


**Figure 1**. Distribution of earliest activated sites in pacing-induced LBBB and in intrinsic LBBB in apical 4-chamber view by longitudinal strain speckle tracking. BS, basal-septal; MS, mid-septal; AS, apico-septal; Al, apico-lateral; ML, mid-lateral; BL, basal-lateral.

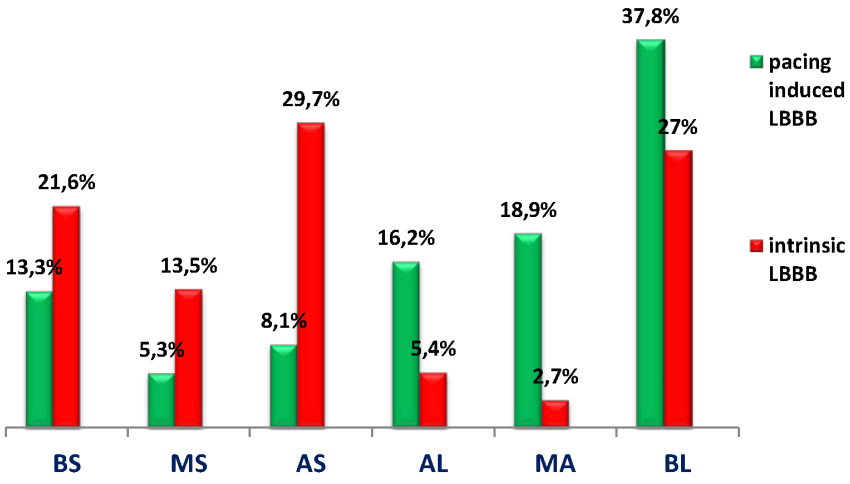


**Figure 2**. Distribution of latest activated sites in pacing-induced LBBB and in intrinsic LBBB in apical 4-chamber view by longitudinal strain speckle tracking.

**Table 2.** Left ventricular dyssynchrony measurements in both groups

| | Intrinsic LBBB | Pacing-induced LBBB | p value |
|---|---|---|---|
| SPWMD by M-Mode (ms±SD) | 144±55 (n=37) | 82±45 (n=36) | 0.001 |
| BS-BL delay by LS (ms±SD) | 154±16 (n=36) | 110±87 (n=33) | 0.165 |
| Max. delay 4C by LS (ms±SD) | 277±118 (n=37) | 251±133 (n=37) | 0.135 |
| AS/MS-BL/ML delay by LS (ms±SD) | 190 ±126 (n=37) | 205±134 (n=35) | 0.624 |
| AS/MS-BL/ML delay ≥130 ms | 59% | 71% | 0.037 |
| Max delay 4ch by LS ≥130 ms | 91% | 86% | 0.66 |
| BS-BL delay ≥130 ms | 47% | 27% | 0.09 |
| SPWMD by M-mode ≥ 130 ms | 59.4% | 11% | 0.02 |

SPWMD, intraventricular septal to posterior wall motion delay; BS-BL delay, difference between time to peak global longitudinal strain of basal-septal and basallateral segments; Max delay 4C, maximal difference in time to peak global longitudinal strain between six segments in 4-chamber view; AS/MS-BL delay, difference between time to peak global longitudinal strain of apicoseptal or midseptal and basallateral segments; A/AS-posterior delay, difference between time to peak global radial strain of anterior or anteroseptal and posterior segments.

## DISCUSSION

In pacing-induced LBBB the right ventricular (RV) pacing induces intra-ventricular conduction disturbance (IVCD). If the ventricular lead is placed in the apical region of RV, this pacing-induced IVCD usually presents electrocardiographically with a left bundle branch block (LBBB) pattern and left axis deviation. The etiology of intrinsic left bundle branch block (LBBB) represents a spectrum that ranges from conduction disease in the proximal parts of the left bundle branch (LBB) to more distal parts in the fascicles or advanced disease in the distal Purkinje fibers. The mechanical activation pattern of the LV depends in intrinsic LBBB on the level of block in the conduction system and in induced LBBB on the position of RV lead within the right ventricle. In the current study, we showed clear differences in mechanical activation pattern between intrinsic and pacing-induced LBBB by using speckle tracking longitudinal strain. This mechanical activation pattern also affects the assessment of LV dyssynchrony in these two groups. We demonstrated that in patients with a pacing-induced LBBB the mid- and apico-septal regions of LV are in the majority of patients the earliest activated regions, whereas in intrinsic LBBB the basal-septal segment is most frequently the earliest activated region. Furthermore, there are differences in latest activation sites between these two groups: in pacing-induced LBBB one of the lateral segments (AL, ML, BL) is in 74% the latest activated segments and in contrast, in intrinsic LBBB the lateral wall is only in 35% of patients the latest segment. For the assessment of dyssynchrony we

used several methods of measuring the delays between LV segments. Measuring the delay in predefined segments like BS and BL showed that LV dyssynchrony was only present in 27% of patients with pacing-induced LBBB, whereas in intrinsic LBBB this was present in 47% of patients (p=0.09). Choosing other predefined segments (MS/AS versus BL/ML $\geq$130 ms) the number of patients with dyssynchrony, according to our definition, increased to 71% and 59%, respectively, in patients with pacing-induced and intrinsic LBBB (p=0.03). When we assessed the maximum delay between any of the segment, the number of patients with dyssynchrony increased to 86% and 91%, respectively, in patients with pacing-induced and intrinsic LBBB. Also, the mean values of the different delays measured depend very much on which method was depicted (Table 2). Using M-mode, (again two basal segments), LV dyssnychrony was present in 11% of the patients with pacing-induced LBBB and in 59.4% of patients with intrinsic LBBB (p=0.02). The results of our study are in contrast with those of Witte et al. [2]. They suggested that patients with RV pacing and heart failure have similar dyssynchrony as patients with intrinsic LBBB. However, they used M-mode (SPWMD $\geq$130 ms), interventricular mechanical (aortopulmonary) delay $\geq$40 ms and TDI $\geq$65 ms (intraventricular delay) as marker of dyssynchrony. An explanation why these basal segments fail to demonstrate LV dyssynchrony may be the fact that in RV apex pacing, not the basal-septal regions, but the apical regions (apico-septal, mid-septal and apico-lateral) are predominantly activated as first. These apical regions are not represented when M-mode (PLAX images) or longitudinal strain imaging of the basal segments is applied. Our findings are in agreement with Xiao et al. [6], they reported that electromechanical delay, contraction and relaxation times, and extent of incoordinate ventricular wall motion differ strikingly between intrinsic and pacing-induced LBBB. In pacing-induced LBBB, activation vector is directed from apical to basal and from right to left. In contrast, in patients with intrinsic LBB, the activation vector is usually directed from basal to apical and from septal to lateral. Therefore, pacing-induced LBBB and intrinsic LBBB are two different entities.

At present time, to our knowledge, no studies have been reported concerning the effects of permanent RV apical pacing (pacing-induced LBBB) on timing of regional wall strain by longitudinal speckle tracking in heart failure patients. We used the longitudinal strain because of better visualizing of apex in relation to other segments of LV. In RV pacing-induced LBBB the assessment of LV dyssynchrony at the level of the basal LV segments causes serious underestimation of the dyssynchrony which is demonstrated by our results regarding the M-mode measurements and basal longitudinal strain method. In RV apical paced patients the mid/apico-septal region is in the majority of patients the earliest activated segment. It is important to visualize and assess all segments of the LV (from basal to apex) rather than being restricted to the basal and mid-segments. The imaging techniques like M-mode, TVI and radial strain are often restricted to basal or mid-segments regions. Therefore, based on

this retrospective analysis, we suggest that speckle tracking might be a preferred method to investigate dyssynchrony, at least in patient with RV pacing.

**Study limitations**

The present study is a retrospective analysis. The data were collected systematically and echocardiograms were analyzed by an independent cardiologist. Validated and normal values for the assessment of LV dyssynchrony by 2D speckle tracking in patients with heart failure and RV pacing are lacking at the moment. We used the LV dyssynchrony cut-off value (130 ms) that was used in echocardiographic studies measuring deformation by radial strain and m-mode techniques in patients with intrinsic LBBB and heart failure. Whether a (maximum) delay $\geq$130 ms assessed by longitudinal strain is clinically relevant was not the purpose of this study. The clinical relevance of assessing regional LS in order of better patient selection for CRT is an important issue. The baseline characteristics of patients with induced LBBB and intrinsic LBBB were different and we can not exclude that this influenced our results.

## CONCLUSION

In this study we demonstrated that RV-pacing-induced LBBB and intrinsic LBBB are not identical with regard to the mechanical activation pattern of the left ventricle: RV pacing results in less early basal activation and more often early mid-septal and late lateral wall activation and in comparison with the mechanical activation in intrinsic LBBB.
Using imaging techniques that only visualize the basal or mid part of the LV may result in a serious underestimation of dyssynchrony in patients with pacing-induced LBBB, therefore speckle tracking is endorsed as method to evaluate dyssynchrony.

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CHAPTER 4

# Response to cardiac resynchronization therapy as assessed by time-based speckle tracking imaging

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## ABSTRACT

***Background*:** Response to cardiac resynchronization therapy (CRT) is still difficult to predict with previously investigated dyssynchrony indices. The predictive value of speckle tracking strain analysis has not been fully delineated yet. The objective of this study was to assess the predictive value of longitudinal (LS) and radial strain (RS) speckle tracking measurements on echocardiographic and clinical response to CRT.

***Methods*:** A total of 138 consecutive patients with functional class II−IV heart failure who underwent CRT were studied. Echocardiography was performed at baseline and during follow-up. Six different time-based LV dyssynchrony indices measured with LS and RS. Echocardiographic response to CRT was defined as a reduction in LV end-systolic volume ≥15% and clinical response as survival without heart failure hospitalization. Multivariable analyses were performed to adjust for potential confounding factors.

***Results*:** Echocardiographic and clinical follow-up was 22±8 and 42±8 months, respectively. Ninety-six patients (70%) were classified as echocardiographic responders and 114 patients (83%) survived without heart failure hospitalization. QRS duration and non-ischemic etiology predicted echocardiographic response to CRT. None of the speckle tracking indices was different between echocardiographic responders and non-responders to CRT. Regarding clinical response, only maximal delay between six segments in 4-chamber view measured with LS was different between responders and non-responders, with 154 ms delay as the optimal cut-off value. Neither stratified analyses in patients with sinus rhythm nor multivariable analyses did change these findings.

***Conclusion*:** Of all time-based measured speckle tracking indices, only maximal delay between six segments in 4-chamber view as assessed with LS was associated with clinical response to CRT.


## INTRODUCTION

Cardiac resynchronization therapy (CRT) is an established treatment for heart failure patients with prolonged QRS duration and reduced LV ejection fraction (LVEF) ≤35%. CRT goals include an increase in left ventricular ejection fraction, reduction of heart failure symptoms, and reduction of heart failure hospitalization and mortality [1−4]. However, indication for CRT based on LVEF and QRS duration results in 30–40% of non-responders and even worsening of cardiac function in some patients [5]. Echocardiographically determined intraventricular dyssynchrony has been used to enhance the rate of response to CRT. Several echocardiography techniques have been used to aide in patient selection for CRT prior to

implantation with promising results in observational single-center trials. However, no ideal echocardiographic approach for the assessment of dyssynchrony has yet been found. The largest prospective trial (PROSPECT) [6] showed poor predictive value of several conventional and tissue Doppler-based methods. In recent years, 2D-speckle tracking echocardiography, including radial, longitudinal, and circumferential strain analysis, has been used to assess left ventricular dyssynchrony [7,8]). However, the predictive value of speckle tracking strain analysis has not been fully delineated yet, as contradictory results have been presented with relatively short clinical and echocardiographic follow-up [9,10]. The aim of the current study was to evaluate the predictive value of 2D-speckle tracking longitudinal and radial strain on echocardiographic and clinical response to CRT in a large cohort of patients.

## METHODS

### Selection of patients

From January 2008 to December 2009, 160 consecutive patients with chronic heart failure (New York Heart Association functional class II−IV), LVEF ≤35% and wide QRS complex ≥120 ms who were scheduled for CRT were included in the present study. All patients were on optimal pharmacological therapy, including angiotensin-converting enzyme inhibitors and beta-blockers. Patients with a recent myocardial infarction (<3 months) or decompensated heart failure were excluded. Etiology was considered ischemic in the presence of significant coronary artery disease (≥50% stenosis in 1 or more of the major epicardial coronary arteries) and/or history of myocardial infarction or prior revascularization by PCI or CABG. Twenty-two patients with poor echocardiographic window at baseline were excluded from the analysis.

### Study protocol and Echocardiographic data acquisition

All patients underwent two-dimensional echocardiography prior to biventricular ICD implantation and at follow-up in the second year after CRT implantation. The images were obtained on a Vivid 7 ultrasound machine (General Electric, Milwaukee, WI) using a 3.5 MHz transducer at a depth of 16 cm in the parasternal (long- and short axis) and apical (2- and 4-chamber) views. The images were stored in cine-loop format by well-trained echocardiographists and reviewed by an independent cardiologist who was not involved in the study. The left ventricular end-diastolic diameter (LVEDD), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic diameter (LVESD) and left ventricular end-systolic volume (LVESV) were measured and the LVEF was calculated using Simpson's technique [11].

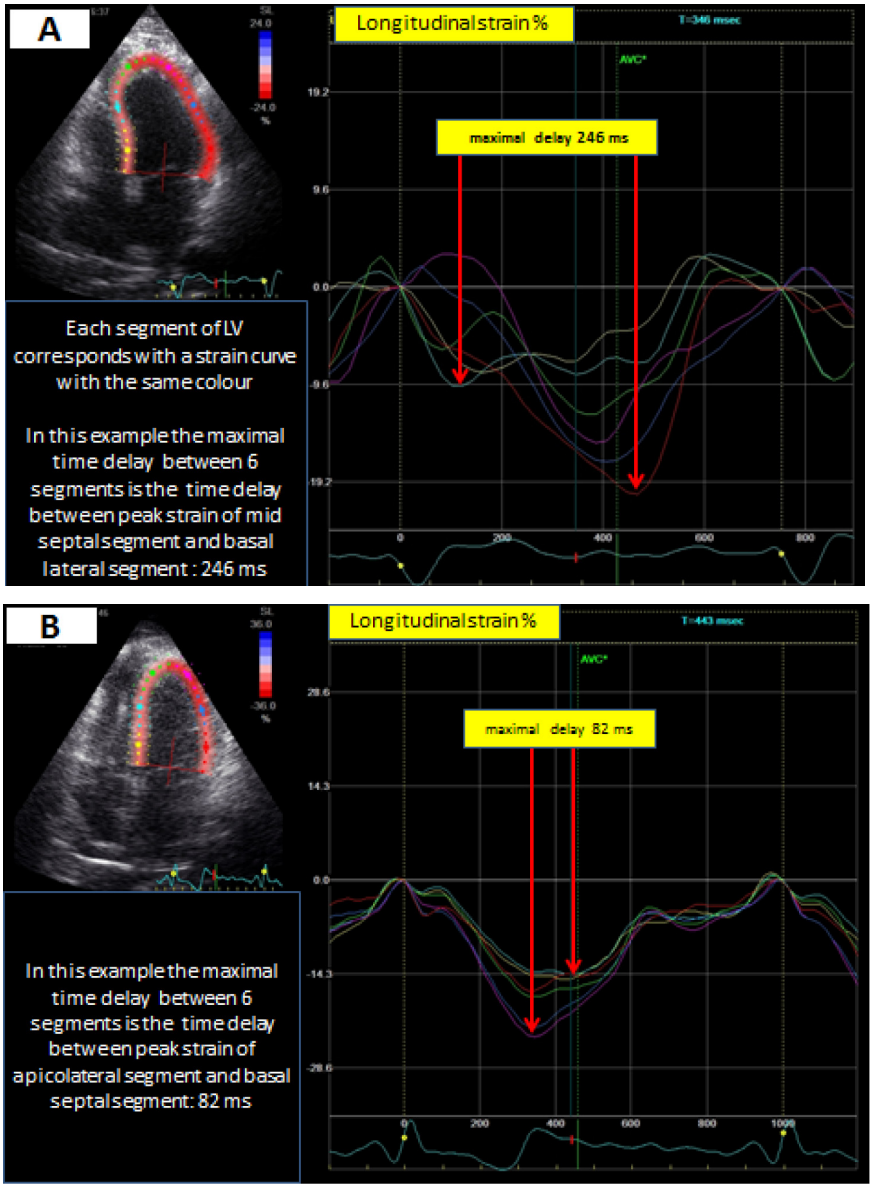


**Figure 1. (A**) An example of speckle tracking longitudinal strain analysis demonstrating LV dyssynchrony in 4-chamber view in a heart failure patient with LBBB. LV dyssynchrony is shown as maximal time-delay between six segments. **(B)** The same patient defined as responder to CRT. LV dyssynchrony measured as maximal time-delay between six segments decreased from 246 ms at baseline (A) to 82 ms after CRT (B).

**Left ventricular dyssynchrony measurements with 2D-speckle tracking**

*Longitudinal and Radial strain imaging:* In the present study, longitudinal and radial strain imaging techniques were used to assess left ventricular dyssynchrony. The analysis was performed using a commercially available software package (EchoPac version 7.0.1, General Electric) with a frame rate of at least 40 frames/s to allow for reliable operation of software and frame rate <40 frames/s considered as non-valid tacking. The endocardial border was manually traced by a point-and-click approach and the region-of-interest width was manually adjusted to include the entire myocardium. Segments of good tracking quality were automatically traced and accepted and poorly tracked segments were rejected. This allowed the user, based on visual assessments, to manually over-ride automatic software assessments. We used two imaging techniques, i.e., longitudinal and radial strain, to visualize the mechanical activation pattern of the left ventricle in three different ways. First, longitudinal strain was measured in the apical 4-chamber view to evaluate three septal segments (basal, mid and apical) and three lateral segments (apical, mid and basal) of the left ventricular wall. Second, longitudinal strain was measured in the 2-chamber apical view to evaluate three inferior segments (basal, mid and apical) and three anterior segments (apical, mid and basal) of the left ventricular wall. Third, radial strain was measured to evaluate the mid-regions of the left ventricle in short axis view to visualize six segments (anterior, antero-septal, septum, inferior, posterior and lateral) of the left ventricle.

For the measurement of LV dyssynchrony we used the same method as described by Ypenburg et al. [12]. In the apical 4-chamber view, the time from QRS onset to peak longitudinal strain, during the entire cardiac cycle, was determined for six separate segments (basal-septal, mid-septal, septal-apical, lateral-apical, mid-lateral and basal-lateral walls). Subsequently, time delay between basal-septal and basal-lateral segments (BS-BL delay) and the maximal time delay between the earliest and latest activated segments were calculated (Figure 1). In the apical 2-chamber view the time from QRS onset to peak longitudinal strain was determined for six separate segments (basal inferior, mid inferior, apical inferior, apical anterior, mid anterior and basal anterior walls). Subsequently, time delay between basal inferior and basal anterior segment (BI-BA delay) and the maximal time delay between the earliest and latest activated segments were calculated. The same measurements as with longitudinal strain were performed with radial strain in six separate segments (anterior, antero-septal, septum, inferior, posterior and lateral) at the level of the papillary muscles. The maximal time delay between these six segments and time delay between antero-septal to posterior segment (AS-P delay) were calculated. The off-line analysis was performed on digitally stored images by an independent observer (A.G.) blinded to the clinical and other echocardiographic information. All speckle tracking left ventricular dyssynchrony measures were additionally performed by another independent, well trained, and experienced

cardiologist (P.P.D.). Furthermore, these measurements were repeated by the first observer, in order to assess inter-observer and intra-observer variability. Inter-observer and intra-observer variability was expressed as intraclass correlation coefficients. Values higher than 0.8 are considered as excellent, values between 0.6 and 0.8 as good, values between 0.4 and 0.6 as moderate, and values below 0.4 as poor concordance**.**

**Echocardiographic response to CRT**

Response to CRT was defined as a reduction ≥15% in LVESV compared to baseline echocardiographic measurement, determined in the second year of echocardiographic follow-up [13,14].

**Clinical response to CRT**

Survival without hospitalization due to worsening of heart failure during follow-up was defined as clinical response to CRT. Of note, clinical status was assessed by independent physicians before CRT and after a mean±SD of 42±8 months.

**Statistical analysis**

Statistical analysis was performed using SPSS statistical software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Continuous variables are expressed as mean±SD and a non-parametric Mann-Whitney U-test was used to analyze differences between groups**.** Categorical variables are presented as number and percentages and the Chi-squared test was used to analyze differences between groups. Paired observations (observations of the same variable at different time points) were analyzed using the non-parametric Wilcoxon test. Logistic regression analysis was performed to identify predictors of echocardiographic response. Cox regression was used to analyze predictors of clinical response. From six different dyssynchrony indices we selected those indices which differ in the univariate analyses between clinical responders and non-responders to CRT. In the multivariate logistic and Cox regression analyses we analyzed these indices after adjustment for clinical variables (LVEF, QRS width, ischemic/non-ischemic cardio-myopathy). Because atrial fibrillation may potentially influence both speckle tracking measurements and response to CRT, stratified analyses performed in patients with sinus rhythm and atrial fibrillation. Because the number of included patients with atrial fibrillation was too small we only presented the results in patients with sinus rhythm.

**Table 1**. Baseline characteristics of study population, according to echocardiographic response to CRT

| | All patients (n=138) | Non-responders (n=42) | Responders (n=96) | p value |
|---|---|---|---|---|
| Age (years) | 68±8 | 70±9 | 67±8 | 0.05 |
| Male gender, n (%) | 96/138 (70%) | 29/42 (69%) | 67/96 (70%) | 0.93 |
| Ischemic, n (%) | 71/138 (51%) | 30/42 (71%) | 41/96 (43%) | 0.002 |
| Non-ischemic, n (%) | 67/138 (49%) | 12/42 (29%) | 55/96 (57%) | |
| Atrial fibrillation, n (%) | 32/138 (23%) | 10/42 (24%) | 22/96 (23%) | 0.90 |
| Sinus Rhythm, n (%) | 106/138 (77%) | 32/42 (76%) | 74/96 (77%) | |
| LBBB, n (%) | 126/132 (95%) | 38/41 (93%) | 88/91 (97%) | 0.37 |
| RBBB, n (%) | 6/132 (4.5%) | 3/41 (7%) | 3/91 (3%) | |
| QRS duration (ms) | 164±23 | 159 ± 20 | 167±23 | 0.05 |
| NYHA functional class | 2.6±0.5 | 2.6±0.5 | 2.6±0.5 | 0.83 |
| LVEF (%) | 26±7 | 25±6 | 26±7 | 0.52 |
| LV end-diastolic volume (ml) | 147±56 | 150±54 | 146±57 | 0.47 |
| LV end-systolic volume (ml) | 109±46 | 111±43 | 108±48 | 0.47 |
| Systolic blood pressure (mmHg) | 123±18 | 121±19 | 124±17 | 0.20 |
| Diastolic blood pressure (mmHg) | 73±11 | 72±10 | 73±11 | 0.36 |
| Diuretics, n (%) | 110/138 (80%) | 38/42 (91%) | 72/96 (75%) | 0.04 |
| Beta-blocker, n (%) | 117/138 (85%) | 35/42 (83%) | 82/96 (85%) | 0.75 |
| Ace-inhibitors or AT II, n (%) | 102/138 (86%) | 32/42 (85%) | 70/96 (87%) | 0.69 |
| Spironolacton, n (%) | 61/138 (44%) | 23/42 (55%) | 38/96 (40%) | 0.10 |
| Position of LV lead | | | | 0.814 |
| Posterior/postero-lateral | 67% | 64% | 69% | |
| Lateral | 22% | 21% | 22% | |
| Midcardiac vein | 4% | 5% | 4% | |
| Epicardial | 7% | 10% | 5% | |
| Max delay six segments by LS (4-chamber) ms | 196±89 | 191±92 | 198±88 | 0.42 |
| BS-BL delay by LS (4-chamber) ms | 119±92 | 119±88 | 118±95 | 0.82 |
| Max delay six segments by LS (2-chamber) ms | 196±99 | 208±117 | 191±90 | 0.55 |
| BI-BA delay by LS (2-chamber) ms | 93±76 | 99±82 | 90±74 | 0.55 |
| AS-Posterior delay by RS (PSAX) ms | 110±95 | 82±77 | 121±100 | 0.15 |
| Max delay six segments by RS (PSAX) ms | 144±108 | 116±86 | 157±115 | 0.10 |

LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular systolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LS, longitudinal strain; RS, radial strain; BS-BL delay, basal septal-basal lateral delay; BI-BA, basal inferior-basal anterior; AS-P delay, antero-septal-posterior delay; PSAX, parasternal short axis view.

**Table 2**. Baseline characteristics of study population, according to clinical response to CRT

| | All patients (n=138) | Responders (n=114) | Non-responders (n=24) | p value |
|---|---|---|---|---|
| Age (years) | 68±8 | 68±8 | 69±9 | 0.578 |
| Male gender, n (%) | 96/138 (70%) | 80/114 (70%) | 16/24 (67%) | 0.734 |
| Ischemic, n (%) | 71/138 (51%) | 56/114 (49%) | 15/24 (63%) | 0.233 |
| Non-ischemic, n (%) | 67/138 (49%) | 58/114 (51%) | 9/24 (38%) | |
| Atrial fibrillation, n (%) | 32/138 (23%) | 27/114 (24%) | 5/24 (21%) | 0.764 |
| Sinus Rhythm, n (%) | 106/138 (77%) | 87/114 (76%) | 19/24 (79%) | |
| LBBB, n (%) | 126/132 (95%) | 104/108 (96%) | 22/24 (92%) | 0.299 |
| RBBB, n (%) | 6/132 (5%) | 4/108 (4%) | 2/24 (8%) | |
| QRS duration (ms) | 164±23 | 165±23 | 160±23 | 0.314 |
| NYHA functional class | 2.6±0.5 | 2.6±0.5 | 2.6±0.5 | 0.637 |
| LVEF (%) | 26±7 | 26±7 | 25±7 | 0.587 |
| LV end-diastolic volume (ml) | 147±56 | 145±51 | 156±76 | 0.931 |
| LV end-systolic volume (ml) | 109 ± 46 | 108±43 | 115±60 | 0.882 |
| Systolic blood pressure (mmHg) | 123±18 | 124±18 | 117±17 | 0.045 |
| Diastolic blood pressure (mmHg) | 73±11 | 73±11 | 71±11 | 0.542 |
| Diuretics, n (%) | 110/138 (80%) | 89/114 (78%) | 21/24 (88%) | 0.296 |
| Beta-blocker, n (%) | 117/138 (85%) | 98/114 (86%) | 19/24 (79%) | 0.399 |
| Ace-inhibitors or AT II, n (%) | 102/138 (86%) | 85/114 (87%) | 17/24 (85%) | 0.687 |
| Spironolacton, n (%) | 61/138 (44%) | 47/114 (41%) | 14/24 (58%) | 0.125 |
| Position of LV lead | | | | 0.73 |
| Posterior/postero-lateral | 67% | 65% | 68% | |
| Lateral | 22% | 21% | 22% | |
| Midcardiac vein | 4% | 6% | 3% | |
| Epicardial | 7% | 9% | 6% | |
| Max delay six segments by LS (4-chamber) ms | 196±89 | 205±90 | 156±70 | 0.010 |
| BS-BL delay by LS (4-chamber) ms | 119±92 | 125±98 | 90±58 | 0.236 |
| Max delay six segments by LS (2-chamber) ms | 196±99 | 193±98 | 213±102 | 0.358 |
| BI-BA delay by LS (2-chamber) ms | 93±76 | 91±74 | 104±84 | 0.507 |
| AS-Posterior delay by RS (PSAX) ms | 110±95 | 111±99 | 104±78 | 0.915 |
| Max delay six segments by RS (PSAX) ms | 144±108 | 146±110 | 136±101 | 0.780 |

All abbreviations explained in Table 1.

## RESULTS

### Baseline characteristics

Of the 160 patients initially included, 22 patients were excluded because of poor quality of the echocardiographic images. Therefore, 138 patients were eventually analyzed. The baseline parameters of the study population according to echocardiographic and clinical response to CRT are summarized in Tables 1 and 2. Mean age was 68±8 years with 70% male gender. 59% had functional class 3 heart failure. Mean QRS duration was 164±23 ms and mean LV EF was 26±7% with 51% ischemic etiology. All patients had optimal medical therapy, including angiotensin-converting enzyme or angiotensin-receptor antagonist (86%), beta-blockers (85%), diuretics (80%) and spironolactone (44%) at maximally tolerated dosages. There were no differences in age and etiology of cardiomyopathy between patients with and without atrial fibrillation. Patients with atrial fibrillation were more often male ($p=0.01$). Furthermore, the QRS duration was significantly shorter in patients with atrial fibrillation compared to sinus rhythm (151±21 ms versus 169±22 ms, $p<0.001$). Only one time-based LV dyssynchrony index, i.e., maximal delay between six segments by longitudinal strain, showed at baseline a significant difference between patients with and without atrial fibrillation (170±80 ms versus 204±90 ms, respectively, $p=0.02$).

### Echocardiography

2484 segments were evaluated using longitudinal strain and radial strain analysis, 310 (12.5%) segments were excluded from analysis because of non-valid tracking or poor 2D images. The inter- and intra-observer variability for the LV dyssynchrony measurements were assessed in 10 randomly selected patients. Intra class correlation for inter-observer variability was 0.71 and 0.68 for intra-observer variability.

### Response to CRT

Long-term echocardiographic follow-up was performed at 22±8 months. According to the predefined echocardiographic criterion of a reduction in LVESV $\geq$15%, 96 (70%) patients were classified as responders to CRT and 42 (30%) as non-responders. Of these 42 non-responders, 30 (71%) had an ischemic cardiomyopathy. 114 patients (83%) survived without heart failure hospitalization and were classified as clinical responders to CRT, 24 patients (17%) died or were hospitalized with heart failure and were classified as clinical non-responders to CRT. During follow-up, there were no significant differences in LVEF and numbers of clinical events between patients with baseline atrial fibrillation compared to sinus rhythm. LVEF was 38±13% in patients with atrial fibrillation and LVEF was 39±13% in

patients with sinus rhythm (p=0.51). Death or heart failure hospitalization was observed in 16% of patients with atrial fibrillation and in 18% of patients with sinus rhythm (p=0.76).

**Effects of CRT on echocardiographic parameters**

During follow-up, responders to CRT showed a significant reduction in end-systolic and diastolic LV volumes compared with non-responders. LVESV, decreased from 108±48 ml to 60±33 in responders to CRT (p<0.001) and in non-responders LVESV did not change significantly (LVESV 111±43 ml at baseline versus 120±41 ml during follow-up, p=0.1). Furthermore, a significant improvement in LVEF was noted in responders to CRT compared with non-responders, i.e., LVEF increased from 26% ±7 to 45% ±10 in the responder group (p<0.001), whereas LVEF did not change significantly in the non-responder group (LVEF 25% ±6 at baseline versus LVEF 26% ±6 during follow-up (p=0.25).

**Effects of CRT on clinical outcome**

Clinical outcome was assessed after a mean follow-up of 42±8 months. During follow-up 24 clinical events occurred (13 patients died and 15 were hospitalized due to worsening heart failure). Four patients who died had also been hospitalized due to heart failure during follow-up. Total mortality was 9.4% (13 patients); 6 (6.5%) patients in echocardiographic responders and 7 (16.7%) patients in non-responders (p=0.064). In the entire population, a significant improvement in clinical status was noted, with a significant reduction in NYHA functional class from 2.6±0.5 to 1.78±0.71 (p<0.001). During follow-up, the NYHA class in the responder group was 1.7±0.7 versus 2.0±0.6 in the non-responder group (p=0.03).

**Table 3**. Uni- and multivariate predictors of echocardiographic response to CRT

| | Univariate analysis | | | Multivariate analysis [a] | | |
|---|---|---|---|---|---|---|
| | OR | 95%CI | p value | OR | 95%CI | p value |
| Max delay six segments by LS 4-chamber (per 10 ms) | 1.01 | 0.97−1.05 | 0.676 | | | |
| QRS duration (ms) | 1.02 | 1.00−1.04 | 0.049 | | | |
| Non-ischemic etiology | 3.35 | 1.53−7.33 | 0.002 | 3.386 | 1.515−7.571 | 0.003 |
| LVEF | 1.03 | 0.97−1.08 | 0.349 | | | |

[a] Maximal delay between six segments by LS adjusted for QRS duration, LVEF at baseline and ischemic/non-ischemic etiology.

**Table 4**. Uni- and multivariate predictors of clinical response to CRT

| | Univariate analysis | | | Multivariate analysis [a] | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | p value | HR | 95% CI | p value |
| Max delay six segments by LS 4-chamber (per 10 ms) | 0.94 | 0.89−0.99 | 0.020 | 0.93 | 0.890−0.991 | 0.02 |
| QRS duration (ms) | 0.99 | 0.97−1.01 | 0.273 | | | |
| Non-ischemic etiology | 0.61 | 0.27−1.39 | 0.239 | | | |
| LVEF | 0.98 | 0.93−1.04 | 0.566 | | | |

[a] Maximal delay between six segments by LS adjusted for QRS duration, LVEF at baseline and ischemic/non-ischemic etiology.

**Baseline speckle tracking indices and echocardiographic response**

In univariate logistic regression analysis, QRS duration and non-ischemic etiology were significantly associated with response to CRT (Table 3). In multivariate logistic regression analysis, non-ischemic etiology independently predicted the echocardiographic response to CRT, after adjustment for confounders (Table 3). Maximal delay between six segments LS failed in both uni-and multivariate analysis to predict echocardiographic response.

**Baseline speckle tracking indices and clinical response**

The maximal delay between six segments LS was significantly longer in responders compared to non-responders (205±90 ms versus 156±70 ms, p=0.01, respectively), see Table 2. In univariate Cox regresssion analysis, this dyssynchrony index was significantly associated (p=0.02) with the time until the composite endpoint of death and heart failure hospitalization (Table 4). Also, in multivariate Cox regresssion analysis this index independently predicted the time until the composite endpoint, after adjustment for confounders (Table 4). Receiver operating characteristic curve analysis was performed to define the optimal cut-off value for maximal delay between six segments to predict the clinical response. The area under the curve for this index was 0.67 (CI 0.55−0.79), and the optimal cut-off value to predict clinical response to CRT was 154 ms, yielding a sensitivity and specificity of, respectively, 63% and 69% (Figures 2 and 3). Stratified analyses were performed in ischemic and non-ischemic cardiomyopathy patients. The max delay six segments at baseline was not different between ischemic and non-ischemic patients (197±90 ms versus 195±88 ms, p=0.97). Moreover, the association between max delay six segments and both echocardiographic and clinical response were identical in the ischemic and non-ischemic group (adjusted OR 1.01 and 0.94, respectively). Due to the smaller sample sizes, the association between max delay six segments and clinical response was statistically not significant in neither the ischemic nor non-ischemic group.

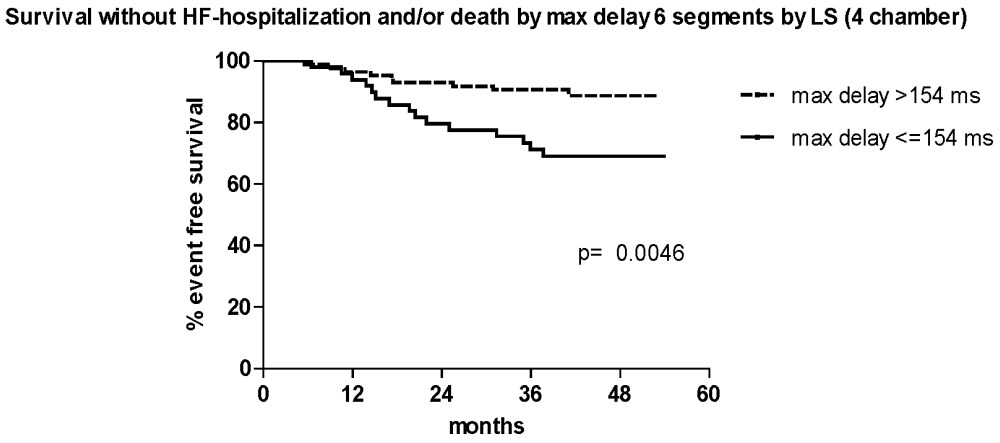


**Figure 2.** Survival without hospitalization due to worsening of heart failure in 138 patients treated with CRT according to maximal delay between six segments measured at baseline with speckle tracking LS.

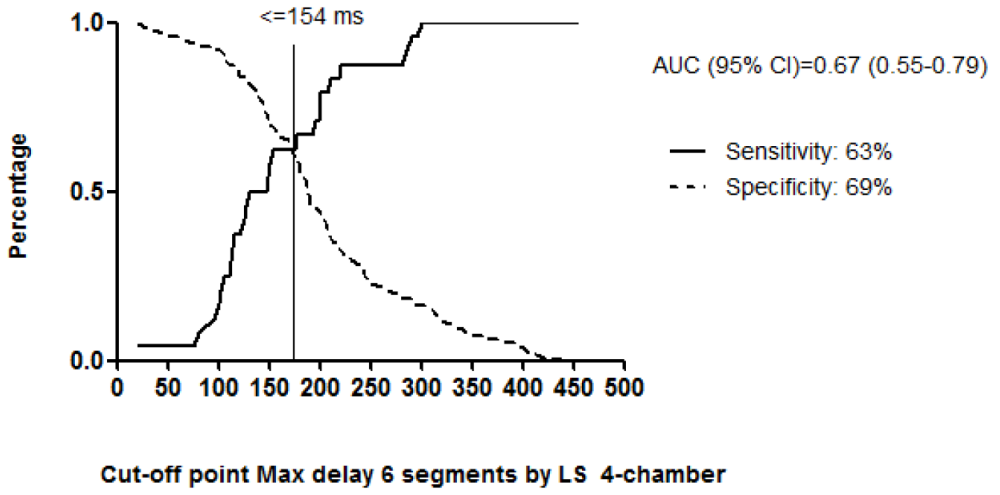


**Figure 3**. Receiver operating characteristics curves for maximal delay six segments by LS. AUC, area under the curve.

**Table 5**. Maximal delay between six segments as measured by longitudinal strain by 2x2 table

| | Clinical response | Clinical non-response | p value | Total number |
|---|---|---|---|---|
| Echocardiographic response | 202±87 ms n=82 | 168±94 ms n=11 | 0.24 | 93 |
| Echocardiographic non-response | 212±101 ms n=28 | 147±43 ms n=13 | 0.02 | 41 |
| p value | 0.856 | 0.865 | | |
| Total | 110 | 24 | | 134 |

**Association between degree of dyssynchrony and outcome**

We demonstrated that in patients with echocardiographic and clinical non-response the maximal delay between six segments was significantly shorter compared to patients with echocardiographic non-response and clinical response (147 vs 212 ms, p=0.02). However, in the group of echocardiographic responders, the maximal delay between six segments was not significantly different between the clinical responders and non-responders (Table 5).

**Prediction of response to CRT in sinus rhythm**

Stratified analyses of the prediction by speckle tracking imaging of either echocardiographic or clinical response to CRT in patients with sinus rhythm did not change the previous finding. In patients with sinus rhythm, there was only an association between maximal delay between six segments in 4-chamber view and clinical response to CRT (after adjustment, HR 0.92, CI 0.87−0.98, p=0.009).

## DISCUSSION

In the present study we assessed the association of baseline longitudinal and radial strain measures with echocardiographic and clinical response to CRT. This is, to our knowledge, one of the largest study populations described at present. We demonstrated that the maximal delay between six segments measured with longitudinal strain in 4-chamber view, was significantly associated with clinical response to CRT. The cut-off value for this maximal delay between six segments in 4-chamber view was 154 ms, with relatively low sensitivity and specificity (63% and 69%, respectively). The six indices that measure the time to maximal deformation of certain segment failed to show a significant and consistent

association with echocardiographic response to CRT. In the current study, we used two imaging techniques, longitudinal and radial strain, to visualize the deformation pattern of the left ventricle in three different ways. The longitudinal strain in apical 4-chamber view visualizes the septal and lateral wall of LV and may identify better the early and late activated segments as expected in left bundle branch block (LBBB). Because the electric signal conducts in diffuse manner in LBBB, both early and late activated segments can be seen in both the longitudinal and short axis view. The radial strain especially visualizes the mid-portion of the LV; however, the apical and basal regions of the LV are difficult to visualize in this view.

In current study, the dyssynchrony indices which visualized only small portion of LV like BS-BL delay, BI-BA delay, AS-P delay failed to predict the response to CRT. The maximal delay in apical 4-chamber view, as assessed in this study, is able to identify early and late segments with maximal deformation and therefore predicts response to CRT. One of the major limitations of time-based indices assessed with speckle tracking is that it measures the timing of maximal deformations. It does not provide information whether this is an active contraction or passive contraction. The value of several 2D speckle tracking imaging techniques were studied in the assessment of ventricular dyssynchrony and its relationship with CRT response and showed varying results. In our study, time-differences between predefined segments measured with longitudinal strain did not predict echocardiographic response to CRT. Our findings are in line with most previous studies [7,10,15,16). One reason for these varying findings between the studies could be that longitudinal and radial strain was assessed in different ways. In present study, we measured the time to peak strain while other studies measured the time to peak systolic strain. In some studies [7,15] the longitudinal and radial strain have been used to determine the timing of maximal strain but in other studies the longitudinal, radial and circumferential strain were used to calculate the average difference between peak and end-systolic strain to predict response to CRT [16]. In one study [16], the strain dyssynchrony index (SDI) assessed with combined longitudinal, radial and circumferential strain could predict both short and long-term outcome after CRT while the baseline values of time delay (measured with longitudinal strain) between basal-septal and basal-lateral segments, time-difference between early- and late-activated segments and time-delay between two opposite walls (septal to lateral) could not predict long-term response to CRT. Our findings confirm a portion of the latter results. Another reason for these varying findings between the studies could be the different endpoints. The majority of studies defined 6 months echocardiographic response as endpoint [7,16] and other studies defined echocardiographic and clinical outcome as endpoints [9,13]. In the current study, echo-cardiographic response was assessed at mean 22±8 months which might be very long and may explain the different results to previous studies [7,9].

Although, several data are available about the predictive value of radial strain on echocardiographic response to CRT, they show conflicting results [7,10,15,16]. In the present study LV dyssynchrony measured by radial strain was unable to predict response to CRT. One study [10] demonstrated that radial strain could not predict response to CRT. More data on the predictive value of radial strain were provided by Delgado et al. [7]. They demonstrated that AS-P delay $\geq$130 ms measured by radial strain could predict acute and long-term response to CRT with good sensitivity (83−90%) and specificity (75−80%). However, more recently, Miyazaki et al. [15] demonstrated in a large prospective study that radial strain was unable to predict the reverse remodeling or clinical response to CRT. The STAR study [9] demonstrated that radial strain was able to predict LVEF response with 86% sensitivity and 67% specificity. The most recent trial, EchoCRT trial [17], studied the benefit of CRT in patients with chronic heart failure and narrow QRS. For the assessment of LV dyssynchrony several echocardiographic techniques including radial strain were used. These echo parameters did not predict the clinical response to CRT. Our current data demonstrate that radial strain was not able to predict echocardiographic or clinical response to CRT.
The time-based dyssynchrony measurement, which looks only at the timing of deformation of a certain segment, provides only information about the timing of maximal deformation of certain segment and does not provide any information about stretching of the opposite segment. Therefore, time-based measurement may not be very important for the assessment of dyssynchrony as we demonstrated in this study. It is conceivable that the opposite wall motion pattern, which looks at the possible stretching of one wall when the opposite wall is contracting almost at the same time, may be more important in prediction of CRT to response, as it provides both mechanical and timing information. However, more research is needed to delineate these issues.

In patients with atrial fibrillation, echocardiographic measurements, including speckle tracking analysis, may be more difficult. This study included 23% patients with atrial fibrillation and showed that although the QRS duration at baseline is significantly smaller in patients with baseline atrial fibrillation, the echocardiographic and clinical response to CRT was comparable to patients with sinus rhythm. However, we could not perform stratified analyses in patients with atrial fibrillation, because the number of included patients with atrial fibrillation was too small. Future studies including more patients with atrial fibrillation should answer whether maximal delay between six segments measured with longitudinal strain in 4-chamber as measured by spackle tracking has predictive value in these patients. A previous study [18] assessed the position of LV lead and demonstrated that the extent of cardiac resynchronization therapy benefit was similar for leads in the anterior, lateral or posterior position. However, the apical lead location was associated with a significantly increased risk

for heart failure/death. Also, in our study there was no association between lead position and neither clinical nor echocardiographic response. Unfortunately, we have no data on apical versus basal position of the LV lead.

**Potential clinical implications**

The maximal delay between six segments measured with longitudinal strain in 4-chamber view may be helpful in prediction of clinical response to CRT. Besides, we demonstrated that radial strain in prediction of response to CRT is not useful.

**Future study**

Time-related indices use simply the time to maximal strain or deformation of certain segments and do not provide sufficient information about the synchrony of global deformation. Visualization of other elements of the contraction pattern by speckle tracking may provide additional information about dyscoordination of certain segments which could be corrected by CRT [19]. Segmental differences in time to the start of strain, or segmental differences in duration of strain could be related to CRT response. Speckle tracking dyssynchrony measures could be expressed for the specific regions where first activation from RV and LV leads (are expected to) take place. Apical rocking and septal rebound stretch [20,21] are reported as measures that provide more information regarding LV global dyscoordination and their relationship with radial and longitudinal strain indices should be assessed.

**Strengths and Limitations**

The present study is a retrospective analysis of a large single-center cohort of consecutive patients treated with CRT. We realize that retrospective analysis is inferior to prospective investigations with pre-specified endpoints and cut-off values. The data were, however, collected systematically by independent physicians. Furthermore, echocardiograms were analyzed and validated by independent cardiologists. A substantial number (n=22) of patients were excluded from analysis because of poor imaging quality and 12.5% of evaluated segments were excluded from analysis because of poor quality [6,15]. Contrary to most other studies, and because of our long-term follow-up, we provided not only echocardiographic outcome measures, but also clinical endpoints, such as death and heart failure hospitalization. We realize that the number of endpoints is relatively small, and we are careful with the interpretation of results. Scar tissue is an important issue in the prediction of CRT response. The most reliable imaging modality to assess scar tissue is cardiac MRI. Unfortunately we did not perform a cardiac MRI before CRT implantation in our study population. Assessment of

scar tissue by echocardiography has some limitations due to poor image quality. Therefore, we have not collected data on scare tissue in our study population.

## CONCLUSION

We assessed six different time-based LV dyssynchrony indices measured with speckle tracking longitudinal and radial strain and demonstrated that only maximal delay between six segments in 4-chamber view measured with LS was significantly longer in clinical responders to CRT. The value of time-based peak speckle tracking measurements to predict clinical and echocardiographic response to CRT seems to be limited.

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CHAPTER 5

# Are changes in the extent of left ventricular dyssynchrony as assessed by speckle tracking associated with response to cardiac resynchronization therapy?

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## ABSTRACT

***Purpose*:** Echocardiographic assessment of left ventricular (LV) dyssynchrony is used to predict response to cardiac resynchronization therapy (CRT). However, the association between reduction in the extent of speckle tracking based LV dyssynchrony and echocardiographic response to CRT has not been explored yet. The aim of this study was to assess the changes in the extent of LV dyssynchrony as a result of CRT and its association with echocardiographic response to CRT in a large consecutive series of patients.

***Methods*:** We studied 138 patients with standard CRT indication. Time-based speckle tracking longitudinal strain (maximal delay between six segments in 4-chamber view) was performed to assess LV dyssynchrony at baseline and after a mean follow-up of 22±8 months. Echocardiographic CRT response was defined as a reduction in LV end-systolic volume ≥15%.

***Results*:** Mean age was 68±8 years (30% female). Mean LV ejection fraction (LVEF) was 26±7%. Ninety-six patients (70%) were classified as echocardiographic responders. In the total study group, LV dyssynchrony decreased from 196±89 ms at baseline to 180±105 ms during follow-up, p=0.01. Of note, in responders there was a pronounced reduction in LV dyssynchrony (198±88 ms at baseline versus 154±50 ms after CRT, p<0.001), whereas in non-responders there was a significant increase (191±92 ms at baseline versus 243±160 ms after CRT, p=0.04). After multivariate analysis, decreased in LV dyssynchrony, wider QRS duration and non-ischemic etiology were independently and significantly associated with CRT response.

***Conclusion*:** Changes in the extent of LV dyssynchrony as measured by speckle tracking after CRT are independently associated with response to CRT.


## INTRODUCTION

Several landmark trials have demonstrated that cardiac resynchronization therapy (CRT) reduces symptoms, mortality, heart failure hospitalization and reverses the ventricular remodeling in 50−70% of patients with symptomatic heart failure and reduced left ventricular ejection fraction (LVEF ≤35%) with wide QRS [1−5]. Selection of patients who benefit from CRT is of major importance, and 2D speckle tracking echocardiography may be helpful in the selection of patients for CRT [6−8]. Although previous studies showed that LV dyssynchrony before CRT as measured by time-based speckle tracking was associated with better long-term survival and could predict improvement of LV ejection fraction (LVEF) after CRT, the definite role of speckle tracking for patient selection in CRT candidates is still not established.

One of the important purposes of CRT is reduction of dyssynchrony and thereby improving LVEF. Previous studies demonstrated an average increase in LVEF in the range of 3−11% after CRT [5,9,10]. Significant reduction in the amount of dyssynchrony as result of CRT, measured as the longest intraventricular delay between six basal LV segments, was related to 'superior response' to CRT [10]. CRT significantly reduced LV dyssynchrony measured by longitudinal and radial speckle tracking in CRT responders compared to CRT non-responders [11]. Most reports relate baseline LV dyssynchrony to CRT response. However, data regarding the changes in LV dyssynchrony assessed by time-based speckle tracking imaging, and its association with long-term CRT response are sparse [10−12]. The aim of the current study was to evaluate the CRT-induced changes in the extent of LV dyssynchrony as measured with time-based speckle tracking. Furthermore, we investigated the relationship between CRT-induced LV dyssynchrony changes with response to CRT in a large cohort of patients treated with CRT for chronic heart failure.

## METHODS

### Selection of patients

From January 2008 to December 2009, 160 consecutive patients with chronic heart failure (New York Heart Association functional class II-IV), LVEF $\leq$35% and wide QRS complex $\geq$120 ms with LBBB, RBBB or IVCD (intra-ventricular conduction delay) who were scheduled for primary CRT-D (cardiac resynchronization therapy with defibrillator) implantation, were included in the present study. Retrospective data collection was approved by the hospital ethics committee, and patients gave written informed consent. Patients with CRT-P (cardiac resynchronization therapy with pacemaker), pre-implantation LVEF >35% according to echocardiographic data, recent myocardial infarction (<3 months) or decompensated heart failure were excluded. Etiology was considered ischemic in the presence of significant coronary artery disease ($\geq$50% stenosis in one or more of the major epicardial coronary arteries) and/or history of myocardial infarction or prior revascularization by PCI or CABG. The patients who died before follow-up echocardiography were excluded from the study. The QRS duration was calculated from the 12-lead ECG. Conventional criteria for LBBB was used which include QRS duration $\geq$120 ms, QS or rS in lead V1, and a monophasic R wave in with no Q waves in leads V6 and I. All patients were on optimal medical therapy, including angiotensin-converting enzyme inhibitors and beta-blockers.

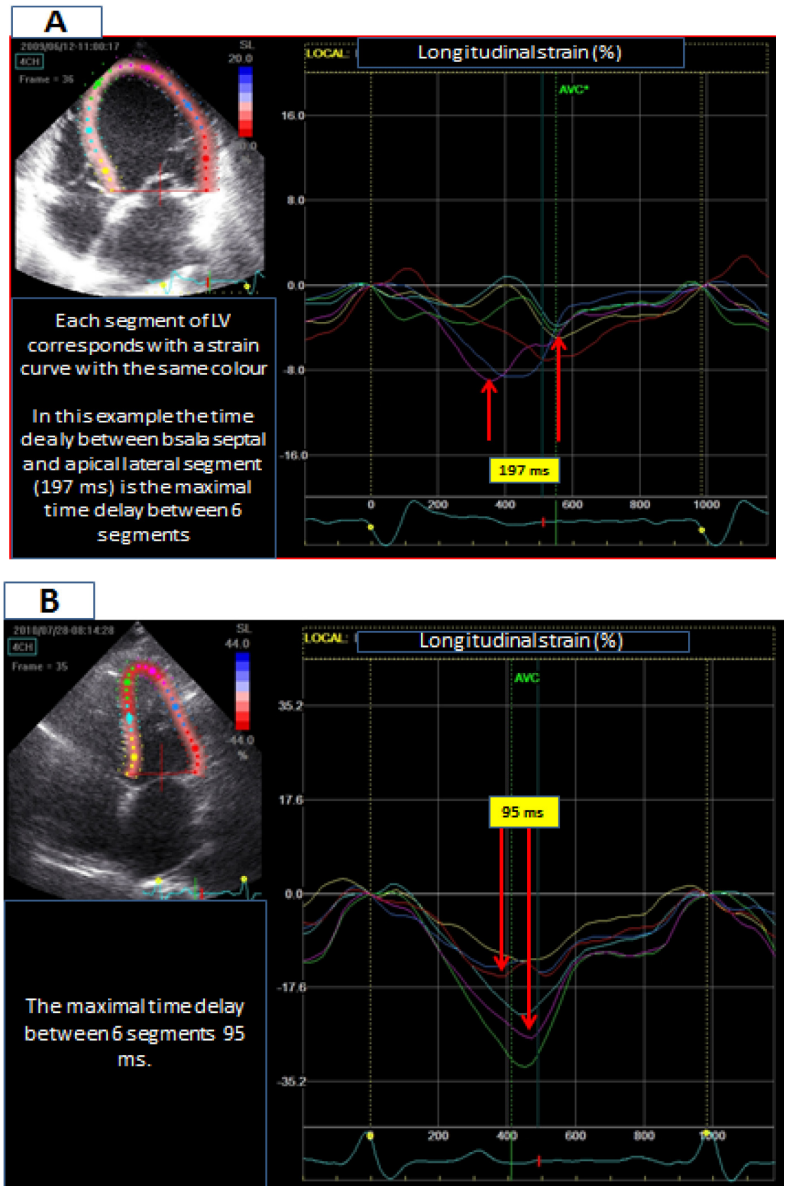


**Figure 1.** An example of speckle tracking longitudinal strain analysis demonstrating LV dyssynchrony in 4-chamber view. (**A)** Baseline LV dyssynchrony is shown as maximal time-delay between six segments 197 ms. (**B)** The same patient defined as responder to CRT**.** LV dyssynchrony measured as maximal time-delay between 6 segments decreased from 197 ms at baseline to 95 ms after CRT.

**The study protocol and echocardiographic data acquisition**

All patients underwent 2D echocardiography prior to biventricular ICD implantation and at follow-up in the second year after CRT implantation. The images were obtained on a Vivid 7 ultrasound machine (General Electric, Milwaukee, WI) using a 3.5 MHz transducer at a depth of 16 cm in the parasternal (long- and short axis) and apical (2- and 4-chamber) views. The images were stored in cine-loop format by well-trained echocardiographists and speckle tracking analysis was performed offline by an independent cardiologist who was not involved in the study. The left ventricular end-diastolic diameter (LVEDD), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic diameter (LVESD) and left ventricular end-systolic volume (LVESV) were measured and the LVEF was calculated using Simpson's technique [13].

**Left ventricular dyssynchrony measurements with 2D-speckle tracking longitudinal strain imaging**

Recently we assessed the predictive value of baseline speckle tracking measurements on response to CRT [14]. We demonstrated that baseline maximal delay between six segments assessed in 4-chamber view with longitudinal strain as the only LV dyssynchrony parameter that independently was associated with clinical response to CRT. Therefore, in the present study we chose for this LV dyssynchrony parameter to assess the CRT-induced changes in the extent of LV dyssynchrony and its relationship with echocardiographic response to CRT. The analysis was performed using EchoPac version 7.0.1, General Electric. The acquisition of the 2D images is performed with at least 40 fps to allow for proper speckle tracking analysis off line. The endocardial border was manually traced by a point-and-click approach and the region-of-interest width was manually adjusted to include the entire myocardium. The software then automatically traced and accepted segments of good tracking quality and rejected poorly tracked segments and allowed the user to manually over-ride its decisions using visual assessments. We used longitudinal strain imaging technique in 4-chamber view to visualize the timing of maximal deformation in each segment of septal and lateral wall. To determine the timing of maximal deformation of three septal segments (basal, mid and apical) and three lateral segments (apical, mid and basal) we measured the time from QRS onset to peak longitudinal strain during entire cardiac cycle for six separate segments (basal-septal, mid-septal, septal-apical, lateral-apical, mid-lateral and basal-lateral walls). Subsequently, the time delay between earliest and the latest segments with peak strain were determined, i.e., maximal time delay between the six segments in 4-chamber view (Figure 1). The off-line analysis was performed on digitally stored images by an independent observer (A.G.) blinded to the clinical and other echocardiographic information. All speckle tracking LV dyssynchrony indices measures were additionally performed by another independent, well

trained and experienced cardiologist (P.P.D.). Furthermore, these measurements were repeated by the first observer, in order to assess inter-observer and intra-observer variability. Inter-observer and intra-observer variability was expressed as intra-class correlation coefficients. Values higher than 0.8 are considered as excellent, values between 0.6 and 0.8 as good, values between 0.4 and 0.6 as moderate, and values below 0.4 as poor concordance [15]

**Definition of response to CRT**

Echocardiographic Response to CRT was defined as a reduction of ≥15% in LV end-systolic volume (LVESV) at the second year of follow-up [10,16−18].

**Statistical analysis**

Statistical analysis was performed using SPSS statistical software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) and SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). Continuous variables are expressed as mean±SD and a non-parametric Mann-Whitney U-test was used to analyze differences between groups. Categorical variables are presented as number and percentages and the Chi-squared test was used to analyze differences between groups. Paired observations (observations of the same variable at different time points) were analyzed using the non-parametric Wilcoxon test. Analysis of variance was used to analyze whether the change in LV dyssynchrony index was different between responders and non-responders and whether other variables (age, gender, LVEF at baseline, QRS width, LBBB/RBBB, non-ischemic/ ischemic etiology) were confounders or effect-modifiers of this relationship. In case of unequal variances between groups, the Satterthwaite test was calculated. Logistic regression analysis was performed to investigate whether a change in LV dyssynchrony index was associated with echocardiographic response. In the multivariate logistic regression analysis the relationship between the LV dyssynchrony parameter and echocardiographic response was analyzed after adjustment for clinical variables (age, gender, LVEF at baseline, QRS width, LBBB/RBBB, non-ischemic/ischemic cardiomyopathy). p values of $<0.05$ were considered statistically significant in all analyses.

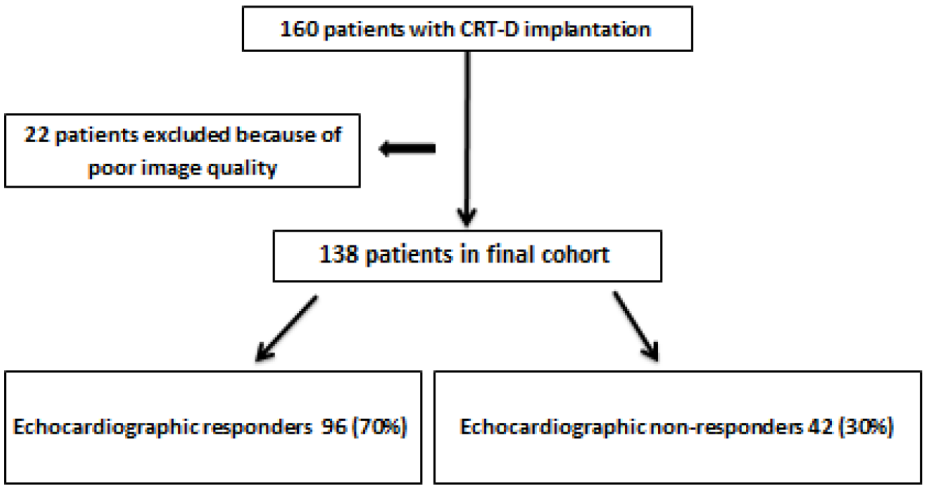


**Figure 2.** Flowchart of study population.

## RESULTS

### Baseline characteristics

Of the 160 patients initially included, 22 patients were excluded because of poor image quality (Figure 2). Therefore, 138 patients were eventually analyzed. Mean age was 68±8 years, 70% was male. 59% had functional class 3 heart failure. Mean QRS duration was 164±23 ms and mean EF was 26±7% with 51% ischemic etiology. The patients who died before follow-up echocardiography were excluded from the study. All patients had optimized medical therapy, including angiotensin-converting enzyme or angiotensin-receptor antagonist (86%), beta-blockers (85%), diuretics (80%) and spironolactone (44%) at maximally tolerated dosages. Using longitudinal strain analysis 1656 segments were evaluated, 207 (12.5%) segments were excluded from analysis because of non-valid tracking or poor 2D imaging. The inter- and intra-observer variability for the LV dyssynchrony measurements were assessed in 10 randomly selected patients. Intra class correlation coefficient for inter-observer variability was 0.71 and 0.68 for intra-observer variability.

**Table 1.** Baseline characteristics according to response to CRT

| | All patients (n=138) | Non-responders (n=42; 30%) | Responders (n=96; 70%) | p value |
|---|---|---|---|---|
| Age (years) | 68±8 | 70±9 | 67±8 | 0.05 |
| Male gender | 70% | 69% | 70% | 0.93 |
| Ischemic | 51% | 71% | 43% | 0.002 |
| Atrial fibrillation | 23% | 24% | 23% | 0.90 |
| LBBB (complete LBBB + IVCD) | 95% | 93% | 97% | 0.37 |
| RBBB | 5% | 7% | 3% | |
| QRS duration (ms) | 164±23 | 159±20 | 167±23 | 0.05 |
| NYHA functional class | 2.6±0.5 | 2.6±0.5 | 2.6±0.5 | 0.83 |
| LVEF (%) | 26±7 | 25±6 | 26±7 | 0.52 |
| LV end-diastolic volume (ml) | 147±56 | 150±54 | 146±57 | 0.47 |
| LV end-systolic volume (ml) | 109±46 | 111±43 | 108±48 | 0.47 |
| Position of LV lead | | | | 0.814 |
| Posterior/postero-lateral | 67% | 64% | 69% | |
| Lateral | 22% | 21% | 22% | |
| Mid-cardiac vein | 4% | 5% | 4% | |
| Epicardial | 7% | 10% | 5% | |

Abbreviations: LBBB, left bundle branch block; RBBB, right bundle branch block; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; IVCD, intra-ventricular conduction delay.

**Response to CRT**

Long-term echocardiographic follow-up was performed at 22±8 months after CRT-D implantation. According to the predefined echocardiographic criterion of a reduction in LVESV $\geq$15%, 96 (70%) patients were classified as responders to CRT and 42 (30%) as non-responders. Differences in baseline parameters between responders and non-responders are summarized in Table 1. Younger age, non-ischemic cardiomyopathy and wider QRS duration were significantly associated with response to CRT. Mean LVEF in responders increased from 26±7% at baseline to 45% ±10 during follow-up ($p<0.001$), whereas in non-responders there were statistically no significant changes in LVEF ($p=0.24$). In univariate analysis, QRS duration, non-ischemic etiology and maximal delay between six segments in 4-chamber view were significantly associated with response to CRT.

**Table 2**. LV dyssynchrony measured by maximal delay between six segments at baseline and after CRT in several subgroups and differences in changes between these subgroups

| | Baseline | Follow-up | Change (mean ± SD) | p value |
|---|---|---|---|---|
| Responders | 198±88 | 154±50 | -43±101 | <0.001 |
| Non-responders | 191±92 | 243±160 | 52±182 | 0.04 |
| Age <68 | 203±93 | 184±124 | -19±154 | 0.04 |
| Age >68 | 189±83 | 176±80 | -13±119 | 0.14 |
| Male | 183±83 | 176±110 | - 7±139 | 0.12 |
| Female | 224±95 | 189±91 | -35±132 | 0.04 |
| Ischemic etiology | 196±90 | 189±117 | -7±155 | 0.20 |
| Non-ischemic etiology | 195±87 | 171±89 | -24±118 | 0.03 |
| Atrial fibrillation | 169±80 | 165±66 | -4±96 | 0.68 |
| Sinus rhythm | 203±90 | 185±113 | -18±148 | 0.01 |
| LBBB (complete LBBB + IVCD) | 200±89 | 181±107 | -19±139 | 0.006 |
| Without LBBB | 136±41 | 186±78 | 50±98 | 0.50 |
| QRS duration ≥150 ms | 202±92 | 189±113 | -12±147 | 0.03 |
| QRS duration <150 ms | 174±74 | 152±62 | -21±102 | 0.18 |
| LVEF <26% | 206±95 | 171±78 | -35±119 | 0.01 |
| LVEF ≥26% | 186±81 | 188±123 | 2±150 | 0.25 |
| Baseline NYHA class 1 or 2 | 204±91 | 174±72 | -30±127 | 0.05 |
| Baseline NYHA class 3 | 190±86 | 184±122 | -6±144 | 0.11 |
| LVESV <100 ml | 180±77 | 164±66 | -16±103 | 0.10 |
| LVESV ≥100 ml | 211±96 | 196±131 | -16±167 | 0.06 |
| LVEDV <135 ml | 182±76 | 165±66 | -16±102 | 0.08 |
| LVEDV ≥135 ml | 209±98 | 195±130 | -13±166 | 0.07 |
| Location of LV lead : | | | | |
| - Posterior/posterolateral/lateral | 196±89 | 182±107 | -13±142 | 0.02 |
| - Mid-cardiac vein | 192±89 | 164±74 | -28±88 | 0.36 |

All abbreviations explained in Table 1.

**Change of LV dyssynchrony during follow-up**

In the total study group, the extent of LV dyssynchrony decreased from 196±89 ms at baseline to 180±105 ms during follow-up, p=0.01. Of note, a significant decrease in the extent LV dyssynchrony was observed in younger patients, females, sinus rhythm, non-ischemic etiology, LBBB, QRS ≥150 ms, LVEF <26%, baseline NYHA 1 or 2, in patients with posterior, posterolateral or lateral position of LV lead and in responders (Table 2). In responders the extent of LV dyssynchrony was decreased significantly, whereas, in non-responders a significant increase in the extent of LV dyssynchrony was observed (Table 2).

**Table 3**. Predictors of response to CRT

| | Univariate | | | Multivariate [a] | | |
|---|---|---|---|---|---|---|
| | OR of response | 95% CI | p value | OR of response | 95% CI | p value |
| Decrease in max delay six segments by LS (4-chamber) (per 10 ms) | 1.06 | 1.02−1.10 | 0.001 | 1.08 | 1.03−1.12 | 0.001 |
| Age | 0.96 | 0.92−1.01 | 0.081 | 0.96 | 0.91−1.01 | 0.144 |
| Male gender | 1.04 | 0.47−2.27 | 0.930 | 2.10 | 0.74−5.93 | 0.162 |
| QRS duration (ms) | 1.02 | 1.00−1.04 | 0.049 | 1.03 | 1.01−1.06 | 0.010 |
| LVEF baseline | 1.03 | 0.97−1.08 | 0.349 | 1.03 | 0.96−1.10 | 0.447 |
| LBBB versus RBBB | 2.32 | 0.45−12.00 | 0.317 | 2.74 | 0.32−23.40 | 0.357 |
| Non-ischemic versus ischemic | 3.35 | 1.53−7.33 | 0.002 | 3.87 | 1.45−10.34 | 0.007 |

[a] Difference in Max delay six segments by LS analyzed after adjustment for age, gender, QRS duration, EF at baseline, LBBB/RBTB and non-ischemic ischemic etiology

After multivariate analysis, adjusting for differences in age, gender, QRS duration, LVEF at baseline, LBBB/RBTB and non-ischemic/ischemic etiology, a decrease in maximal delay between six segments in 4-chamber view was independently and significantly associated with response to CRT (Table 3).

**Difference of changes in maximal delay between six segments in subgroups**

Difference of changes in the extent of LV dyssynchrony was compared in 11 subgroups (responders vs non-responders, male vs female, age >68 vs <68 years, ischemic vs non-ischemic etiology, atrial fibrillation vs sinus rhythm, LBBB vs RBBB, QRS duration >150 ms vs <150 ms, LVEF <26% vs >26% etc.). Only responders to CRT had a significant different change of LV dyssynchrony as compared to non-responders ($p<0.003$). In all other subgroups there was no significant difference of CRT-induced change. ANOVA test was used to investigate whether the significant difference in the LV dyssynchrony changes between responders and non-responders was influenced by either confounding or effect modifying factors. None of these 11 factors were a confounder or effect modifier in relation to the difference of the LV dyssynchrony change between responders and non-responders (Table 4).

**Table 4**. Analysis of variance of the difference between max delay six segments in 4-chamber view before and after CRT

| | | Mean difference max delay | ANOVA p value [a] |
|---|---|---|---|
| | Non-responders | +52 | |
| | Responders | -43 | 0.003 |
| 1 | Age <68 (years) | -19 | |
| | Age >68 (years) | -13 | 0.866 |
| 2 | Male | -7 | |
| | Female | -35 | 0.080 |
| 3 | Ischemic etiology | -7 | |
| | Non-ischemic etiology | -24 | 0.586 |
| 4 | Atrial fibrillation | -4 | |
| | Sinus rhythm | -18 | 0.214 |
| 5 | RBTB | +50 | |
| | LBBB | -18 | 0.442 |
| 6 | QRS duration <150 ms | -21 | |
| | QRS duration ≥150 ms | -12 | 0.923 |
| 7 | EF <26 % | -35 | |
| | EF ≥26 % | +2 | 0.320 |
| 8 | NYHA=1 of 2 | -30 | |
| | NYHA=3 | -6 | 0.775 |
| 9 | LVESV <100 (ml) | -16 | |
| | LVESV ≥100 (ml) | -16 | 0.242 |
| 10 | LVEDV <135 (ml) | -16 | |
| | LVEDV ≥135 (ml) | -13 | 0.351 |
| 11 | lateral/posterior/posterolateral | -13 | |
| | Mid-cardiac vein | -28 | 0.939 |

[a] Because the responder and non-responder groups have unequal variances of difference in max delay the Satterthwaite test is calculated.

None of these 11 factors were a confounder or effect modifier in relation to the difference of the LV dyssynchrony change between responders and non-responders.

## DISCUSSION

This retrospective single center study, describes the CRT-induced changes in LV dyssynchrony in a large cohort of patients. This study assessed the utility of serial longitudinal strain imaging technique to quantify the changes in the extent of LV dyssynchrony in CRT patients. Furthermore, we investigated the association of these changes with response to CRT. This study demonstrates that the reduction of LV dyssynchrony measured with longitudinal strain imaging is independently and significantly associated with echocardiographic response to CRT.

The predictive value of baseline time-based speckle tracking techniques have been investigated [6−8,19−21] and showed conflicting results. Recently, we assessed the predictive value of baseline speckle tracking measurements on response to CRT [15]. We demonstrated that baseline maximal delay between six segments in 4-chamber view measured with longitudinal strain was the only LV dyssynchrony parameter that independently predicted the clinical response to CRT. Only few data [5,6,9,17−18] are available on changes in LV dyssynchrony after CRT. One small-sized study [10] with 37 patients investigated the reduction of dyssynchrony, as measured by IVMD (inter-ventricular mechanical delay) and the longest intraventricular delay between six basal LV segments, and showed a significant reduction in longest intraventricular delay between six basal LV segments in 'super responders' to CRT compared to non-responders. Another small-sized study [17] used two echocardiographic indices measured with longitudinal and radial strain and showed only a significant decrease in CRT responders. In the current study, we used longitudinal strain imaging technique to visualize the deformation pattern of the septal and lateral wall of the left ventricle to measure the maximal delay between six segments. This dyssynchrony parameter showed a significant reduction in the amount of LV dyssynchrony in responders to CRT and showed an increase in the amount of LV dyssynchrony in non-responders. Furthermore, after adjustment for potential confounders, this dyssynchrony parameter was independently associated with CRT response. This means that by every 10 ms reduction in LV dyssynchrony increased the odds ratio of response to CRT (CRT response increased with 8% per 10 ms reduction in the extent of LV dyssynchrony). This relationship increased exponentially after 30 ms reduction in the extent of LV dyssynchrony (Table 3). In current study we demonstrated that the extent of LV dyssynchrony significantly was increased in non-responders to CRT. Patients without LBBB showed increased LV dyssynchrony during follow-up, which may express suboptimal effects of CRT. In the recent years, it has been demonstrated that both LBBB morphology and QRS duration are powerful predictor of CRT response. However, a recent meta-analysis [22] of five randomized trials demonstrated that

QRS duration is a powerful predictor of the effects of CRT on morbidity and mortality and that QRS morphology did not provide additional information. The current study demonstrated that QRS duration is one the predictors of CRT response and is in line with this meta-analysis [22].

**Technical issues of speckle tracking analysis**

There are some difficulties using speckle tracking analysis like frame rates/s, tracing of endocardial border, region of interest and non-valid tracking. Speckle tracking analysis is always offline. Therefore, frame rate should be at least 40 frames/s to allow for reliable operation of software. The endocardial border should be manually traced and the region-of-interest width should be manually adjusted to include the entire myocardium if necessary. Segments of poorly tracked (non-valid tracking) should be rejected which allows the user to over-ride automatic software assessments. Despite these technical issues, speckle tracking is a reliable tool to assess LV dyssynchrony in experienced hands.

**Clinical application of using speckle tracking**

Non-response is an important and unresolved issue in CRT. In this study we demonstrated that speckle tracking analysis at follow-up is one of the methods to assess efficacy of CRT, and can be further helpful to discriminate those with and without response to CRT. The most important benefit of speckle tracking analyzing during follow-up is recognizing of 'non-responders' who require possible more intensive monitoring. Moreover, the effect of AV/VV delay optimization in non-responders can be evaluated by speckle tracking analysis to see whether the extent of LV dyssynchrony decreases after optimization. Speckle tracking has been used prior to implantation to determine the latest activation segments for implantation of left ventricular lead [16]. Speckle tracking has also the potential to be used during the implantation to guide the location of left ventricular lead in order to measure the acute response to CRT. This simultaneous speckle tracking analyzing may minimize the non-responders rate in CRT patients. However, this needs to be investigated in prospective study.

**Limitations**

The present study is a retrospective analysis of a large single-center cohort of consecutive patients treated with CRT. We realize that retrospective analysis is inferior to prospective investigations with pre-specified endpoints and cut-off values. The data were, however, collected systematically by independent physicians. Furthermore, echocardiograms were analyzed and validated by independent cardiologists. In this study, we focused on echocardiographic response to CRT rather than clinical response due to small numbers of clinical events. Intra-class correlation coefficient for reproducibility of LV dyssynchrony was

not excellent in our cohort and variability in assessment of dyssynchrony is one of the most common problems in echocardiography. Non-response to CRT is probably not solely due to insufficient patient selection. Suboptimal LV lead placement must also be considered. However, there were no differences between responders and non-responders regarding the location of LV lead. Also unfavorable pacemaker settings can contribute to non-response to CRT. Unfortunately we were not able to perform systematically echo-guided optimization after device implantation.

## CONCLUSION

We assessed the changes in the extent of LV dyssynchrony using maximal delay between six segments in 4-chamber view measured with time-based speckle tracking longitudinal strain. This LV dyssynchrony parameter showed a pronounced reduction in the extent of LV dyssynchrony in responders and significant increase in non-responders to CRT. Furthermore, the reduction of LV dyssynchrony was independently and significantly associated with response to CRT.

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CHAPTER 6

# Septal rebound stretch as predictor of echocardiographic response to cardiac resynchronization therapy

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## ABSTRACT

***Aim*:** Septal rebound stretch (SRSsept) reflects an inefficient deformation of the septum during systole and is a potential new echocardiographic tool to predict response to Cardiac Resynchronization Therapy (CRT). However, there are only limited data on the potential predictive value of SRSsept on echocardiographic response. We evaluated the predictive value of SRSsept on echocardiographic response to CRT in a large population.

***Methods and results*:** A total of 138 consecutive patients with functional class II−IV heart failure who underwent CRT were studied. Echocardiography was performed at baseline and after a mean follow-up period of 22±8 months. Echocardiographic response to CRT was defined as a reduction in LV end-systolic volume ≥15%. Receiver operating characteristic curve analysis was performed to define the optimal cut-off value for SRSsept. Multivariable analyses were performed to adjust for potential confounders.

Mean age was 68±8 years (30% female). Mean baseline LV ejection fraction was 26±7%, 51% had ischemic etiology. LBBB or LBBB like morphology was present in 95% of patients. Mean SRSsept was 4.4±3.2%, 56% of patients had SRSsept ≥4%. Ninety-six patients (70%) were echocardiographic responders. Baseline SRSsept was significantly higher in responders compared to non-responders (5.1±3.2 vs 3.0±2.7, $p<0.001$). The optimal cut-off value for SRSsept to predict response to CRT was 4.0%. After both univariate (OR 3.74, 95% CI 1.72−8.10) and multivariate analyses (OR 3.71, 95% CI 1.49−9.2), baseline SRSsept >4% independently predicted the response to CRT.

***Conclusions*:** Baseline septal rebound stretch is independently associated with echocardiographic response to CRT.


## INTRODUCTION

Cardiac resynchronization therapy (CRT) has proven effectiveness in the treatment of severe heart failure, improving symptoms and quality of life as well as decreasing mortality in a majority of treated patients [1−5]. Unfortunately, CRT is ineffective in 30−40% of patients and in some cases it can even worsen symptoms [6]. Several echocardiography techniques have been used to aid in patient selection for CRT prior to implantation with promising results in observational single-center trials. However, no ideal echocardiographic approach for the assessment of dyssynchrony has yet been found. The largest prospective trial (PROSPECT) [7] showed poor predictive value of several conventional and tissue Doppler-based echocardiographic methods. In recent years, 2D-speckle tracking echocardiography has been

used to assess left ventricular (LV) dyssynchrony with inconsistent results [8−11]. These time-based mechanical LV dyssynchrony measurements did however not take into account the inefficient regional myocardial deformation during systole, which can be reverted by CRT. Stretching in the septum during systole can be echocardiographically quantified by Septal Rebound Stretch (SRSsept) and is a novel measure for inefficient septal deformation. Although SRSsept has the potential to predict CRT response, only few studies have been performed [12−14]. Moreover, these studies were small sized and had methodological limitations. The aim of our current study was to assess the predictive value of SRSsept on echocardiographic response to CRT in a large study population.

## METHODS

### Selection of patients

From January 2008 to December 2009, 160 consecutive patients with chronic heart failure (New York Heart Association functional class II−IV), LVEF $\leq$35% and wide QRS complex $\geq$120 ms who were scheduled for CRT, were included in the present study. Patients with pre-existent pacemaker or ICD implantations were excluded in order to avoid chronic RV pacing which may affect the assessment of SRSsept. Also patients with a recent myocardial infarction (<3 months) or decompensated heart failure were excluded. Etiology was considered ischemic in the presence of significant coronary artery disease ($\geq$50% stenosis in one or more of the major epicardial coronary arteries) and/or history of myocardial infarction or prior revascularization by PCI or CABG. 22 patients with poor echocardiographic window at baseline were excluded from the analysis (Figure 1). All patients were on optimal medical therapy, including angiotensin-converting enzyme inhibitors and beta-blockers. This prospective registry was approved by the institutional board. Baseline characteristics included age, gender, etiology of heart failure, clinical history, medical therapy, NYHA functional class, ECG and procedural data were collected prospectively and analysed retrospectively. Routine follow-up visits were scheduled at 2 months post implant, and then every 6 months thereafter. The routine follow-up in some of our patients took place in referring hospitals. The clinical status of all survivals at the closure of the study (December 2013) was verified. Data on mortality and hospitalization were collected from reviewing our hospital records, referring hospitals and by contacting general practitioners.

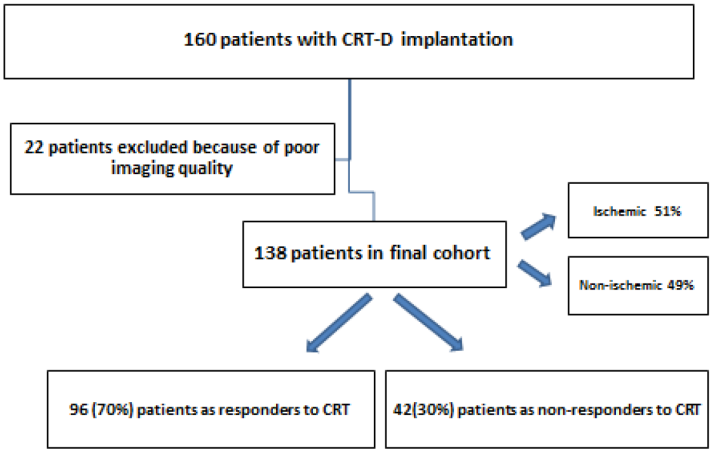


**Figure 1.** Flowchart of study population.

**The study protocol and echocardiographic data acquisition**

All patients underwent two-dimensional echocardiography prior to biventricular ICD implantation and at follow-up in the second year after CRT implantation. The images were obtained on a Vivid 7 ultrasound machine (General Electric, Milwaukee, WI) using a 3.5 MHz transducer at a depth of 16 cm in the parasternal (long-and short axis) and apical (2- and 4-chamber) views. The images were stored in cine-loop format by well-trained echocardiographists and reviewed by an independent cardiologist who was not involved in the study. The left ventricular end-diastolic diameter (LVEDD), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic diameter (LVESD) and left ventricular end-systolic volume (LVESV) were measured and the LVEF was calculated using Simpson's technique [15].

**LV dyssynchrony measurement with Septal Rebound Stretch (SRSsept)**

The analysis was performed using EchoPac version 7.0.1, General Electric. The acquisition of the 2D images was performed with at least 40 fps to allow for proper speckle tracking analysis off line. The analysis was performed by a blinded cardiologist to whom only gray-scale imaging of the septal wall and aortic flow recordings was available. Longitudinal speckle tracking technique was used to assess the deformation in the septal wall. The region of interest was set along the endocardial border from the base to the apex, excluding the

apical cap, and adapted to match the wall thickness and checked visually and adjusted if necessary. Global wall deformation (i.e., calculated over the entire length of the wall) was used for analysis. SRSsept was defined as the cumulative amount of systolic stretch after prematurely terminated shortening in septum (Figure 2). The effective septal shortening was defined as the end-systolic (i.e., at aortic valve closure) value of deformation.

Furthermore, we used the inter-ventricular mechanical delay (IVMD) to assess the interventricular mechanical dyssynchrony as it has been reported by previous study [7] as a predictor of response to CRT, however, with low sensitivity and specificity.

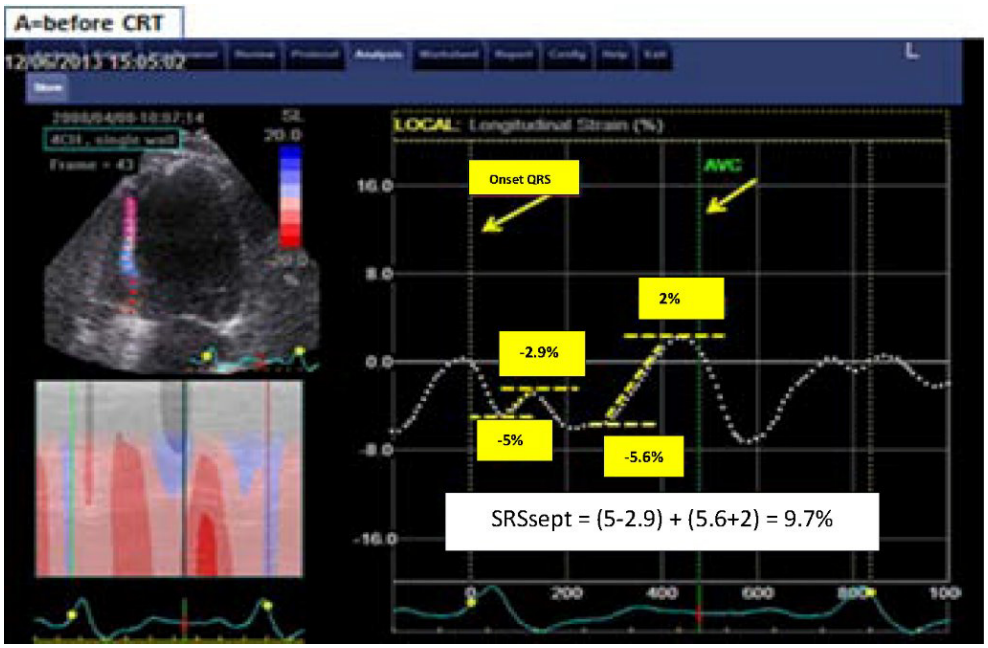


**Figure 2.** Example of septal rebound stretch (SRSsept) measurement. Global longitudinal deformation measured over the entire length of the septum is represented by the dash white lines. Negative slope of the deformation curve indicates shortening, positive slope indicates stretching. Systolic stretch that occurs after initial shortening defines systolic rebound stretch. If more than 1 episode of stretch occurs, the absolute amount of stretch is summed to calculate systolic rebound stretch. In this patient with high amount of SRSsept, systolic shortening is interrupted early during systole, resulting in prominent systolic stretching. Note that stretching and shortening occurring after AVC ( aortic valve closure) are ignored for rebound stretch measurement.

The off-line analyses were performed on digitally stored images by an independent observer (A.G.) blinded to the clinical and other echocardiographic information. All SRSsept measures were additionally performed by another independent, well trained, and experienced cardiologist (P.P.D.). Furthermore, these measurements were repeated by the first observer, in order to assess inter-observer and intra-observer variability. Inter-observer and intra-observer variability were expressed as standard error of measurement (SEM).

**Echocardiographic response to CRT**

Response to CRT was defined as a reduction of ≥15% in LVESV compared to baseline echocardiographic measurement, at the second year of echocardiographic follow-up [7,11].

**Statistical analysis**

Continuous variables are expressed as mean±SD and a non-parametric Mann-Whitney U-test was used to analyze differences between groups. Categorical variables are presented as number and percentages and the Chi-squared test was used to analyze differences between groups. Paired observations (observations of the same variable at different time points) were analyzed using the non-parametric Wilcoxon test. Logistic regression analysis was performed to identify whether SPSsept and IVMD predicted echocardiographic response. In the multivariate logistic regression analyses baseline SRSsept as continuous variable and as dichotomized variable defined by the optimal cut-off value, as well as IVMD were analyzed separately after adjustment for clinical variables (age, gender, LVEF, QRS width, LBBB/RBBB, ischemic/non-ischemic cardiomyopathy). Receiver operating characteristic curve analysis was performed to find the optimal cut-off value for baseline SRSsept to predict echocardiographic response. In subsequent analyses, SRSsept was analyzed as a continuous variable and as a dichotomous variable as defined by the optimal cut-off value. In all analyses p values of $<0.05$ were considered statistically significant. Statistical analysis was performed using SPSS statistical software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).

## RESULTS

**Baseline characteristics**

Of the 160 patients initially included, 22 patients were excluded due to poor 2D image quality. Therefore, 138 patients were eventually analyzed. The baseline characteristics of study population according to echocardiographic response are summarized in Table 1. Mean

age was 68±8 years with 70% male gender. 59% had functional class 3 heart failure. Mean QRS duration was 164±23 ms with 95% LBBB or LBBB like morphology and mean EF was 26±7% with 51% ischemic etiology. Echocardiographic follow-up was performed at 22±8 months. According to the predefined criterion of a reduction in LVESV $\geq$15%, 96 (70%) patients were classified as responders to CRT and 42 (30%) as non-responders. 30 of 42 (71%) non-responders had an ischemic cardiomyopathy. All patients had optimized medical therapy, including angiotensin-converting enzyme or angiotensin-receptor antagonist (86%), beta-blockers (85%), diuretics (80%) and spironolactone (44%) at maximally tolerated dosages.

**Echocardiographic analysis**

LV dyssynchrony indices were analyzed at baseline and at mean follow-up of 22±8 months. During analysis of SRSsept, 828 segments were evaluated and only 3% of segments were excluded from analysis due to non-valid tracking. The inter- and intra-observer variability for SRSsept was assessed in 20 randomly selected patients. The standard error of measurement (SEM) for the inter-observer variability was 0.67. The SEM for the intra-rater variability was 1.04.

**Effects of CRT on echocardiographic parameters**

During the follow-up, responders showed a significant reduction in end- systolic and diastolic LV volumes compared with non-responders (LVESV in responders reduced from 108±48 ml to 60±33, $p<0.001$ and in non-responders from 111 ml ±43 to 120 ml ±41, $p=0.1$). Furthermore, a significant improvement in LVEF was noted in responders compared with non-responders (from 26% ±7 to 45% ±10, $p<0.001$ and from 25% ±6 to 26% ±6, $p=0.25$, respectively).

**Effects of CRT on clinical outcome**

Clinical outcome was assessed after a mean follow-up of 57±12 months. During follow-up 32 combined clinical events occurred. 20 patients died 11/42 (26.2%) in non-responders group and 9/96 (9.4%) in responders ($p=0.010$). Due to worsening of heart failure, 20 patients were hospitalized (11 in non-responders group and 9 in responders, $p=0.010$). Eight patients who died were also hospitalized due to heart failure during follow-up. In the entire population a significant improvement in clinical status was noted, with a reduction in NYHA functional class from 2.6±0.5 to 1.78±0.71 ($p<0.001$). The NYHA class during follow-up in the responder group was 1.7±0.7 and in the non-responder group was 2.0±0.6 ($p=0.03$).

**Table 1**. Baseline characteristics of study population according to echocardiographic response to CRT

| | All patients (n=138) | Non-responders (n=42; 30%) | Responders (n=96; 70%) | p value |
|---|---|---|---|---|
| Age (years) | 68±8 | 70±9 | 67±8 | 0.05 |
| Male gender | 70% | 69% | 70% | 0.93 |
| Ischemic | 51% | 71% | 43% | 0.002 |
| Non-ischemic | 49% | 29% | 57% | |
| Atrial fibrillation | 23% | 24% | 23% | 0.90 |
| Sinus rhythm | 77% | 76% | 77% | |
| LBBB or LBBB like morphology | 95% | 93% | 97% | 0.37 |
| RBBB | 5% | 7% | 3% | |
| QRS duration (ms) | 164±23 | 159±20 | 167±23 | 0.05 |
| NYHA functional class | 2.6±0.5 | 2.6±0.5 | 2.6±0.5 | 0.83 |
| LVEF (%) | 26±7 | 25±6 | 26±7 | 0.52 |
| LV end-diastolic volume (ml) | 147±56 | 150±54 | 146±57 | 0.47 |
| LV end-systolic volume (ml) | 109±46 | 111±43 | 108 ±48 | 0.47 |
| Systolic blood pressure (mmHg) | 123±18 | 121±19 | 124±17 | 0.20 |
| Diastolic blood pressure (mmHg) | 73±11 | 72±10 | 73±11 | 0.36 |
| Medication use | | | | |
| Diuretics | 80% | 91% | 75% | 0.04 |
| Beta-blocker | 85% | 83% | 85% | 0.75 |
| Ace-inhibitors or AT II | 86% | 85% | 87% | 0.69 |
| Spironolacton | 44% | 55% | 40% | 0.10 |
| SRSsept (%) | 4.4±3.2 | 3.0±2.7 | 5.1±3.2 | <0.001 |
| IVMD (ms) | 43.4±25.5 | 35.9±21.6 | 47.2±26.7 | 0.045 |
| Position of LV lead | | | | 0.814 |
| Posterior/postero-lateral | 67% | 64% | 69% | |
| Lateral | 22% | 21% | 22% | |
| Midcardiac vene | 4% | 5% | 4% | |
| Epicardial | 7% | 10% | 5% | |

Abbreviations: LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular systolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; SRSsept, systolic rebound stretch in septum; IVMD, inter-ventricular mechanical delay.

**Baseline SRSsept and response to CRT**

The cumulative amount of systolic stretch after prematurely terminated shortening in septum could be quantified in 97% of patients. As displayed in Table 1, the baseline value of SRSsept in non-responders and responders was significantly different (3.0% ±2.7 vs 5.1% ±3.2, respectively, p<0.001). Receiver operating characteristic curve analysis was performed to define the optimal cut-off value for SRSsept to predict the echocardiographic response. The area under the curve for SRSsept was 0.70 (CI 0.59−0.80), and the optimal cut-off value to

predict response to CRT was >4%, yielding a sensitivity and specificity of, respectively, 66% and 66% (Figure 3). When patients divided in two groups according to SRSsept ≥4% versus <4%, 56% of patients had SRSsept ≥4%. Furthermore, SRSsept <4% was more common in male gender and in patients with ischemic cardiomyopathy. SRSsept >4% was more common in patients with wider QRS duration (Table 2). In univariate and multivariate analysis, SRSsept ≥4% independently predicted the response to CRT (Table 3). In univariate analysis, the QRS duration and non-ischemic etiology independently predicted the response to CRT.

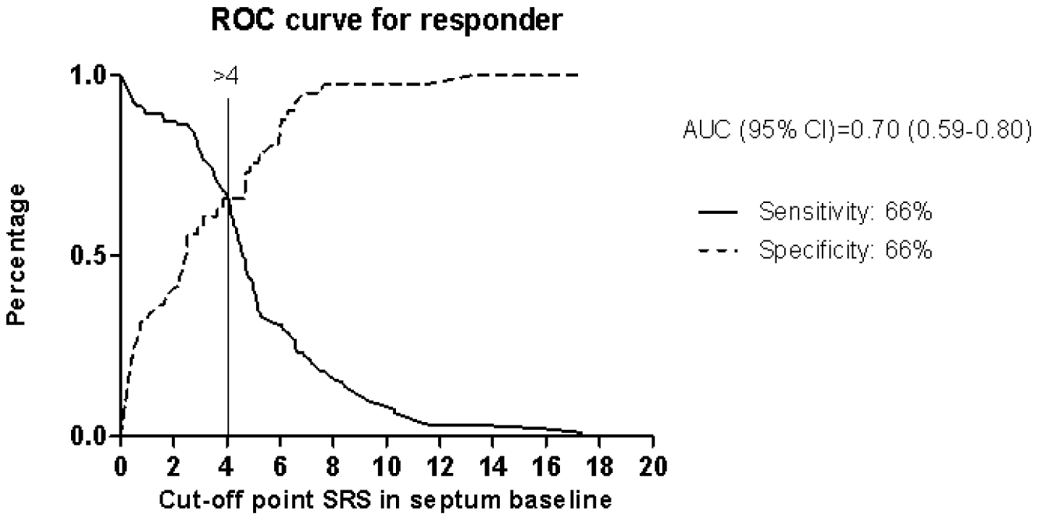


**Figure 3.** ROC curve for responder**.** Receiver operating characteristics curves for SRSsept with reverse remodelling as outcome. AUC, area under the curve.

**Table 2.** Baseline characteristics of study population according to SRSsept ≥4% vs <4%

| | All patients (n=138) | SRSsept <4% (n=59; 44%) | SRSsept ≥4% (n=76; 56%) | p value |
|---|---|---|---|---|
| Age (years) | 68±8 | 67±9 | 69±8 | 0.226 |
| Male gender | 70% | 80% | 62% | 0.026 |
| Ischemic | 51% | 63% | 42% | 0.018 |
| Non-ischemic | 49% | 37% | 58% | |
| Atrial fibrillation | 23% | 27% | 20% | 0.312 |
| Sinus rhythm | 77% | 73% | 80% | |
| LBBB or LBBB like morphology | 95% | 93% | 97% | 0.236 |
| RBBB | 5% | 7% | 3% | |
| QRS duration (ms) | 165±23 | 156±23 | 171±20 | <0.001 |
| NYHA functional class | 2.6±0.5 | 2.6±0.5 | 2.6±0.5 | 0.885 |
| LVEF (%) | 26±7 | 27±7 | 25±7 | 0.219 |
| LV end-diastolic volume (ml) | 147±56 | 146±56 | 148±57 | 0.912 |
| LV end-systolic volume (ml) | 109±47 | 107±46 | 110±47 | 0.776 |
| Systolic blood pressure (mmHg) | 123±18 | 125±19 | 122±17 | 0.422 |
| Diastolic blood pressure (mmHg) | 73±11 | 72±12 | 73±10 | 0.455 |

All abbreviations explained in Table 1.

**Table 3**. Uni- and multivariate predictors of response to CRT by logistic regression analysis

| | Univariate analysis | | | Multivariate analysis [a] | | |
|---|---|---|---|---|---|---|
| | Odds ratio | 95%CI | p value | Odds ratio | 95%CI | p value |
| Age | 0.96 | 0.92−1.01 | 0.082 | | | |
| Male gender | 1.04 | 0.47−2.27 | 0.930 | | | |
| Non-ischemic etiology | 3.35 | 1.53−7.33 | 0.002 | | | |
| QRS duration (ms) | 1.02 | 1.00−1.04 | 0.049 | | | |
| LBBB versus RBBB | 2.32 | 0.45−12.0 | 0.317 | | | |
| LVEF (%) | 1.03 | 0.97−1.08 | 0.349 | | | |
| SRSsept % | 1.31 | 1.12−1.54 | 0.001 | 1.38 | 1.13−1.70 | 0.002 |
| SRSsept (≥4% vs <4%) | 3.74 | 1.72−8.10 | 0.001 | 3.71 | 1.49−9.22 | 0.005 |
| IVMD | 1.02 | 1.00−1.04 | 0.033 | 1.01 | 0.98−1.03 | 0.582 |

All abbreviations explained in Table 1.
[a] Predictors analyzed separately after adjustment for age, gender, QRS duration, EF at baseline, LBBB/RBBB and ischemic/non-ischemic etiology.

## DISCUSSION

In this study with the largest study population until now, we demonstrated a strong and independent association between baseline SRSsept and echocardiographic response to CRT. These findings are in line with previous small studies, and possibly this will be an important new echocardiographic tool in predicting response to CRT.
Speckle tracking imaging technique provides information on deformation of certain segments of the myocardial wall. The timing of maximum deformation of a certain segment of the myocardial wall has been used to assess the LV dyssynchrony. This method, also known as time-based index, has been studied to predict the response to CRT. These studies demonstrated, however, conflicting results regarding the value of time-based radial and longitudinal dyssynchrony indices in prediction of CRT response [8,9,11,16−20]. In the EchoCRT trial [21], studying potential benefit of CRT in patients with chronic heart failure and narrow QRS, several echocardiographic techniques including radial strain (time-based index) did not predict mortality after either CRT or no CRT. One of the plausible reasons that these time-based indices failed to predict reverse remodelling after CRT is that these indices look only to the timing of maximum deformation of a certain segment and do not provide information about stretching (push away) of another segment at the same time [14].

It is important to stress that septal rebound stretch (SRSsept) measurement, performed by longitudinal speckle tracking analyses, does not look at the timing of deformation. However, SRSsept is based on the amount of stretch in the septal wall after the initial contraction during systole [12]. SRSsept selectively measures the amount of systolic stretch that occurs after early shortening and disregards the systolic pre-stretching and post-systolic shortening, both are inefficient deformations associated with the delayed activated segments. SRSsept assesses the amount of dyssynchrony-related wasted energy that can be recruited by CRT. Conversion of SRSsept into shortening is one of the primary working mechanisms through which CRT improves ventricular function [12]. The value of baseline SRSsept in predicting long-term prognosis, improvement in LV remodelling and neurohormonal activation after implantation of CRT device has been recently demonstrated [13]. Furthermore, SRSsept rather than time delay indices provided significant incremental value over clinical characteristics in prediction of CRT response [14]. In the current study baseline SRSsept independently predicted the echocardiographic response to CRT. Our study, as far as we can ascertain, is the largest study with 138 included patients with echocardiographic follow-up in all patients at a mean of 22±8 months and provides further evidence for the predictive value of SRSsept in response to CRT. Definition of response to CRT is still a matter of debate. In the present study, we assessed LV

reverse remodelling as response to CRT after a mean 2-year follow-up. Previous study (REVERSE study) showed that the maximal amount of functional and LV remodelling improvements was reached at 2 years following CRT and these improvements sustained in 5-year follow-up [22]. Therefore, we used the available echocardiograms at 2 years following the implantation to define the echocardiographic response to CRT. The most optimal cut-off value of SRSsept for predicting response to CRT can be questioned. A previous study [13] used a baseline SRSsept of $\geq$4.7% in predicting survival without heart transplantation or assist device. However, they did not report sensitivity and specificity of the SRSsept. In our study the area under the curve for SRSsept was 0.70 and the optimal cut-off value to predict response to CRT was 4% with both a sensitivity and specificity of 66%. We acknowledge that sensitivity and specificity are not high and it may be a limitation for SRSsept as dyssynchrony index.

**Clinical application of SRSsept**

Non-response is an important and unresolved issue in CRT. The costs and potential procedure-related complications of CRT underline the importance of identifying CRT non-responders. Although current patient selection guidelines for CRT utilize QRS width as a surrogate for dyssynchrony, the results of our study support the additional value of SRSsept. Based on our study, a cut-off value of SRSsept $\geq$4% can be used, but future studies should confirm our findings.

## LIMITATIONS

The present study is a retrospective analysis of prospective registry of a large single-center cohort of consecutive patients treated with CRT. We realize that retrospective analysis is inferior to prospective investigations with prespecified endpoints and cut-off values. The data however was collected systematically and longitudinally by independent physicians. Furthermore, echocardiograms were analyzed and validated by independent cardiologists. Although measurement variability might have been negatively influenced by the inclusion of patients with atrial fibrillation, the current study population most closely resembles daily practice. Strain measurement is sensitive to acute change in load and the calculations for SRSsept require measurements of timing of aortic valve closure to define end-systole. However, these measurements were at different times potentially different loading conditions and heart rates from which the LV images were acquired. Thus, the marking of the end-systolic phase may add a source of potential error to the measurements of SRSsept. Non-

response to CRT is probably not solely due to insufficient patient selection. Suboptimal LV lead placement must also be considered. However, there were no differences between responders and non-responders regarding the location of LV lead in our study population. Also unfavorable pacemaker settings can contribute to non-response to CRT. Unfortunately, we were not able to perform echo-guided optimization after device implantation.

## CONCLUSION

We demonstrated that stretch-based assessment of LV dyssynchrony measured with SRSsept was able to predict echocardiographic response to CRT. These findings indicate that baseline SRSsept >4% helps identifying potential CRT responders.

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CHAPTER 7

# Apical rocking is predictive of response to cardiac resynchronization therapy

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## ABSTRACT

***Purpose*:** Identification of patients who will benefit from cardiac resynchronization therapy (CRT) is challenging. 'Apical rocking' is frequently observed in asynchronously contracting ventricles and small studies suggested that it may predict CRT response. We assessed the predictive value of LV apical rocking on echocardiographic and clinical response to CRT in a large cohort of patients treated with CRT.

***Methods*:** Echocardiography was performed in 137 consecutive patients prior to CRT, and repeated during follow-up. Apical rocking was defined as motion of the left ventricular (LV) apical myocardium perpendicular to the LV long axis. Echocardiographic response to CRT was defined as a reduction in LV end-systolic volume $\geq$15% and clinical response as survival without heart failure hospitalization. All echocardiograms were assessed by independent cardiologists, blinded for baseline, clinical and follow-up data. Multivariable analyses were performed to adjust for potential confounders.

***Results*:** Mean echocardiographic and clinical follow-up was 22±8 and 57±12 months, respectively. Apical rocking was present in 49% of the patients. Apical rocking was more common in females, younger patients, and in patients with non-ischemic cardiomyopathy. Echocardiographic response to CRT was observed in 69%, clinical response in 77% of the patients. Apical rocking was associated with both echocardiographic response (OR 10.77, 95%CI 4.12−28.13) and clinical response to CRT (HR 2.73, 95%CI 1.26−5.91). Also, after multivariable analyses, apical rocking was associated with both echocardiographic (OR 9.97, 95%CI 3.48−28.59) and clinical response to CRT (HR 2.13, 95%CI 0.94−4.83).

***Conclusions*:** Apical rocking is independently associated with both echocardiographic and clinical response to CRT.


## INTRODUCTION

Cardiac resynchronization therapy (CRT) reduces symptoms, morbidity and mortality and improves cardiac function in the majority of patients with symptomatic heart failure and reduced left ventricular ejection fraction (LVEF $\leq$35%) with wide QRS (>120 ms) [1−5]. However, indication for CRT based on left ventricular ejection fraction (LVEF) and QRS duration, results in 30–40% of non-responders and even worsening of cardiac function in some patients [6,7].The challenges of correctly identifying patients who will benefit from this costly therapy, however, remains. One of the factors which may influence the likelihood of response to CRT is lack of presence of baseline left ventricular dyssynchrony. The definition

and evaluation of LV dyssynchrony are still subject to debate. Different echocardiographic parameters, including speckle tracking, have been proposed to identify potential CRT responders, without consensus on the predictive value of any of these parameters [8−13]. In the past 2−3 years, left ventricular apical rocking has been introduced as a new parameter for the assessment of left ventricular dyssynchrony [14,15]. A short initial septal contraction within the isovolumic contraction period results in a short inward motion of the septum and causes the apex to move septally. The delayed activation of the lateral wall then pulls the apex laterally during the ejection time while stretching the septum. This typical motion pattern of the apex of left ventricle is described as 'apical rocking'. Only few studies have assessed the value of apical rocking in predicting CRT response [14,15]. Moreover, these studies were small sized and described only echocardiographic CRT response. The aim of our current study was to assess the independent predictive value of apical rocking on echocardiographic and long-term clinical response to CRT in a large study population.

## METHODS

### Selection of patients and data collection

From January 2008 to December 2009, 160 consecutive patients with chronic heart failure (New York Heart Association functional class II−IV), depressed left ventricular ejection fraction (LVEF) ≤35% and wide QRS complex ≥120 ms who were scheduled for CRT were included in the present study. Patients with pre-existent pacemaker or ICD implantations were excluded in order to avoid chronic RV pacing which may affect the assessment of apical rocking. All patients were on optimal medical therapy, including angiotensin-converting enzyme inhibitors and beta-blockers. Patients with a recent myocardial infarction <3 months or decompensated heart failure were excluded. Etiology was considered ischemic in the presence of significant coronary artery disease (≥50% stenosis in one or more of the major epicardial coronary arteries) and/or history of myocardial infarction or prior revascularization by PCI or CABG. Twenty-three patients with poor echocardiographic window at baseline were excluded from the analysis. This study is based on a prospective registry and was approved by the institutional board. Baseline characteristics included age, gender, etiology of heart failure, clinical history, medical therapy, NYHA functional class, ECG and procedural data were collected prospectively and analyzed retrospectively. Routine follow-up visits were scheduled at 2 months post implant, and then every 6 months thereafter. The routine follow-up in some of our patients took place in referring hospitals. The clinical status of all survivals at the closure of the study (December 2013) was verified. Data on mortality and

hospitalization were collected from reviewing our hospital records, referring hospitals and by contacting general practitioners. Furthermore, the Dutch national population registry, which keeps records of all deaths, was checked in all patients.

**The study protocol and echocardiographic data acquisition**

All patients underwent two-dimensional echocardiography before biventricular ICD implantation and at follow-up in the second year after CRT implantation. The images were obtained on a Vivid 7 ultrasound machine (General Electric, Milwaukee, WI) using a 3.5 MHz transducer at a depth of 16 cm in the parasternal (long- and short axis) and apical (2- and 4-chamber) views. The images were stored in cine-loop format by well-trained echocardiographists and reviewed by an independent cardiologist who was not involved in the study. The left ventricular end-diastolic diameter (LVEDD), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic diameter (LVESD) and left ventricular end-systolic volume (LVESV) were measured and the left ventricular ejection fraction (LVEF) was calculated using Simpson's technique [16].

**Visual assessment of LV-apical rocking**

Apical rocking was defined as a short initial septal contraction which results in short inward motion of the septum and pulls the apex to the septum and then the delayed activation of the lateral wall which pulls the apex laterally during the ejection time while stretching of the septum takes place. This definition was used to assess visually the presence of apical rocking. The presence of apical rocking was visually assessed in 4-chamber apical view by three cardiologists each with more than 6 years of echocardiography experience. All cardiologists had only access to the grey scale image loops of the three apical image planes. The echocardiographers acquiring images and three cardiologist involved in offline analysis were not blinded to some general data like age, sex and QRS duration. But they were blinded to the relevant data as medical history and measured LVEF. Inter-observer and intra-observer agreement were expressed as kappa coefficients. Values higher than 0.8 are considered as excellent, values between 0.6 and 0.8 as good, values between 0.4 and 0.6 as moderate, and values below 0.4 as poor agreement.

**Endpoints**

Echocardiographic response to CRT was defined as a reduction of $\geq$15% in LVESV compared to baseline echocardiographic measurement, at the second year of echocardiographic follow-up [17,18]. Survival without hospitalization due to worsening of heart failure during follow-up was defined as clinical response to CRT. Furthermore,

functional status was assessed by independent physicians before CRT and after 57±12 months.

**Power calculation**

For power calculation the assumption was that apical rocking was present in 50% of patients, that in 90% of patients with apical rocking echocardiographic response could be observed compared to 50% in patients without apical rocking. Furthermore, it was assumed that the sensitivity should be 0.6–0.7 and specificity of 0.8–0.9.To test whether the sensitivity is different from 0.5, a minimum of 134 patients would be needed (at a power of 0.9 and a 5% alpha). Furthermore, to test whether the specificity is different from 0.5, a minimum of 77 patients would be needed (at a power of 0.9 and an alpha of 5%).

**Statistical analysis**

Statistical analysis was performed using SPSS statistical software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Continuous variables are expressed as mean±SD and significance of differences are calculated using the non-parametric Mann-Whitney U-test. Categorical variables are presented as number and percentages and significance of differences between groups was calculated using the Chi-squared test. Significance of differences between paired observations (observations of the same variable at different time points) were analyzed using the non-parametric Wilcoxon test. Logistic regression analysis was performed to estimate the association between apical rocking and echocardiographic response. Clinical variables (age, gender, LVEF, QRS width, LBBB/RBBB, ischemic/non-ischemic cardiomyopathy) were entered into the logistic regression analysis as confounders. Time until long-term clinical outcome (death and/or hospitalization) was plotted using Kaplan-Meier estimates, and groups were compared using log-rank tests. We performed Cox regression analysis to estimate the association between apical rocking and clinical outcome, using the same confounders as for the echocardiographic response. p values of $<0.05$ were considered statistically significant in all analyses.

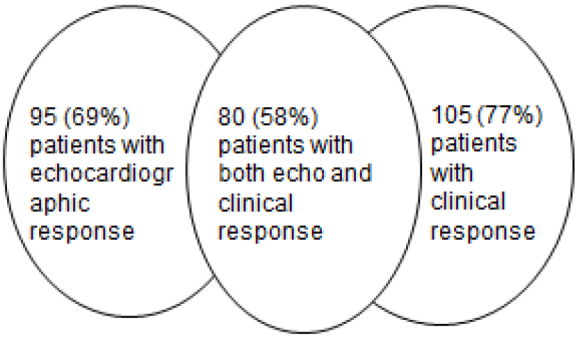


**Figure 1**. Proportion of patients with only echocardiographic, clinical and both echocardiographic and clinical response to CRT

## RESULTS

### Baseline characteristics

Of the 160 patients initially included, 23 patients were excluded because of poor image quality. Therefore, 137 patients were eventually analyzed (Figure 1). General characteristics of study population according to echocardiographic response are summarized in Table 1 and according to clinical response are summarized in Table 2. Mean age was 68±8 years with 70% male gender. 59% had functional class 3 heart failure. LBBB was present in 95% of patients, mean QRS duration was 164±22 ms and mean EF was 26±7% with 51% ischemic etiology. All patients had optimized medical therapy, including angiotensin-converting enzyme or angiotensin-receptor antagonist (86%), beta-blockers (85%), diuretics (80%) and spironolactone (44%) at maximally tolerated dosages. Echocardiographic and clinical non-responders had significantly more diuretics, including spironolactone.

### Presence of apical rocking

Apical rocking was present in 49% of patients (68/137). Apical rocking was significantly more common in females than in males (63% vs 43%, p=0.03), in patients with non-ischemic cardiomyopathy (65% vs 34%, p<0.001) and in younger patients (see Table 3). Almost one quarter of patients (23%) had atrial fibrillation at baseline. Apical rocking was present in 50% of these patients which was comparable to patients in sinus rhythm.

**Table 1.** General characteristics of study population according to echocardiographic response to CRT

| | All patients (n=137) | Non-responders (n=42; 31%) | Responders (n=95; 69%) | p value |
|---|---|---|---|---|
| Age (years) | 68±8 | 70±9 | 67±8 | 0.05 |
| Male gender | 70% | 69% | 70% | 0.93 |
| Ischemic | 51% | 71% | 43% | 0.002 |
| Atrial fibrillation | 23% | 24% | 23% | 0.91 |
| LBBB | 95% | 93% | 97% | 0.37 |
| RBBB | 4.5% | 7% | 3% | |
| QRS duration (ms) | 164±23 | 159±20 | 167±23 | 0.05 |
| NYHA functional class | 2.6±0.5 | 2.6±0.5 | 2.6±0.5 | 0.83 |
| EF (%) | 26±7 | 25±6 | 26±7 | 0.52 |
| LV end-diastolic volume (ml) | 147±56 | 150±54 | 146±57 | 0.47 |
| LV end-systolic volume (ml) | 109±46 | 111±43 | 108±48 | 0.47 |
| Systolic blood pressure (mmHg) | 123±18 | 121±19 | 124±17 | 0.20 |
| Diastolic blood pressure (mmHg) | 73±11 | 72±10 | 73±11 | 0.37 |
| Medication use | | | | |
| Diuretics | 80% | 90% | 75% | 0.04 |
| Beta-blocker | 85% | 83% | 85% | 0.75 |
| Ace-inhibitors/ ARBs | 86% | 90% | 84% | 0.34 |
| Spironolactone | 44% | 55% | 40% | 0.10 |
| Position of LV lead | | | | 0.814 |
| Posterior/postero-lateral | 67% | 64% | 69% | |
| Lateral | 22% | 21% | 22% | |
| Midcardiac vene | 4% | 5% | 4% | |
| Epicardial | 7% | 10% | 5% | |
| Presence of apical rocking | 49% | 14% | 64% | <0.001 |

Abbreviations: LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter, LVESD, left ventricular end-systolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume.

**Table 2**. General characteristics of study population according to clinical response to CRT

| | All patients (n=137) | Non-responders (n=32; 23%) | Responders (n=105; 77%) | p value |
|---|---|---|---|---|
| Age (years) | 68±8 | 71±8 | 67±8 | 0.02 |
| Male gender | 70% | 69% | 70% | 0.90 |
| Ischemic | 51% | 63% | 48% | 0.15 |
| Atrial fibrillation | 23% | 25% | 23% | 0.78 |
| LBBB | 95% | 94% | 96% | 0.63 |
| RBBB | 5% | 6% | 4% | |
| QRS duration (ms) | 164±23 | 160±21 | 166±23 | 0.16 |
| NYHA functional class | 2.6±0.5 | 2.6±0.5 | 2.6±0.5 | 0.89 |
| EF (%) | 26±7 | 24±7 | 26±7 | 0.10 |
| LV end-diastolic volume (ml) | 147±56 | 158±69 | 144±51 | 0.35 |
| LV end-systolic volume (ml) | 109±46 | 120±57 | 106±42 | 0.27 |
| Systolic blood pressure (mmHg) | 123±18 | 117±16 | 125±18 | 0.02 |
| Diastolic blood pressure (mmHg) | 73±11 | 70±10 | 74±11 | 0.08 |
| Medication use | | | | |
| Diuretics | 80% | 91% | 76% | 0.08 |
| Beta-blocker | 85% | 84% | 85% | 0.94 |
| Ace-inhibitors/ARBs | 86% | 81% | 87% | 0.44 |
| Spironolactone | 44% | 63% | 39% | 0.02 |
| Position of LV lead | | | | 0.73 |
| Posterior/postero-lateral | 67% | 65% | 68% | |
| Lateral | 22% | 21% | 22% | |
| Midcardiac vene | 4% | 6% | 3% | |
| Epicardial | 7% | 9% | 6% | |
| Presence of apical rocking | 49% | 28% | 55% | 0.007 |

All abbreviations explained in Table 1.

**Table 3.** Characteristics of study population according to presence of apical rocking

| Baseline characteristics | All patients (n=137) | Apical rocking present (n=68) | Apical rocking absent (n=69) | p value |
|---|---|---|---|---|
| Age (years) | 68±8 | 67±8 | 70±8 | 0.03 |
| Male gender | 70% | 61% | 79% | 0.03 |
| Ischemic | 52% | 36% | 67% | <0.001 |
| Atrial fibrillation | 23% | 24% | 23% | 0.89 |
| LBBB | 95% | 98% | 92% | 0.21 |
| RBBB | 5% | 2% | 8% | |
| QRS duration >150 (ms) | 72% | 78% | 67% | 0.17 |
| QRS ≤150 ms | 28% | 22% | 33% | |
| NYHA functional class | 2.6±0.5 | 2.5±0.6 | 2.6±0.5 | 0.23 |
| EF (%) | 26±7 | 26±7 | 26±7 | 0.82 |
| LV end-diastolic diameter (mm) | 62±7 | 62±7 | 61±7 | 0.98 |
| LV end-systolic diameter (mm) | 53±8 | 53±8 | 53±8 | 0.67 |
| LV end-diastolic volume (ml) | 147±56 | 149±61 | 145±51 | 0.10 |
| LV end-systolic volume (ml) | 109±46 | 110±51 | 108±42 | 0.86 |

All abbreviations explained in Table 1.

**Table 4.** Uni- and multivariate predictors of echocardiographic response to CRT by logistic regression analysis

| Variable | Univariate analysis | | | Multivariate analysis [a] | | |
|---|---|---|---|---|---|---|
| | Odds ratio | 95% CI | p value | Odds ratio | 95% CI | p value |
| Age | 0.96 | 0.92−1.01 | 0.08 | | | |
| Male gender | 1.04 | 0.47−2.27 | 0.93 | | | |
| Non-ischemic etiology | 3.35 | 1.53−7.33 | 0.002 | | | |
| QRS duration (ms) | 1.02 | 1.00−1.04 | 0.04 | | | |
| RBBB | 0.43 | 0.08−2.24 | 0.31 | | | |
| EF (%) | 1.03 | 0.97−1.08 | 0.34 | | | |
| Presence of apical rocking | 10.77 | 4.12 −28.13 | <0.001 | 9.97 | 3.48 −28.59 | <0.001 |

[a] After adjustment for age, gender, QRS duration, EF at baseline, LBBB/RBTB and ischemic/non-ischemic etiology.

**Reproducibility of apical rocking**

To quantify inter- and intra-observer variability for assessment of apical rocking we reviewed the total study population by three cardiologists. For inter-observer variability the kappa was 0.85 and for intra-observer variability the kappa was 0.90.

**Apical rocking and echocardiographic response**

All patients were analyzed at baseline and at mean follow-up of 22±8 months. According to the predefined echocardiographic criterion of a reduction in LVESV $\geq$15%, 95 (69%) patients were classified as echocardiographic responders to CRT. 30 of 42 (71%) non-responders had an ischemic cardiomyopathy. During follow-up, end-systolic volumes (LVESV) decreased significantly in responders, from 108±48 ml to 60±33, p<0.001 and in non-responders there was a non-significant increase in LVESV from 111±43 ml to 120±41, p=0.1). Furthermore, during follow-up end-diastolic volumes (LVEDV) decreased significantly in responders, from 146±57 ml to 100±40, p<0.001 and there was a non-significant increase in non-responders from 150±54 ml to 158±56, p=0.37). In addition, a significant improvement in LVEF was noted in responders compared with non-responders (from 26% ±7 to 45% ±10, p<0.001 and from 25% ±6 to 26% ±6, p=0.25, respectively). At baseline, the presence of apical rocking between echocardiographic responders and non-responders was significantly different (64% versus 14%, p<0.001, see Table 1). In univariate and multivariate analysis, the presence of apical rocking was independently associated with echocardiographic response to CRT (Table 4). The presence of apical rocking predicted the echocardiographic response to CRT with a sensitivity of 64% and specificity of 86%. The area under the curve was 0.75 (CI=0.66−0.84). The positive predictive value was 91%, the negative predictive value 51%, with an accuracy of 71%.

**Apical rocking and clinical outcome**

Clinical outcome was assessed after a mean follow-up of 57±12 months. 105 patients (77%) who survived without heart failure hospitalization were classified as clinical responders and 32 patients (23%) who died or were hospitalized with heart failure were classified as clinical non-responders to CRT. During follow-up, clinical events occurred in 32 patients (20 patients died and 20 were hospitalized due to worsening of heart failure). Eight patients who died were also hospitalized due to heart failure during follow-up. In the entire population, a significant improvement in functional status was noted, with a reduction in NYHA functional class from 2.6±0.5 to 1.8±0.7 (p<0.001). The NYHA functional class during follow-up in the clinical responder group was 1.7±0.7 vs 2.3±0.6 in the non-responder group (p=0.008). Presence of apical rocking between clinical responders and non-responders was significantly different (55% vs 28%, p=0.007). Results of both univariate and multivariate analyses of the potential

association between apical rocking and clinical response are summarized in Table 5. The apical rocking predicted clinical response (survival without heart failure hospitalization) to CRT with a sensitivity of 55% and a specificity of 72%. The positive predictive value of apical rocking in predicting clinical response was 87% and the negative predictive value was 33% and the accuracy was 59%. Absence of apical rocking was associated with a higher mortality and heart failure hospitalization (Figure 2).

**Apical rocking and QRS duration**

We included 137 patients, mean±SD QRS duration was 164±23 ms. In total 126 patients had QRS >130 ms and 11 patients QRS ≤130 ms. The presence of apical rocking was different between these 2 groups. In patients with QRS >130 ms 64 (50.8%) patients had apical rocking whereas, in patients with QRS ≤130 ms 3 (27%) patients had apical rocking.

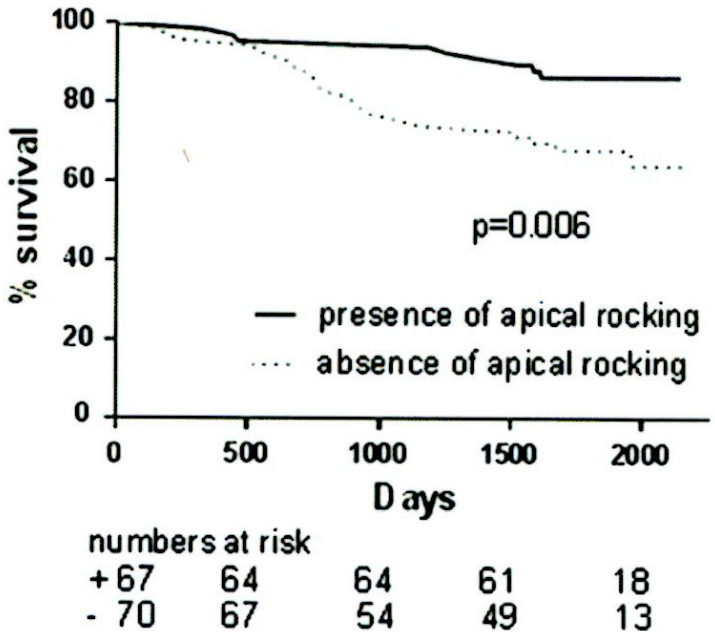


**Figure 2.** Survival without heart failure hospitalization after CRT in patients with or without LV apical rocking.

**Table 5.** Uni- and multivariate predictors of clinical events (death and/or HF-hospitalization) by Cox regression analysis

| Variable | Univariate analysis | | | Multivariate analysis [a] | | |
|---|---|---|---|---|---|---|
| | Hazard ratio | 95% CI | p value | Hazard ratio | 95% CI | p value |
| Age | 1.05 | 1.00 −1.10 | 0.04 | | | |
| Male gender | 0.97 | 0.46 −2.04 | 0.92 | | | |
| Non-ischemic etiology | 0.59 | 0.29 −1.20 | 0.14 | | | |
| QRS duration (ms) | 0.99 | 0.97 −1.00 | 0.16 | | | |
| RBBB | 1.61 | 0.38 −6.74 | 0.51 | | | |
| EF (%) | 0.95 | 0.90− 1.00 | 0.06 | | | |
| Presence of apical rocking | 0.35 | 0.16 −0.76 | 0.008 | 0.44 | 0.19 −0.99 | 0.046 |

[a]After adjustment for age, gender, QRS duration, EF at baseline, LBBB/RBTB and ischemic/non-ischemic etiology.

## DISCUSSION

In the present study we assessed the association of apical rocking with echocardiographic and clinical response to CRT. This study showed that apical rocking is independently associated with both echocardiographic and clinical response to CRT.

In the past years, several dyssynchrony indices have been developed to identify patients who will respond to CRT with promising results in single center trials. Unfortunately, these indices have performed poorly in larger clinical trials, showing high inter-observer variability and failing to accurately segregate responders and non-responders to CRT before the implantation [7,10,11,13,17−20].

### Apical rocking

Apical rocking is a typical early septal contraction in patients with left bundle branch block, which pulls the apex towards the septum. Delayed activation of the lateral wall pulls then the apex laterally during the ejection time while the septum is stretching. Apical rocking can be visualized in a standard echocardiographic 4-chamber view in patients with left ventricular dyssynchrony. This is in contrast to several dyssynchrony measures, which require well trained echocardiographist and special imaging software and techniques. Both regional myocardial functional abnormalities (due to scar tissue) and temporal abnormalities (due to activation delay) contribute to apical rocking, and thus both are incorporated in a single echocardiographic parameter [21,22]. Apical rocking retains important regional information on the myocardial contraction sequence [23] and overcomes several limitations of peak

velocity parameters and avoids the challenges of myocardial deformation measurements. The ability of apical rocking to reflect LV mechanical dyssynchrony has already been demonstrated by its superior predictive power for echocardiographic CRT response [14]. Previous studies compared a quantitative measurement of apical rocking, defined as the percentage of the cardiac cycle with reverse motion of the septum and the apex, with visual assessment of apical rocking and demonstrated a comparable accuracy in predicting CRT response [14,24]. Therefore, we decided in this study to use only visual assessment, which in theory could be more easily assessed. Our study demonstrated that visual assessment of apical rocking was feasible and reproducible. Our study, as far as we can ascertain, is the largest study with 137 included patients. Additionally, in contrast to previous studies, our study has both long-term echocardiographic and clinical follow-up.
Definition of response to CRT is still a matter of debate. The trials which assessed the value of LV dyssynchrony parameters in prediction of CRT response, have used LVESV $\geq$15% as endpoint and the trials which assessed the clinical benefit of CRT, have used survival without heart failure hospitalization as endpoint. In present study, we assessed LV reverse remodeling as echocardiographic response to CRT after a mean 2 years follow-up. A previous study (REVERSE study) showed that the maximal amount of functional and LV remodeling improvements was reached at 2 years following CRT and these improvements sustained in 5 years follow-up [25]. Younger age, male gender and non-ischemic etiology were associated with apical rocking. These parameters are known for their association with CRT response. Additionally, apical rocking was still significantly associated with CRT response, after correction for these and other clinical variables associated with CRT response.

Atrial fibrillation did not affect the assessment of apical rocking. Presence of apical rocking in AF patients was similar to patients in sinus rhythm. In the current study, the presence of apical rocking was associated with clinical response to CRT and the absence of apical rocking was associated with significantly higher death rates and/or heart failure hospitalization during follow-up. As far as we can ascertain, there are no published data on predictive value of apical rocking for long-term clinical response to CRT. Our results are the first evidence for association of apical rocking and long-term clinical response. One of the major issues in assessment of LV dyssynchrony is the applicability of such a dyssynchrony index in daily clinical practice. One of the advantages of visual assessment of apical rocking, contrary to several dyssyncrony indices, is that it can be assessed relatively easy and is not time consuming. One of the disadvantages of apical rocking is that not every patient with classic CRT indication shows apical rocking. In our study population, apical rocking was present in only 49%, whereas 69% of the study population responded to CRT. In 64% of CRT responders, apical rocking was present, which means that 1/3 of patients could not be

recognized as potential CRT responders. Although we predefined our endpoints carefully, and found a strong association between apical rocking and both echocardiographic and clinical response, we realize that our results should be confirmed in large multicenter trials.

**Relationship between QRS duration and apical rocking**

A meta-analysis of five randomized trials demonstrated that QRS duration is a powerful predictor of the effects of CRT on morbidity and mortality in heart failure patients [26]. One of the recent trials, which studied the effects of CRT in patients with QRS <130 ms and LV dyssynchrony, demonstrated that CRT in such patients was harmful [27]. However, this trial used speckle tracking radial strain to assess LV dyssynchrony. In our study, we demonstrated that the presence of apical rocking was different between patients with QRS >130 ms and ≤130 ms. In patients with QRS ≤130 ms, 3 (27%) patients had apical rocking and 8 (72%) patients had no apical rocking. Although these numbers were too small, we observed that the majority of patients with QRS ≤130 ms had no apical rocking. We observed that apical rocking was associated with response to CRT and that the majority of patients (8 out of 11) with QRS <130 ms did not have apical rocking. Therefore, our results support the existing evidence that CRT in patients with QRS <130 ms should not be recommended. To assess the real value of apical rocking in patients with QRS <130 ms, future studies with more patients should be conducted.

**Clinical application of apical rocking**

Visual assessment of apical rocking is relatively easy and is reproducible. Although current patient selection guidelines for CRT utilize QRS width as a surrogate for dyssynchrony, the results of our study support the additional value of apical rocking. Due to its relatively high positive predictive value, the presence of apical rocking is associated with echocardiographic and clinical CRT response. Large prospective and multicenter center studies are needed to confirm our findings. The future trials should include more patients with QRS ≤150 ms or even ≤130 ms to assess the value of apical rocking in these patients.

**Limitations**

The present study is a prospective registry of a large single-center cohort of consecutive patients treated with CRT. We held 137 patients after excluding patients with CRT-P, upgrading from other devices to CRT-D, patients who went back to their own hospitals after the implantation and patients with poor image quality. We have not performed power calculation. Visual assessment of apical rocking may be inferior to measuring of the motion and velocities of myocardial walls in mm and cm/s. Since the start of the study, several new echocardiographic dyssynchrony indices have been introduced, with particularly calculation

of apical transverse motion [15,21]. However, the study by Tournoux et al. [15] compared a quantitative measurement of apical rocking, defined as the percentage of the cardiac cycle with reverse motion of the septum and the apex, with visual assessment of apical rocking and demonstrated a comparable accuracy in predicting CRT response. In order to enhance the reliability of visual assessment of apical rocking, a substantial number (n=23) of patients were excluded from analysis because of limited acoustic windows. The current study population resembles most closely daily practice with inclusion of patients with atrial fibrillation and we demonstrated that visualization of apical rocking was not negatively influenced by the inclusion of patients with atrial fibrillation. In contrary to most other studies, and because of our long-term follow-up, we provided not only echocardiographic outcome measures, but also hard clinical endpoints such as all-cause mortality and heart failure hospitalization. Non-response to CRT is probably not solely due to insufficient patient selection. Suboptimal LV lead placement must also be considered. However, care was taken to minimize this risk by coronary venogram-guided lead placement and all leads were placed in the posterior or lateral region if possible. Unfortunately, we were not able to perform echo-guided optimization after device implantation. In the present study the echocardiograms and assessment of apical rocking were performed at rest. Recent publication suggested [28], however, that low-dose dobutamine stress echocardiography could result in more dyssynchrony and might improve the predictive value of apical rocking.

## CONCLUSION

We demonstrated that apical rocking was, as visually assessed, independently associated with echocardiographic and clinical response to CRT. Moreover, when apical rocking was present the probability of echocardiographic and clinical response was high.

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CHAPTER 8

# Association of apical rocking with long-term major adverse cardiac events in patients undergoing cardiac resynchronization therapy

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## ABSTRACT

***Aim*:** Correctly identifying patients who will benefit from cardiac resynchronization therapy (CRT) is still challenging. 'Apical rocking' is observed in asynchronously contracting ventricles and is associated with echocardiographic response to CRT. The association of apical rocking and long-term clinical outcome is however unkown at present. We assessed the predictive value of LV apical rocking on long-term clinical outcome in patients treated with CRT.

***Methods and results*:** Consecutive heart failure patients treated with primary indication for CRT-D between 2005 and 2009 were included in a prospective registry. Echocardiography was performed prior to CRT to assess apical rocking, defined as motion of the left ventricular (LV) apical myocardium perpendicular to the LV long axis. Major adverse cardiac event (MACE) was defined as combined endpoint of cardiac death and/or heart failure hospitalization and/or appropriate therapy (ATP and/or ICD shocks). All echocardiograms were assessed by independent cardiologists, blinded for clinical data. Multivariable analyses were performed to adjust for potential confounders. 295 patients with echocardiography prior to implantation were included in final analyses. Apical rocking was present in 45% of the study patients. Apical rocking was significantly more common in younger patients, females, patients with sinus rhythm, non-ischemic cardiomyopathy, in patients with LBBB and wider QRS duration. During a mean clinical follow-up of 5.2±1.6 years, 92 (31%) patients reached the endpoint of the study (MACE). Patients with MACE had shorter QRS duration, more ischemic cardiomyopathy and were more often on Amiodarone. In univariate analyses, MACE was associated with shorter QRS duration, ischemic etiology and absence of apical rocking. After multivariable analyses, apical rocking was associated with less MACE (HR 0.44, 95% CI 0.25−0.77).

***Conclusions*:** Apical rocking is an independent predictor of favorable long-term outcome in CRT-D patients.


## INTRODUCTION

Several clinical trials have demonstrated that cardiac resynchronization therapy (CRT) reduces heart failure symptoms, hospitalization and mortality. CRT improves cardiac function in the majority of patients with symptomatic heart failure and reduced left ventricular ejection fraction (LVEF $\leq$35%) with wide QRS (>120−130 ms) [1−4]. However, present guidelines for selection of CRT candidates result in 30–40% non-responders and even worsening of cardiac function in some patients [5,6]. The challenges of correctly identifying patients who

will benefit from this costly therapy therefore remain. One of the factors which may influence the likelihood of response to CRT is the lack or presence of left ventricular dyssynchrony. The definition and evaluation of LV dyssynchrony are still subject to debate. Different echocardiographic parameters have been proposed to identify potential CRT responders, without consensus on the predictive value of any of these parameters [7−12]. In the past years, left ventricular apical rocking has been introduced as a new parameter for the assessment of left ventricular dyssynchrony [13,14]. A short initial septal contraction within the isovolumic contraction period results in a short inward motion of the septum and causes the apex to move septally. The delayed activation of the lateral wall then pulls the apex laterally during the ejection time while stretching the septum. This typical motion pattern of the apex of left ventricle is described as 'apical rocking'. Only few studies have assessed the value of apical rocking in predicting CRT response [13−15]. Moreover, these studies were small sized and described only echocardiographic CRT response. The aim of our current study was to assess the independent predictive value of apical rocking on long-term clinical outcomes in a large study population.

## METHODS

### Selection of patients

From January 2005 to December 2009, 347 consecutive patients with primary indication for CRT-D implantation were included in a prospective registry and followed for a median of 5.2 years (inter-quartile range [IQR] 4.5−6.5). This registry was approved by the institutional review board. Patients were excluded from the analyses if: (1) patients received cardiac resynchronization therapy without defibrillation therapy (CRT-P), (2) pre-implantation LVEF was $\geq$35% according to echocardiographic data, (3) patients had a recent myocardial infarction or CABG (<3 months). To be included in the final analysis, the patients were required to have an echocardiogram before CRT-D implantation and during follow-up. Based on these criteria, a total of 295 patients were included in the analyses (Figure 1). Indication for CRT-D implantation was determined according to the guidelines at the time of implantation. In all patients, LVEF was $\leq$35% and QRS duration was >120 ms because of LBBB, RBBB or non-specific intra-ventricular conduction disorders (IVCD). Heart failure was diagnosed according to the European Society of Cardiology guidelines and the severity of symptoms was categorized into four functional classes as defined by the New York Heart association (NYHA) criteria. Etiology was considered ischemic in the presence of significant coronary artery disease ($\geq$50% stenosis in 1 or more of the major epicardial coronary arteries) corresponding with the area of wall motion abnormality, and/or history of myocardial

infarction or prior revascularization by PCI or CABG. Medical therapy was optimized to reach the highest tolerated dosages of angiotensin-converting enzyme inhibitors and beta-blockers.

**Device implantation**

Cardiac resynchronization therapy devices from all major manufacturers (Medtronic Inc., St. Jude Medical, Boston Scientific, Biotronik and Sorin Group) were implanted. The majority of coronary sinus leads were bipolar and were positioned in the lateral, posterolateral or posterior region when feasible (83%). The anterior and anterolateral positions were considered suboptimal and avoided if possible (8%). 9% of left ventricular leads were positioned epicardially during open heart surgery prior to CRT-D implantation. After implantation, tailored device programming was performed before discharge with three consecutive zones in the large majority of patients. A monitor zone between 170−200 beats/min, anti-tachycardia pacing (ATP) and shock therapy zone between 200−230 beats/min and a shock zone >230 beats/min. In the ATP and shock therapy zone, arrhythmias were initially attempted to be terminated by two bursts and one ramp and defibrillator shocks were used if the arrhythmia continued. Routine follow-up visits were scheduled at 2 months post implant, and every 6 months thereafter. As part of usual care, during follow-up, ICD printouts were obtained to determine the number and type of arrhythmias and number of appropriate and inappropriate shocks. The routine follow-up in some of our patients took place in referring hospitals.

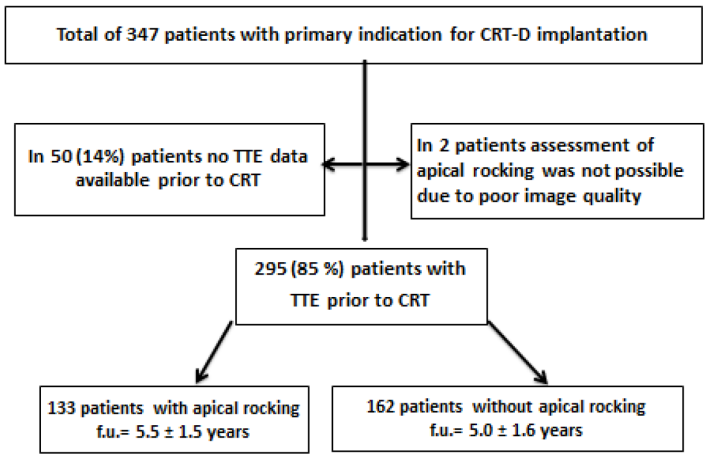


**Figure 1**. Flowchart of study population.

**Data collection**

Baseline characteristics included age, gender, etiology of heart failure, clinical history, medical therapy, NYHA functional class. ECG and procedural data were collected prospectively and analyzed retrospectively. The clinical status of all patients was verified at the closure of the study (December 2013).

**Echocardiographic data acquisition**

All patients underwent two-dimensional echocardiography before biventricular ICD implantation and at follow-up in the second year after CRT implantation. The images were obtained on a Vivid 7 ultrasound machine (General Electric, Milwaukee, WI) using a 3.5 MHz transducer at a depth of 16 cm in the parasternal (long- and short axis) and apical (2- and 4-chamber) views. The images were stored in cine-loop format by well-trained echocardiographists and reviewed by an independent cardiologist who was not involved in the study. The left ventricular end-diastolic diameter (LVEDD), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic diameter (LVESD) and left ventricular end-systolic volume (LVESV) were measured and the left ventricular ejection fraction (LVEF) was calculated using Simpson's technique [16].

**Visual assessment of LV apical rocking**

Apical rocking was defined as a short initial septal contraction which results in short inward motion of the septum and pulls the apex to the septum and then the delayed activation of the lateral wall which pulls the apex laterally during the ejection time while stretching of the septum takes place. This definition was used to assess visually the presence of apical rocking. The presence of apical rocking was visually assessed in 4-chamber apical view by three cardiologists each with more than 6 years of echocardiography experience. All cardiologists had only access to the grey-scale image loops of the three apical image planes and were unaware of any patient data including information about response to CRT. Inter-observer and intra-observer agreement were expressed as kappa coefficients. Values higher than 0.8 are considered as excellent, values between 0.6 and 0.8 as good, values between 0.4 and 0.6 as moderate, and values below 0.4 as poor agreement.

**Event sub-classification and definitions**

Data on mortality were collected from reviewing our hospital records, referring hospitals and by contacting general practitioners. Causes of death were categorized into two groups, cardiac death and non-cardiac death according to previous study [17]. The cardiac death was further categorized into death from ventricular tachyarrhythmia, heart failure-related death and sudden cardiac death. Non-cardiac death was further divided in malignancy, infection

including sepsis and pneumonia, COPD and aortic dissection. In 2 patients, the cause of death was classified as unknown (in 1 patient the family physician was unknown and in another patient digital file was not present).

**Endpoint**

Major adverse cardiac event (MACE) was defined as the combined endpoint of cardiac death and/or heart failure hospitalization and/or appropriate therapy (ATP and/or ICD shocks).

**Statistical analysis**

Statistical analysis was performed using SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY). Continuous variables are expressed as mean±SD and significance of differences between independent groups was calculated using the non-parametric Mann-Whitney U-test. Categorical variables are presented as number and percentages and significance of differences between groups were calculated using the Chi-squared test or Fisher's exact test as appropriate. Cox regression analysis was performed to assess the association of apical rocking with MACE. Clinical variables (age, gender, LVEF, sinus rhythm or atrial fibrillation, QRS width, LBBB/RBBB and ischemic/non-ischemic cardiomyopathy) were entered into the Cox regression analysis as confounders. Time until MACE was plotted using Kaplan-Meier estimates, and groups were compared using log-rank tests. We evaluated the additional value of apical rocking above clinical variables (age, gender, LVEF, sinus rhythm or atrial fibrillation, QRS width, LBBB/RBBB and ischemic/non-ischemic cardiomyopathy) in prediction of MACE by means of the likelihood ratio test. The likelihood ratio test is the difference between the -2 log likelihood of the model with and the model without apical rocking which is Chi-square distributed with 1 degree of freedom. p values of $<0.05$ were considered statistically significant in all analyses.

## RESULTS

Initially 347 patients with prophylactic CRT-D indication were registered in our hospital database. In 50 patients echocardiographic evaluation before the implantation was not available, in 2 patients the assessment of apical rocking was not possible due to poor image quality. Therefore, the study population consisted of 295 patients. Mean age was 67±9 years with 30% female gender. Mean NYHA functional class was 2.5±0.6 and 81% had LBBB with mean QRS duration of 155±30 ms. Mean LVEF was 24.8% ±6.6, non-ischemic etiology was present in 49% of patients. Apical rocking was present in 45% of patients. Apical rocking was

significantly more common in younger patients, females, patients with sinus rhythm, non-ischemic cardiomyopathy, in patients with LBBB and wider QRS duration. All patients were on optimal medical therapy for heart failure. General characteristics of total study population and according to the presence or absence of apical rocking are summarized in Table 1.

**Inter- and intra-observer variability**

To quantify the inter- and intra-observer variability for assessment of apical rocking we reviewed 140 (47%) patients by three cardiologists. The inter-observer variability kappa was 0.85 and intra-observer variability kappa was 0.90.

**Table 1**. General characteristics of study population according to apical rocking

| | All patients (n=295) | Patients with apical rocking (n=133) | Patients without apical rocking (n=162) | p value |
|---|---|---|---|---|
| Age (years) | 67±9 | 65±10 | 69±8 | 0.001 |
| Female | 30% | 41% | 22% | <0.001 |
| LVEF (%) | 24.8±6.6 | 25.0±6.8 | 24.7±6.5 | 0.929 |
| Sinus rhythm | 75% | 81% | 71% | 0.038 |
| QRS duration (ms) | 155±30 | 164±29 | 148±29 | <0.001 |
| LBBB | 81% | 91% | 73% | <0.001 |
| RBBB | 6% | 3% | 9% | 0.055 |
| IVCD | 12% | 6% | 18% | 0.003 |
| NYHA functional class | 2.5±0.6 | 2.5±0.7 | 2.5±0.6 | 0.637 |
| Non-ischemic etiology | 49% | 71% | 31% | <0.001 |
| Diuretics | 82% | 77% | 86% | 0.044 |
| Beta-Blocker | 82% | 85% | 80% | 0.290 |
| AT-II receptor blockers | 43% | 48% | 40% | 0.137 |
| ACE-inhibitors | 76% | 77% | 75% | 0.782 |
| Spironolacton | 44% | 42% | 45% | 0.611 |

LVEF, left ventricular ejection fraction; LBBB, left bundle branch block; RBBB, right bundle branch block; IVCD, intra-ventricular conduction disorder; NYHA, New York Heart Association.

**Table 2.** Clinical endpoints of the study population according to apical rocking during long-term follow-up

| | All patients (n=295) | Patients with apical rocking (n=133) | Patients without apical rocking (n=162) | p value |
|---|---|---|---|---|
| Clinical follow-up duration (years) | 5.2±1.6 | 5.5±1.5 | 5.0±1.6 | 0.016 |
| NYHA functional class follow-up (mean±SD) | 2.0±0.8 | 1.8±0.8 | 2.1±0.7 | 0.003 |
| LVEF follow-up (%) (mean±SD) | 36.6±12.2 | 42.8±10.5 | 31.6±11.2 | <0.001 |
| Percentage biventricular pacing | 93.8±13.4 | 95.3±9.0 | 92.6±16.2 | 0.061 |
| Appropriate ATP therapy | 6% | 4% | 7% | 0.181 |
| Appropriate ICD shock | 9% | 5% | 12% | 0.036 |
| Inappropriate ICD shock | 10% | 9% | 12% | 0.451 |
| All-cause mortality | 21% | 13% | 28% | 0.001 |
| Non-cardiac and unknown cause of death | 10% | 8% | 12% | 0.328 |
| MACE | 31% | 19% | 41% | <0.001 |
| Appropriate therapy (ATP and/or shock) | 12% | 9% | 15% | 0.130 |
| Heart failure hospitalization | 21% | 11% | 29% | <0.001 |
| Cardiac death | 11% | 5% | 17% | 0.001 |

ATP, anti-tachy pacing; ICD, implantable cardioverter defibrillator; MACE, major cardiac adverse event.

**Long-term outcome**

Patients were followed for 5.2±1.6 years and 85.5% completed at least 4 years of follow-up. During follow-up, 63 (21%) patients died. In 97% patients the mode of death was obtained, 52% (33 patients) had a cardiac death. During follow-up, 21% (62/295) of patients were admitted to the hospital due to worsening of heart failure. Appropriate CRT-D (ATP or ICD-shock) intervention occurred in 12% (36/295) of patients and inappropriate CRT-D intervention in 10% (31/295) of patients. Total MACE occurred in 31% of the patients (Table 2). During follow-up, the patients with apical rocking had significantly better NYHA functional class, higher LVEF and experienced higher percentage of biventricular pacing compared to patients without apical rocking. All-cause mortality was significantly lower in patients with apical rocking compared to patients without apical rocking (13% vs 28% p<0.001). Furthermore, MACE was significantly lower in patients with compared to patients without apical rocking (19% vs 41%, p<0.001), Table 2.

**Table 3.** General characteristics of study population according to MACE

| | All patients (n=295) | Patients without MACE (n=204) | Patients with MACE (n=91) | p value |
|---|---|---|---|---|
| Age (years) | 67±9 | 67±9 | 68±9 | 0.176 |
| Female | 30% | 32% | 27% | 0.432 |
| LVEF (%) baseline | 24.8±6.6 | 25.0±6.9 | 24.3±6.0 | 0.513 |
| LVEF (%) follow-up | 36.6±12.2 | 39.5±11.2 | 30.2±11.8 | <0.001 |
| Sinus rhythm | 75% | 79% | 68% | 0.064 |
| QRS duration (ms) | 155±30 | 159±31 | 147±27 | 0.001 |
| LBBB | 81% | 81% | 82% | 0.904 |
| RBBB | 6% | 7% | 5% | 0.590 |
| IVCD | 12% | 12% | 13% | 0.794 |
| NYHA functional class | 2.5±0.6 | 2.5±0.6 | 2.6±0.6 | 0.248 |
| Non-ischemic etiology | 49% | 54% | 38% | 0.013 |
| Diuretics | 82% | 80% | 86% | 0.225 |
| Beta-blocker | 82% | 83% | 80% | 0.604 |
| AT-II receptor blockers | 43% | 43% | 43% | 0.929 |
| ACE-inhibitors | 76% | 75% | 77% | 0.703 |
| Spironolacton | 44% | 42% | 47% | 0.490 |
| LV lead position | | | | |
| Posterior/poterolateral | 204 (69%) | 138 (67%) | 66 (72%) | NS |
| Lateral | 47 (16%) | 34 (17%) | 13 (14%) | NS |
| Anterolateral/anterior | 13 (4%) | 10 (5%) | 3 (3%) | NS |
| Mid-cardiac vein | 8 (3%) | 6 (3%) | 2 (2%) | NS |
| Epicardial | 23 (8%) | 16 (8%) | 7 (7%) | NS |
| Apical position | 89 (33%) | 55 (29%) | 34 (40%) | NS |
| Non-apical position | 183 (67%) | 133 (71%) | 50 (59%) | NS |
| Clinical follow-up duration (years) | 5.2±1.6 | 5.5±1.4 | 4.6±1.7 | <0.001 |
| NYHA class follow-up (mean±SD) | 2.0±0.8 | 1.9±0.8 | 2.3±0.7 | 0.001 |
| Percentage biventricular pacing | 93.8±13.4 | 95.5±9.8 | 90.1±18.8 | 0.005 |
| Presence of apical rocking | 45% | 53% | 27% | <0.001 |

All abbreviations explained in Table 1.

**Apical rocking and MACE**

A total of 204 patients (69%) survived without heart failure hospitalization or appropriate therapy (ATP and/or ICD shocks). A total of 91 (31%) patients died from cardiac death or were hospitalized with heart failure or treated appropriately with ICD, and were classified as patients with MACE. Patients with MACE had significantly shorter QRS duration, had more ischemic aetiology and were more on amiodarone. Furthermore, NYHA functional class was higher and percentage of biventricular pacing was lower compared to patients without MACE (Table 3). Presence of apical rocking between the patients with and without MACE was significantly different (27% vs 53%, respectively, p<0.001) (Table 3 and Figure 2). Results of both univariate and multivariate analyses of the association between apical rocking and MACE are summarized in Table 4. In univariate analyses, MACE was associated with shorter QRS duration, ischemic aetiology and absence of apical rocking. In multivariate analyses, the incidence of MACE was lower in patients with apical rocking (HR 0.44, 95%CI 0.25−0.77, p=0.004) and those with shorter QRS duration (HR 0.87, 95%CI 0.79−0.96, p=0.005). The value of the likelihood ratio test of the comparison of the model with and the model without apical rocking is 8.90 (df=1) with significant p value (p=0.003).

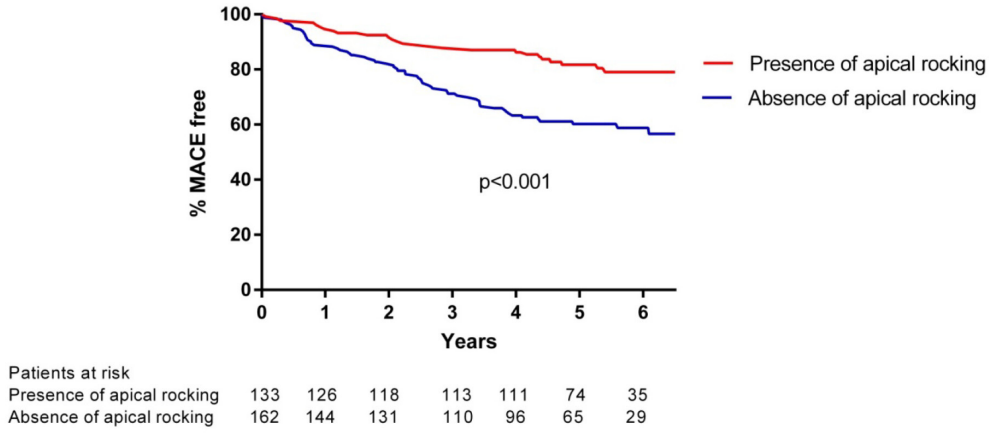


**Figure 2.** Survival without heart failure hospitalization after CRT in patients with or without LV apical rocking.

**Table 4.** Uni- and multivariable predictors of MACE

| | Univariable | | | Multivariable | | |
|---|---|---|---|---|---|---|
| | HR | 95%CI | p value | HR | 95%CI | p value |
| Age (years) | 1.02 | 1.00−1.05 | 0.086 | 1.02 | 0.99−1.05 | 0.197 |
| Female | 0.79 | 0.50−1.25 | 0.317 | 1.43 | 0.85−2.39 | 0.176 |
| LVEF (%) baseline | 0.99 | 0.96−1.02 | 0.580 | 0.98 | 0.95−1.02 | 0.364 |
| Sinus rhythm vs Afib | 0.59 | 0.37−0.93 | 0.024 | 0.65 | 0.37−1.14 | 0.136 |
| QRS duration (per 10 ms) | 0.91 | 0.85−0.97 | 0.005 | 0.87 | 0.79−0.96 | 0.005 |
| LBBB vs non-LBBB | 0.94 | 0.53−1.68 | 0.843 | 0.59 | 0.31−1.12 | 0.108 |
| Non-ischemic etiology | 0.58 | 0.38−0.88 | 0.010 | 0.63 | 0.37−1.07 | 0.084 |
| Presence of apical rocking | 0.39 | 0.25−0.62 | <0.001 | 0.44 | 0.25−0.77 | 0.004 |

All abbreviations explained in Table 1.

**Apical rocking in patients with QRS <150 ms**

Sub-analysis of patients with QRS <150 ms identified 108 patients. Apical rocking was present in 30% (33) of patients compared to 53% in patients with QRS ≥150 ms (p<0.001). MACE was more common in patients without apical rocking compared to patients with apical rocking (49% vs 24%, p=0.015).

**Apical rocking in patients with ischemic etiology**

Wall motion abnormalities (scar tissue due to myocardial infarction) were assessed in all 150 (51%) patients with ischemic etiology. 43% of patients had wall motion abnormalities in the anterior or antero-septum segments. Among this group only 3% had apical rocking compared to 35% apical rocking in patients without wall motion abnormality in anterior or antero-septum segments.

## DISCUSSION

In the present study we assessed the association of baseline apical rocking with major adverse cardiac events during long-term follow-up in patients who underwent CRT-D implantation. This study showed that the presence of apical rocking before CRT is independently associated with a lower incidence of long-term MACE. The significant p value of the likelihood ratio test supports the additional value of apical rocking above clinical variables in prediction of long-term MACE.

**Apical rocking**

In the past years, several dyssynchrony indices have been developed to identify patients who will respond to CRT with promising results in single-center trials. Unfortunately, these indices have performed poorly in larger clinical trials, showing high inter-observer variability and failing to accurately segregate responders and non-responders to CRT before the implantation [6,9,10,12,18−21].

Apical rocking is a typical early septal contraction in patients with left bundle branch block, which pulls the apex towards the septum. Delayed activation of the lateral wall pulls then the apex laterally during the ejection time while the septum is stretching. Apical rocking can be visualized in a standard echocardiographic 4-chamber view in patients with left ventricular dyssynchrony. This is in contrast to several dyssynchrony indices, which require well trained echocardiographist and special imaging software and techniques. Both regional myocardial functional abnormalities (due to scar tissue) and temporal abnormalities (due to activation delay) contribute to apical rocking, and thus both are incorporated in a single echo-cardiographic parameter [22,23]. In current study, among the group of patients with scar tissue in distal part of septum or antero-septum due to myocardial infarction only 3% had apical rocking compared to 35% in patients with scar tissue in other part of LV. It suggests that scar tissue in distal part of septum or antero-septum affects the presence of apical rocking. Apical rocking retains important regional information on the myocardial contraction sequence [24] and overcomes several limitations of peak velocity parameters and avoids the challenges of myocardial deformation measurements. The ability of apical rocking to reflect LV mechanical dyssynchrony has already been demonstrated by its superior predictive power for echocardiographic CRT response [13]. Previous studies compared a quantitative measurement of apical rocking, defined as the percentage of the cardiac cycle with reverse motion of the septum and the apex, with visual assessment of apical rocking and demonstrated a comparable accuracy in predicting CRT response [13,25]. We recently published our data on the predictive value of apical rocking in 137 patients and showed the association of apical rocking with both long-term echocardiographic response and incidence of heart failure [15].

In the current study, we had a much larger number of CRT patients, which consisted of CRT-D patients (CRT and defibrillator therapy). We used MACE during long-term follow-up as outcome measure. CRT results in positive remodelling of the ventricles, and had beneficial effects on cardiac function. This is reflected in both reduction in heart failure symptoms and hospitalization, and also a reduction of cardiac mortality and ventricular tachyarrhythmias (e.g., appropriate ICD therapy). Therefore, MACE is one of the most robust clinical outcome measures reflecting CRT success. The current study, to the best of our knowledge, is the first

and largest study which assessed the association between apical rocking and long-term MACE. The predictive value of absence of apical rocking has been recently studied in a relatively small cohort of CRT patients (n=40) in which absence of apical rocking predicted early hemodynamic non-response after 1 month of CRT [14]. One of the major issues in assessment of LV dyssynchrony is the applicability of a dyssynchrony index in daily clinical practice. One of the advantages of visual assessment of apical rocking, contrary to several other dyssynchrony indices, is that it can be assessed relatively easy and is not time consuming. Other indices have lower inter- and intra-observer agreement, even in core echocardiographic centers [6]. It seems that there is a relationship between QRS duration and presence of apical rocking. In our study population apical rocking was present in 45% of patients, while in patients with QRS <150 ms it is 30%. One of the disadvantages of apical rocking is that not every patient with classic CRT indication shows apical rocking. In our study population, apical rocking was present in only 45% of patients, whereas 70% of the study population did not have MACE. However, when apical rocking is present the percentage of MACE during long-term follow-up is only 19% compared to 41% when apical rocking was not present. Apical rocking was present in 53% of patients without MACE and in 27% of patient with MACE.

**Clinical implication of apical rocking**

Visual assessment of apical rocking is relatively easy and is reproducible. Although current patient selection guidelines for CRT utilize QRS width as a surrogate for dyssynchrony, the results of our study support the additional value of apical rocking in prediction of long-term MACE. Further prospective and multicenter studies are needed to confirm our findings, particularly in patients with QRS duration <150 ms.

**Strengths and limitations**

Both the large number of the study population and the long-term clinical follow-up are probably the major strengths of the current study. There are also several limitations of this study. It concerns a prospective registry of consecutive patients treated with CRT-D in a high experienced CRT center. A subgroup analysis is limited by limited numbers in each group. Visual assessment of apical rocking may be inferior to measuring of the motion and velocities of myocardial walls in mm and cm/s. Since the start of the study, several new echocardiographic dyssynchrony indices have been introduced, particularly with calculation of apical transverse motion [14,22]. However, the study by Tournoux et al. [14] compared a quantitative measurement of apical rocking, defined as the percentage of the cardiac cycle with reverse motion of the septum and the apex, with visual assessment of apical rocking and demonstrated a comparable accuracy in predicting CRT response. The current study

population resembles most closely daily practice with inclusion of patients with atrial fibrillation, and we demonstrated that visualization of apical rocking was not negatively influenced by the inclusion of patients with atrial fibrillation. A new ischemic event in patients with ischemic etiology during long-term follow-up can affect the outcome of the patients. Unfortunately, data on new ischemic events in our study population are not available, which is an important limitation. Suboptimal LV lead placement must also be considered. However, care was taken to minimize this risk by coronary venogram-guided lead placement and all leads were placed in the posterior or lateral region if possible. Unfortunately, we were not able to perform echo-guided optimization after device implantation. In the present study the echocardiograms and assessment of apical rocking were performed at rest. A recent publication suggested [26], however, that low-dose dobutamine stress echocardiography could result in more dyssynchrony and might improve the predictive value of apical rocking.

## CONCLUSION

We demonstrated that apical rocking was present in 45% of the study population. Apical rocking before CRT is independently associated with a lower incidence of long-term MACE.

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CHAPTER 9

# Predictors and long-term outcome of super-responders to cardiac resynchronization therapy

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ABSTRACT

***Background*:** The level of improvement in left ventricular ejection fraction (LVEF) in super-responders to CRT is exceptional. However, the long-term prognosis of these patients is not yet known in a large population. We determined predictors and long-term outcome of super-response to CRT.
***Methods*:** A cohort of 347 patients with CRT-D as primary prevention were registered. Super-response was defined by LVEF >50% at follow-up echocardiogram. Best-subset regression analysis identified predictors of super-response to CRT. End points were major adverse cardiac events (MACE), i.e., all-cause mortality or heart failure hospitalization, cardiac death and appropriate ICD therapy during follow-up.
***Results*:** 56 (16%) patients with LVEF >50% were classified as super-responders to CRT. Female gender (OR=3.06 95%CI 1.54−6.05), non-ischemic etiology (OR=2.70 95%CI 1.29−5.68), higher LVEF at baseline (OR=1.07 95%CI 1.02−1.13) and wider QRS duration (OR=1.17 95%CI 1.04−1.32) were predictors of super-response. Cumulative incidence of MACE at a median of 5.3 years was 18% in super-responders, 22% in responders and 51% in non-responders ($p<0.001$). None of the super-responders died from cardiac death, whereas cardiac death rate was 9% in responders and 25% in non-responders ($p<0.001$). None of the super-responders experienced appropriate ICD therapy, whereas this was 10% in responders and 21% in non-responders ($p<0.001$). In super-responders the adjusted HR for MACE was 0.37 (95%CI 0.19−0.73) and for total mortality 0.44 (95%CI 0.20−0.95).
***Conclusions*:** Female gender, non-ischemic etiology, higher LVEF at baseline and wider QRS duration were independently associated with super-response to CRT. Super-response to CRT was associated with persistent excellent prognosis regarding survival and appropriate ICD therapy during long-term follow-up.

## Introduction

Several large clinical trials have demonstrated that cardiac resynchronization therapy (CRT) reduces symptoms, mortality, heart failure hospitalization and improved cardiac function in the majority of patients with symptomatic heart failure and reduced left ventricular ejection fraction (LVEF $\leq$35%) with wide QRS (>120 ms) [1−3]. There is, however, wide variability in the extent of LV remodelling and improvement in LVEF with CRT. Recent studies have indicated that in certain patients, i.e., 'super-responders', there is an exceptional improvement in LV function after CRT leading to an apparent marked recovery with LVEF >50% and

improvement of LVEF associated with reduced heart failure deaths, ICD shocks and hospitalization [4−6]; also, previous studies demonstrated an excellent long-term prognosis of super-responders [7−12]. However, these studies used different definitions for super-responders and reported different survival and ICD intervention rates. Furthermore, most studies had a relative short follow-up period, and did not assess independent predictors of super-response. Therefore, the aims of our study were to identify the patient's characteristics associated with super-response to CRT, and to evaluate the long-term all-cause and cardiac death, hospitalization due to worsening of heart failure and appropriate defibrillator intervention rate in patients with super-response, in a large cohort.

## METHODS

### Selection of patients

From January 2004 to December 2009, 433 consecutive patients with primary indication for CRT-D implantation were included in registry and followed for median 5.5 years (inter-quartile range [IQR] 4.5−6.5). This registry was approved by institutional review board. Patients were excluded from the analyses if: (1) they had been implanted with cardiac resynchronization therapy without defibrillator (CRT-P), (2) when pre-implantation LVEF was ≥35% accordin g to echocardiographic data, and (3) the patient had had a recent myocardial infarction or CABG (<3 months). In order to be included in the final analysis, the patients were required to have an echocardiogram before CRT-D implantation and during follow-up. Paired echocardiograms from both baseline and follow-up were not available in 86 (20%) patients (of these 86 patients, 42 (48%) patients died before follow-up echo-cardiograms were performed). Therefore, these patients were excluded from the analysis (Figure 1). LVEF assessment was made in all baseline and follow-up examinations (mean echocardiographic follow-up 2.3 years (IQR 1.4−3.9)) examinations. Patients were divided into three groups based on LVEF at follow-up echocardiograms. Patients with LVEF >50% were labeled as 'super-responders' (n=56), those with LVEF=30−50% as 'responders' (n=153), and those with LVEF <35% as 'non-responders' (n=138) [8]. Indication for CRT-D implantation was determined according to the guidelines at time of implantation. In all patients, LVEF was ≤35% and QRS duration was >120 ms because of LBBB, RBBB or non-specific intra-ventricular conduction disorders (IVCD). Heart failure was diagnosed according to the European Society of Cardiology guidelines and the severity of symptoms was categorized into four functional classes as defined by the New York Heart association (NYHA) criteria. Etiology was considered ischemic in the presence of significant coronary

artery disease (≥50% stenosis in one or more of the major epicardial coronary arteries) and/or history of myocardial infarction or prior revascularization by PCI or CABG. Medical therapy was optimized to reach the highest tolerated dosages of angiotensin-converting enzyme inhibitors and beta-blockers.

**Device implantation**

Cardiac resynchronization therapy devices from all major manufacturers (Medtronic, St. Jude Medical, Boston Scientific, Biotronik and Sorin Group) were implanted. The majority of coronary sinus leads were bipolar and were positioned in the lateral, posterolateral or posterior region when feasible (83%). The anterior and anterolateral positions were considered suboptimal and avoided if possible (8%). 9% of coronary sinus leads were positioned epicardially, mostly during open-heart surgery prior to CRT-D implantation. After implantation, tailored device programming was performed before discharge with three consecutive zones in large majority of patients. (1) VT monitor zone between 170−200 beats/min, (2) VT zone with anti-tachycardia pacing (ATP) and shock therapy between 200−230 beats/min, and (3) VF zone with ICD shock >230 beats/min. In ATP and shock therapy zone, arrhythmias were initially attempted to be terminated by two bursts and one ramp and defibrillator shocks were used if the ventricular arrhythmia continued.

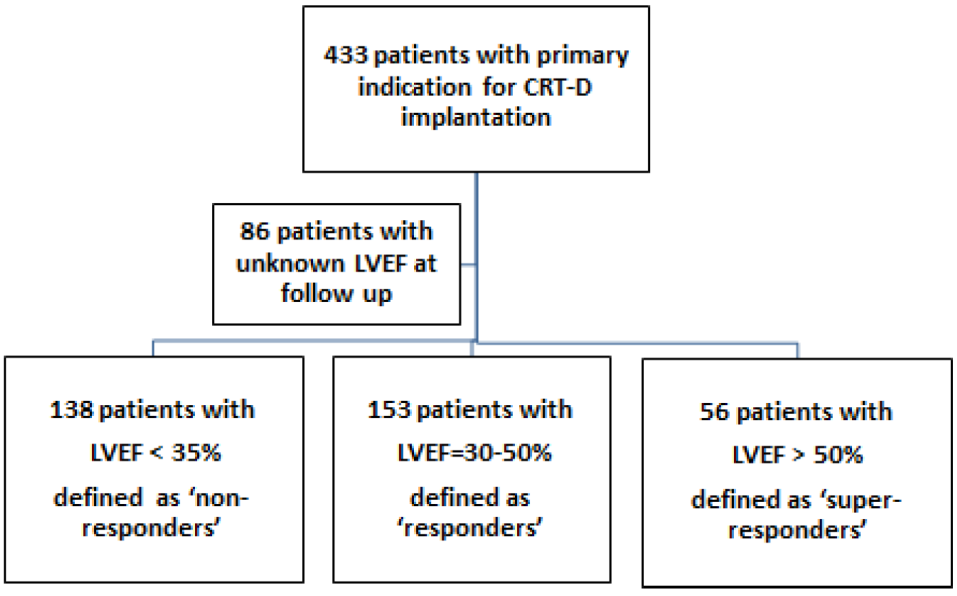


**Figure 1**. Flowchart of study population.

**Follow-up**

Baseline characteristics included age, gender, etiology of heart failure, clinical history, medical therapy, NYHA functional class, ECG and procedural data were collected prospectively and analyzed retrospectively. Routine follow-up visits were scheduled at 2 months post implant, and every 6 months thereafter. As part of routine clinical care during follow-up, ICD printouts were checked, ICD treatments were registered and intracardiac electrograms (EGM) were classified by device-cardiologist. Appropriate ICD therapy (ATP and shocks) was defined as ICD therapy delivered in response to sustained ventricular tachycardia or ventricular fibrillation. The routine follow-up in some of our patients took place in referring hospitals. The clinical status of all survivals at the closure of the study (December 2013) was verified. The baseline echocardiographic data were collected just before implantation and follow-up echocardiograms were repeated after 6−18 months and usually once per year in the years following implantation. The echocardiogram performed between 6 and 18 months after the implantation was used to determine the LVEF response to CRT. The echocardiography images were obtained on a Vivid 7 ultrasound machine (General Electric, Milwaukee, WI) using a 3.5 MHz transducer at a depth of 16 cm in the parasternal (long and short axis) and apical (2- and 4-chamber) views. The images were stored in cine-loop format by well-trained echocardiographists and reviewed by an independent cardiologist who was not involved in the study. The left ventricular end-diastolic diameter (LVEDD), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic diameter (LVESD) and left ventricular end-systolic volume (LVESV) were measured, if possible, and the LVEF was calculated using Simpson's technique [13].

**Event sub-classification and definitions**

Data on mortality were collected from reviewing our hospital records, referring hospitals and by contacting general practitioners. Furthermore, mortality was assessed by linkage of national mortality records with the local hospital database. Causes of death were categorized into 2 groups, cardiac death and non-cardiac death according to a previous study [14]. Cardiac death was further categorized into death from ventricular tachyarrhythmia, heart failure death and sudden cardiac death. Non-cardiac death was further divided in (malignancy, infection including sepsis and pneumonia, COPD and aorta dissection). In 5 patients (6%), cause of death was classified as unknown (in 2 patients the family physician was unknown; in 3 other patients the digital files were not present).

**Endpoints**

The endpoints were defined as follows: (1) Major adverse cardiac event (MACE) was defined as combined all-cause mortality and/or hospitalization due to worsening of heart failure. (2) All-cause mortality. (3) Cardiac death. (4) Appropriate ICD therapy.

**Statistical analysis**

Statistical analysis was performed using SPSS statistical software (IBM Corp., Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Continuous variables are expressed as mean±SD and significance of differences between the three groups were calculated using the non-parametric Kruskal-Wallis test. Categorical variables are presented as number and percentages and significance of differences between groups were calculated using the chi-squared test or the Fisher exact test as appropriate. For paired categorical data the McNemar's test was used. Logistic regression analysis was performed to identify predictors of super-response as one group versus non-response or response as the other group. Cox regression was used to analyze predictors of time until long-term clinical outcome (hospitalization due to heart failure and/or death). The following variables were entered as predictors into the multivariable logistic and Cox regression analysis: age, gender, LVEF, QRS width, NYHA at baseline, atrial fibrillation, percentage of biventricular pacing, and ischemic/non-ischemic cardiomyopathy. The pool of variables considered were those found to be significant at a $p<0.10$ in univariable analysis. In a stepwise backward regression procedure predictors with a p value greater than 0.05 were removed from the model and then the model was refit. Kaplan-Meier estimates for heart failure hospitalization or all-cause death as well as cardiac death or appropriate ICD shock or ATP therapy across LVEF response categories were determined and statistically evaluated with the log-rank test. All p values reported are two-sided with a significance level of $p<0.05$.

## RESULTS

**Overall population characteristics**

Initially 433 patients with prophylactic CRT-D indication were registered in our hospital database. In 86 patients paired echocardiographic evaluations during baseline and follow-up were not available. Therefore, the study population consisted of 347 patients. Mean age was 67±9 years with 70% male gender. Mean NYHA functional class was 2.5±0.6 and 83% had LBBB with mean QRS duration of 154±30 ms. Mean LVEF was 24.8%±6.9. Ischemic etiology was present in 51% of patients. All patients were on optimal medical therapy for

heart failure and 94% experienced adequate biventricular pacing (biventricular pacing ≥94%). Echocardiographic follow-up was performed at median 2.3 years (IQR 1.4−3.9). General characteristics of study population according to the echocardiographic response are summarized in Table 1. A total of 56 (16%) patients were classified as super-responders Female gender (OR=4.13 95%CI 2.28−7.48), non-ischemic etiology (OR=3.14 95%CI 1.68−5.86), higher LVEF at baseline (OR= 1.06 95%CI 1.02−1.11) and wider QRS duration (OR=1.16 95%CI 1.05−1.29) were associated with super-response to CRT. Also after multivariable analysis, female gender (OR=3.06 95%CI 1.54−6.05), non-ischemic etiology (OR=2.70 95%CI 1.29−5.68), higher LVEF at baseline (OR=1.07 95%CI 1.02−1.13) and wider QRS duration (OR=1.17 95%CI 1.04−1.32) were independently associated with super-response to CRT.

**Table 1.** General characteristics of study population by responder category

| | All patients (n=347) | Non-responder (LVEF <35%) (n=138) | Responder (LVEF=30−50%) (n=153) | Super-responder (LVEF >50%) (n=56) | p value |
|---|---|---|---|---|---|
| Age (years) | 67±9 | 67±9 | 66 ±9 | 66±8 | 0.453 |
| Female | 30% | 20% | 28% | 57% | <0.001 |
| Baseline LVEF (%) | 24.8±6.9 | 22.2 ±6.0 | 26.2±6.8 | 27.1±7.5 | <0.001 |
| Sinus rhythm | 75% | 77% | 72% | 78% | 0.543 |
| QRS duration (ms) | 154±30 | 154±28 | 150±30 | 165±32 | 0.009 |
| LBBB | 83% | 78% | 84% | 92% | 0.086 |
| RBBB | 6% | 10% | 5% | 2% | 0.081 |
| IVCD | 11% | 12% | 12% | 6% | 0.498 |
| NYHA | 2.5±0.6 | 2.5±0.6 | 2.4±0.7 | 2.5±0.6 | 0.194 |
| Non-ischemic etiology | 49% | 34% | 54% | 61% | <0.001 |
| Diuretics | 80% | 85% | 75% | 82% | 0.112 |
| Beta-blocker | 81% | 77% | 81% | 91% | 0.072 |
| AT-II antagonists | 48% | 47% | 48% | 52% | 0.839 |
| ACE-inhibitors | 77% | 78% | 74% | 82% | 0.404 |
| Spironolactone | 42% | 42% | 42% | 41% | 0.992 |

Abbreviations: LVEF, left ventricular ejection fraction; LBBB, left bundle branch block; RBBB, right bundle branch block; IVCD, intraventricular conduction delay.

**Table 2.** Clinical and echocardiographic outcome of 347 patients by responder category

| | All patients (n=347) | Non-responders | Responders | Super-responders | p value |
|---|---|---|---|---|---|
| Clinical follow-up duration median (IQR) years | 5.3 (4.5−6.5) | 5.1 (4.1−6.3) | 5.3 (4.6−6.7) | 5.7 (4.6−6.9) | 0.05 |
| NYHA follow-up (mean±SD) | 2.0±0.8 | 2.1±0.7 | 1.9±0.8 | 1.8±0.7 | 0.07 |
| LVEF follow-up (mean±SD) | 36.9±12.3 | 24.4±6.2 | 41.5±4.3 | 54.9±6.0 | <0.001 |
| Appropriate therapy (ATP and/or shock) | 13% | 21% | 10% | 0% | <0.001 |
| ATP successful | 5% | 6% | 7% | 0% | 0.15 |
| Appropriate ICD shock | 10% | 19% | 7% | 0% | <0.001 |
| Inappropriate ICD shock | 12% | 12% | 12% | 13% | 0.98 |
| Percentage of Biv-pacing | 94±13 | 93±15 | 94±10 | 95±15 | 0.02 |
| All-cause mortality | 23% | 37% | 14% | 13% | <0.001 |
| HF hospitalization | 22% | 36% | 14% | 9% | <0.001 |
| MACE (all-cause mortality and/or heart failure hospitalization) | 33% | 51% | 22% | 18% | <0.001 |
| Cardiac death | 14% | 25% | 9% | 0% | <0.001 |
| Non-cardiac and unknown cause of death | 9% | 12% | 5% | 13% | 0.26 |

Abbreviations: IQR= inter-quartile-range, ATP= anti-tachycardia-pacing.

**Long-term outcome**

Patients were followed for median 5.3 years (IQR 4.5−6.5). During this period 80 (23%) patients died (all-cause mortality). In 75 (94%) patients the cause of death was obtained. The cause of death was in 48 cases (14%) cardiac death, in 27 cases (8%) non-cardiac death and in 5 cases (1%) unknown. During total follow-up, 22% of patients were admitted to hospital due to worsening heart failure. In total MACE occurred in 33% and all-cause mortality in 23% of the entire population (Table 2). During follow-up, in 13% of patients appropriate (ATP or ICD shock) and in 12% of patients inappropriate CRT-D intervention occurred. Patients with MACE were significantly older, had more atrial fibrillation, a less wide QRS duration and more ischemic etiology compared to patients without MACE. Furthermore, in patients with MACE NYHA class during follow-up was significantly higher, appropriate ICD therapy was higher and percentage of biventricular pacing was lower compared to patients without MACE (Table 3).

**Table 3**. Characteristics of study population according to MACE (all-cause mortality and/or heart failure hospitalization)

| | All patients (n=347) | Without MACE (n=233) | With MACE (n=114) | p value |
|---|---|---|---|---|
| Age (years) | 67±9 | 66±9 | 69±8 | 0.001 |
| Female | 30% | 32% | 25% | 0.144 |
| LVEF (%) baseline | 24.8±6.9 | 25.0±7.0 | 24.2±6.8 | 0.271 |
| Sinus rhythm | 75% | 79% | 68% | 0.036 |
| QRS duration (ms) | 154.5±30.3 | 156.8±30.8 | 149.6±28.7 | 0.026 |
| LBBB | 83% | 84% | 81% | 0.515 |
| RBBB | 6% | 5% | 9% | 0.301 |
| IVCD | 11% | 11% | 11% | 0.981 |
| NYHA class baseline | 2.5±0.6 | 2.4±0.6 | 2.5±0.6 | 0.083 |
| Non-ischemic etiology | 49% | 54% | 37% | 0.002 |
| Diuretics | 80% | 79% | 83% | 0.293 |
| Beta-blocker | 81% | 83% | 77% | 0.209 |
| AT-II receptor blockers | 48% | 45% | 56% | 0.044 |
| ACE -inhibitors | 77% | 76% | 78% | 0.728 |
| Spironolactone | 42% | 41% | 43% | 0.752 |
| NYHA class follow-up | 2.0±0.8 | 1.8±0.7 | 2.5±0.7 | <0.001 |
| Appropriate therapy (ATP and/or shock) | 13% | 8% | 23% | <0.001 |
| Inappropriate ICD shock | 12% | 11% | 15% | 0.262 |
| Percentage of Biv-pacing | 94±13 | 96±10 | 91±17 | 0.001 |
| Super-response to CRT | 16% | 20% | 9% | <0.001 |
| Response to CRT | 44% | 51% | 30% | <0.001 |
| Non-response to CRT | 40% | 29% | 61% | <0.001 |

Abbreviations as in Tables 1 and 2.

**Super-responders and long-term outcome**

In Figures 2 and 3 the (reverse) Kaplan-Meier survival curves of the clinical endpoints by LVEF response categories are depicted. Super response is associated with a lower probability of adverse clinical outcomes ($p<0.001$). The cumulative incidence of all-cause mortality in super-responders was significantly lower compared to responders and non-responders (13% vs 9% vs 25%, $p<0.001$). In addition, the cumulative incidence of MACE was significantly lower in super-responders compared to the other groups (18% vs 22% vs 51%, $p<0.001$). The cumulative incidence of appropriate CRT-D intervention was (0% vs 10% vs 21%, $p<0.001$). Cardiac death rate was (0% vs 8% vs 38%, $p<0.001$). The rate of non-cardiac death or unknown cause of death was not significantly different between the 3 groups (9% vs 7% vs

13%, p=0.43). Inappropriate CRT-D intervention was not significantly different between the three groups (p=0.98). Remarkably, in super-responders the rate of inappropriate CRT-D intervention was higher than the rate of appropriate intervention (13% vs 0%, p=0.013) (Table 2). In total 12 (13%) patients in super-responder group experienced inappropriate CRT-D intervention with cause of atrial fibrillation in 7 patients, lead malfunctioning in 4 patients and T-wave oversensing in 1 patient.

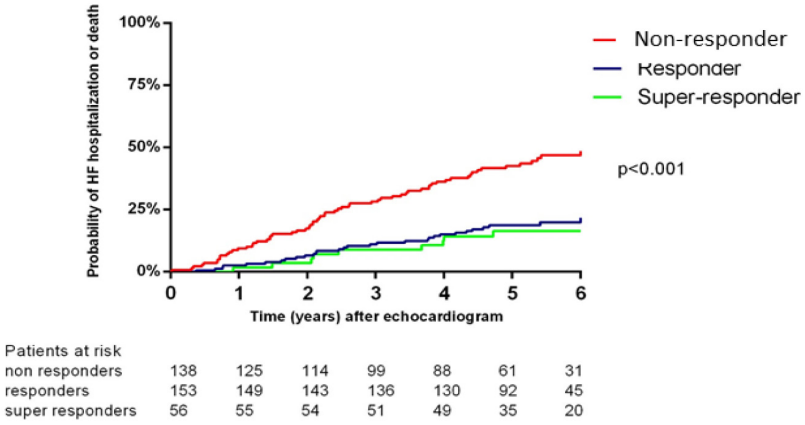


**Figure 2**. All-cause mortality and/or HF hospitalization by response category.

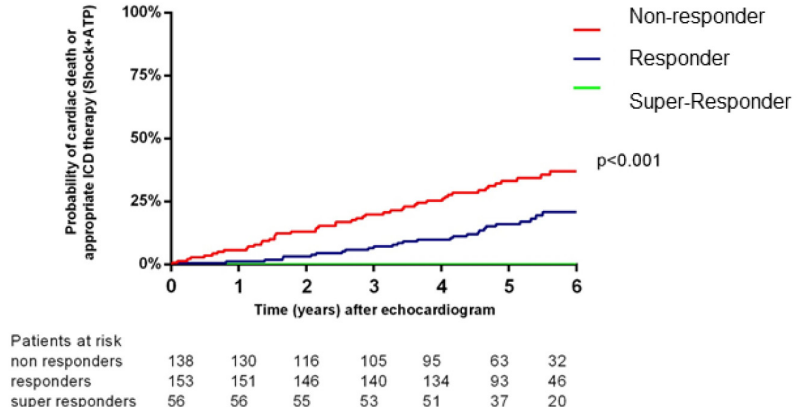


**Figure 3**. Cardiac death or appropriate ICD therapy by response category.

**Table 4**. Multivariable predictors of all endpoints (MACE, all-cause mortality)

| Endpoints | Multivariable analysis [a] | | |
|---|---|---|---|
| | Variables [a] | HR (95%CI) | p value |
| MACE | Super-responders vs other groups | 0.37 (0.19−0.73) | 0.004 |
| | Biventricular-pacing (per 10%) | 0.73 (0.66−0.82) | <0.001 |
| | Age (per 10 years) | 1.54 (1.22−1.95) | <0.001 |
| All-cause mortality | Super-responders vs other groups | 0.44 (0.20−0.95) | 0.037 |
| | NYHA class baseline | 1.68 (1.15−2.46) | 0.007 |
| | Age (per 10 years) | 1.81 (1.36−2.42) | <0.001 |

[a] Only significant predictors are listed.

**Multivariable analyses**

MACE was independently associated with super-response to CRT, percentage of biventricular pacing and age. All-cause mortality was independently associated with super-response to CRT, NYHA class at baseline and age. Cardiac death, in univariable analysis, was associated with age, ischemic etiology, percentage of biventricular pacing and super-response to CRT. Multivariable analysis for cardiac death and appropriate ICD-therapy could not be estimated because none of the super-responders died from cardiac causes or experienced appropriate ICD therapy. Super-responders had at follow-up an independent decreased risk of MACE (HR 0.37 95%CI 0.19−0.73) and all-cause mortality (HR 0.44 95%CI 0.20−0.95) (Table 4).

## DISCUSSION

We demonstrated in a large registry that also after long-term follow-up, super-responders to CRT had a much better prognosis than either responders or non-responders. Annual cardiac death rate and appropriate CRT-D intervention in super-responders was even zero. Since the annual rate of inappropriate intervention in super-responders was high, downgrading CRT-D to CRT-P in super-responders can be a matter of debate, although only randomized trials can definitely demonstrate whether this can be performed safely.

**Improvement of LVEF after CRT**

The degree of response to CRT is variable due to different definitions of improvement or normalization of LVEF. Reduced LVEF is associated with risk of ventricular arrhythmia and sudden death. Randomized controlled trials and guidelines for prophylactic defibrillator implantation to prevent sudden death have relied heavily on this LVEF measurement to qualify for device candidacy [10]. Given the clinical reliance on LVEF as an indication for therapy and for assessing response to CRT-D therapy, we justified the classification of responsiveness to CRT-D on the extent of improvement in LVEF among our study patients. In our study, super-responders had LVEF of mean 54.9±6.0%.

A previous study had shown that the maximal amount of functional and LV remodelling improvement was reached at 2 years following CRT and these improvements sustained in 5 years follow-up [3]. In the current study we performed echocardiographic follow-up at median 2.8 years (IQR 1.4−3.9), which means that all potential LV remodelling has taken place. The definition for super-response to CRT varies between the studies [7−11]. In this study we defined super-response as LVEF ≥50%. Some studies used an absolute LVEF ≥35% or LVEF≥50%, while others used the top quartile of LVEF changes as definition for super-response [6−11]. Using these definitions, super-response was observed in 24−30% [7,11].

In the current study we demonstrated that among several baseline characteristics, female gender, non-ischemic cardiomyopathy, higher LVEF at baseline and wider QRS duration were predictors of super-response to CRT. However, previous studies reported more predictors for super-response to CRT. Female gender, non-ischemic cardiomyopathy, wide QRS ≥150 ms, LBBB, body mass index, QRS shortening after CRT and smaller baseline left atrial volume index were among the predictors for super-responders [6−17]. This difference may be due to slightly different study populations. Our study is smaller, population was older (mean age 67 years) and had more severe heart failure symptoms compared to MADIT-CRT trial which included younger (mean age 63 years) patients with less severe heart failure symptoms.

**Long-term outcome in 'super-responders' to CRT**

In the current study we observed an excellent long-term prognosis without cardiac death or appropriate ICD intervention in super-responders. The all-cause mortality was 13%. One recent study [9] with 330 patients and mean follow-up of 4.1 years showed cardiovascular death of 4% in patients with LVEF overcrossing 35% by CRT. In MADIT-CRT [6] all-cause death occurred in 1.6% and all-cause death or appropriate CRT-D therapy in 5.2% of super-responders. However, in MADIT-CRT, follow-up was shorter (median 15 months). Another recent trial with 259 CRT patients and mean follow-up of 5.6 years showed a cardiovascular mortality of 1.5% and all-cause mortality of 6% in super-responders defined as LVEF >50%

[8]. One of the largest trials[12] with 814 CRT patients, in which 92 (11.7%) patients had an LVEF >50% defined as super-responders to CRT, compared the long-term survival in super-responders with an age- and sex-matched sample from the general population. All-cause mortality in super-responders at mean follow-up (5.7±2.4 years) was 16% and 4.4% (3 patients) received appropriate shocks for VT or VF. The annualized all-cause mortality rate for the super-responders was 3.3% and was not significantly different (p=0.53) from the calculated survival of the age-and sex-matched sample from the general population. One of the major limitations of this latter study [12] is that the investigators reported only data on all-cause mortality and did not report the rate of cardiac death. A CRT-D device prevents specifically cardiac death and not all-cause mortality. Therefore, the findings of our study with no cardiac death in super-responders are more important and provide more insight in the cause of death of super-responders.

**ICD therapy in 'super-responders' to CRT**

*Appropriate ICD intervention***:** Reverse remodelling is associated with risk reduction for ventricular arrhythmia [18,19] CRT partially restores dyssynchron LV contraction and regional heterogeneity of action potential duration which may reduce ventricular arrhythmias [20]. In the current study, no appropriate ICD intervention occurred in super-responders. One previous study reported an appropriate ICD intervention rate of 7% at 5.6 years in super-responders [8]. In MADIT-CRT the secondary endpoint of all-cause death or ICD-therapy was 5.2% at 2 years. However, follow-up of this study was too short and the investigators did not report the exact percentage of ICD therapy. Another study [9] reported no appropriate ICD- intervention observed in patients with 'functional response' to CRT (i.e., LVEF >35% 4 months after implantation) at 3-year follow-up; this follow-up is relatively short compared to our study. One of the recent trial [20] reported appropriate ICD therapy in 27% of super-responders compared to 34% in non-responders during 5-year follow-up. The authors concluded that after the first year of implantation there was no association between the extent of CRT response and reduction of appropriate device therapy. Furthermore, LVEF >45% or <45% did not predict ICD-therapy after the first year of implantation. It is remarkable that LVEF >45% at follow-up did not predict the ICD therapy.

There are some differences between this study [20] and our study. In our study we defined the super-response as LVEF $\geq$50%, whereas, they defined super-response as decreased LVESV $\geq$30%. Another difference is that the echocardiographic follow-up occurred at 6 months after implantation, whereas, we performed at median 2.8 years, which means that all potential LV remodelling has taken place. Device therapy zone is also different, which could lead to more therapy. In our study the risk of significant ventricular tachyarrhythmia in super-responders was entirely eliminated by almost normalization of LVEF as a result of CRT. The most recent

meta-analysis [21] showed that recovery of LVEF post-CRT is associated with significantly reduced appropriate ICD therapy. Patients with recovery of LVEF to ≥45% and those with a primary prevention indication for ICD with LVEF recovery appear to be at lowest risk. The findings of this meta-analysis are entirely in line with our results.

**Clinical implications**

Our data showed an excellent prognosis of super-responders regarding cardiac death or appropriate ICD intervention. Given, the risks and discomfort portended by inappropriate shocks, we suggest that the decision of downgrading CRT-D to CRT-P at the time of elective replacement indication (ERI) or shock-lead problems should be discussed very carefully with every single patient. Moreover, based on our findings, conducting a randomized trial in super-responders, when ERI is reached, comparing continued CRT-D with downgrading to CRT-P should be encouraged.

**Strengths and limitations**

Both the large number of the study population and the long-term clinical and echocardiographic follow-up are probably the major strengths of the current study. There are also several limitations of this study. It concerns observations of a single center that has a great deal of experience with CRT. Furthermore, although the registry was prospective, the current analysis was retrospective. We also did not evaluate other echocardiographic parameters besides LVEF. Some of the echocardiographic findings such as mitral regurgitation, diastolic function and right ventricular function may influence the improvement of LVEF and clinical outcomes of patients. One of limitations is that our echocardiographic follow-up was performed at a median of 2.8 years from implantation. While the majority of studies reported at 6−12 months after implantation, our study focused on patients with available baseline and follow-up echocardiograms. A proportion of patients (20%) were excluded from the analysis. These patients included those who died before follow-up echo and those who were lost to follow-up because of referral to their own regional hospital. However, this proportion of 20% is lower compared to the MADIT-CRT trial, which excluding 31% of patients [6]. Suboptimal LV lead placement or unfavourable pacemaker settings may, at least in part, have contributed to diminished improvement of LVEF and poorer outcome after CRT. In our population, there is no information available on device programming and optimization during follow-up.

## CONCLUSION

Super-responders to CRT have an excellent prognosis during median follow-up of 6 years. Female gender, non-ischemic etiology, higher LVEF at baseline and wider QRS duration are predictors of super-response.

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CHAPTER 10

# Association of apical rocking with super-response to cardiac resynchronization therapy

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## ABSTRACT

***Background*:** Super-responders to cardiac resynchronization therapy (CRT) show an exceptional improvement in left ventricular ejection fraction (LVEF). Previous studies showed that apical rocking was independently associated with echocardiographic response to CRT. However, little is known about the association of apical rocking and super-response to CRT.

***Objectives*:** To determine the independent association of LV apical rocking on super-response to CRT in a large cohort.

***Methods*:** A cohort of 297 consecutive heart failure patients treated with primary indication for CRT-D were included in an observational registry. Apical rocking was defined as motion of the left ventricular (LV) apical myocardium perpendicular to the LV long axis. 'Super-response' was defined by the top quartile of LVEF response based on change from baseline to follow-up echocardiogram. Best-subset regression analysis identified predictors of LVEF super-response to CRT.

***Results*:** Apical rocking was present in 45% of patients. Super-responders had an absolute mean LVEF increase of 27% (LVEF 22.0% ±5.7 at baseline and 49.0% ±7.5 at follow-up). Apical rocking was significantly more common in super-responders compared to non-super-responders (76% and 34%, $p<0.001$). In univariate analysis, female gender (OR 2.39 95%CI 1.38−4.11), lower LVEF at baseline (OR 0.91 95%CI 0.87−0.95), non-ischemic etiology (OR 4.15 95%CI 2.33−7.39) and apical rocking (OR 6.19 95%CI 3.40−11.25) were associated with super-response. In multivariate analysis, apical rocking was still strongly associated with super-response (OR 5.82, 95%CI 2.68−12.61). Super-responders showed an excellent clinical prognosis with a very low incidence of heart failure admission, cardiac mortality and appropriate ICD therapy.

***Conclusion*:** Apical rocking is independently associated with super-response to CRT.


## INTRODUCTION

Cardiac resynchronization therapy with defibrillator (CRT-D) has proven to improve heart failure (HF) morbidity, quality of life, and survival in those with reduced left ventricular ejection fraction (LVEF), advanced HF symptoms, and increased QRS duration [1−5]. Recent studies have indicated super-response in a proportion of patients treated with CRT [6,7]. Identifying potential super-responders to CRT is an important issue because of their excellent prognosis. Previous studies attempted to find easily identifiable clinical factors to predict

super-response to CRT. Female gender, body mass index <30 kg/m$^2$, left bundle branch block (LBBB), QRS duration >150 ms, smaller LV and left atrial (LA) dimensions, shorter duration of HF symptoms, and non-ischemic cardiomyopathy were factors associated with super-response to CRT [8−11], albeit with a relatively weak relation. There is an obvious need for a stronger predictor for these patients. Apical rocking is an easily measured echocardiographic parameter, and has been introduced as a promising predictor of CRT [12−14]. However, to our knowledge, there are no data on the value of apical rocking as a predictor of super-response to CRT. Therefore, the aim of the current study was to assess the value of apical rocking as an independent predictor of super-response to CRT in a large cohort of patients treated with CRT-D.

## METHODS

### Selection of patients

Between 2005 and 2009, patients with primary indication for CRT-D were included in a prospective registry. This study is an extension of our previous study [14] with larger number of patients and longer duration of follow-up. This prospective registry has been approved by the Institutional Review Board. Exclusion criteria were: (1) patients with CRT-P, (2) pre-implantation LVEF >35% according to echocardiographic data, and (3) patients with a history of recent myocardial infarction or CABG (<3 months). Indication for CRT-D implantation was determined according to the guidelines at the time of implantation. In all patients, LVEF was $\leq$35% and QRS duration was >120 ms with LBBB, RBBB or non-specific intra-ventricular conduction disorders (IVCD). Conventional criteria for LBBB were used, which include QRS duration $\geq$120 ms, QS or rS in lead V1, and a monophasic R wave in leads V6 and I without Q waves. Heart failure was diagnosed according to the European Society of Cardiology guidelines. Medical therapy was optimized to reach the highest tolerated dosages of angiotensin-converting enzyme inhibitors and beta-blockers. To be included in the final analysis, patients were required to have an echocardiographic examination before CRT-D implantation and during follow-up. Based on these criteria, a total of 297 patients were eligible for this study as depicted in Figure 1. LVEF assessment was made in all baseline and follow-up. LVEF was calculated using the Simpson's technique [15].

### Device implantation

Cardiac resynchronization therapy devices from all major manufacturers (Medtronic, St. Jude Medical, Boston Scientific, Biotronik and Sorin Group) were implanted. The majority of

coronary sinus leads were bipolar. After implantation, tailored device programming was performed before discharge with three consecutive zones in the large majority of patients. A monitor zone between 170−200 bpm, fast VT zone between 200−230 bpm and VF-zone >230 bpm. In fast VT zone, arrhythmias were initially attempted to be terminated by two bursts and one ramp followed by defibrillator shocks if the arrhythmia continued. Routine follow-up visits were scheduled at 2 months post implant, and every 6 months thereafter. During follow-up, ICD printouts were checked, ICD treatments were registered and intracardiac electrograms (EGM) were classified by a dedicated device cardiologist. Appropriate ICD therapy (ATP and shocks) was defined as ICD therapy delivered in response to sustained ventricular tachycardia or ventricular fibrillation.

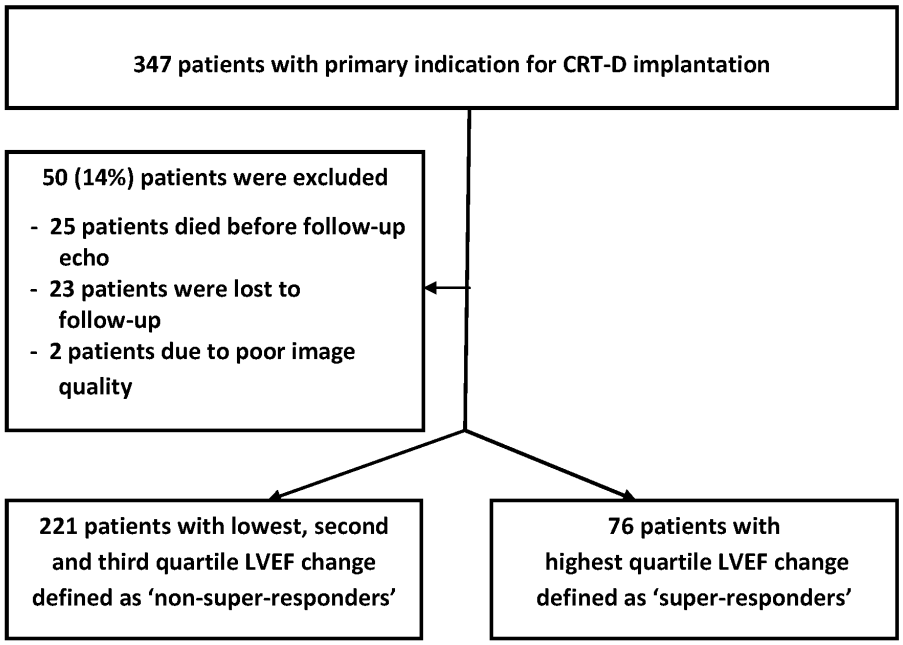


**Figure 1.** Flowchart of study population.

**Visual assessment of LV apical rocking**

Apical rocking was defined as a short initial septal contraction which results in short inward motion of the septum and pulls the apex to the septum and then the delayed activation of the lateral wall which pulls the apex laterally during the ejection time while stretching of the septum takes place. The presence of apical rocking was visually assessed in 4-chamber apical view by three experienced cardiologists who were blinded to the medical history, measured LVEF, and clinical outcome of study population. The presence of apical rocking in some patients was difficult to assess adequately, in these cases we followed the democratic majority. Inter- and intra-observer variability was expressed as kappa coefficients. Values higher than 0.8 are considered as excellent, values between 0.6 and 0.8 as good, values between 0.4 and 0.6 as moderate, and values below 0.4 as poor agreement.

**Table 1.** General characteristics of study population by apical rocking

| | With apical rocking (n=134) | Without apical rocking (n=163) | p value |
|---|---|---|---|
| Age (years) | 65±10 | 69±8 | 0.001 |
| Female | 41% | 22% | <0.001 |
| LVEF (%) | 25.0±6.8 | 24.7±6.5 | 0.929 |
| Sinus rhythm | 81% | 71% | 0.038 |
| QRS duration (ms) | 164±29 | 148±29 | <0.001 |
| LBBB | 91% | 73% | <0.001 |
| RBBB | 3% | 9% | 0.055 |
| IVCD | 6% | 18% | 0.003 |
| NYHA functional class | 2.5±0.7 | 2.5±0.6 | 0.637 |
| Non-ischemic etiology | 71% | 31% | <0.001 |
| Diuretics | 77% | 86% | 0.044 |
| Beta-blocker | 85% | 80% | 0.290 |
| AT-II receptor blockers | 48% | 40% | 0.137 |
| ACE inhibitors | 77% | 75% | 0.782 |
| Spironolacton | 42% | 45% | 0.611 |

**Table 2.** General characteristics of study population by responder category

| | Non-super-responder n=221 | Super-responder n=76 | p value |
|---|---|---|---|
| Age (years) median (IQR) | 69.3 (61.5−74.3) | 67.6 (59.4−72.9) | 0.262 |
| Female | 25% | 45% | 0.002 |
| LVEF (%) median (IQR) | 25.0 (21.0−30.0) | 22.0 (18.0−25.5) | <0.001 |
| Sinus rhythm | 75% | 76% | 0.821 |
| QRS duration (ms) median (IQR) | 160 (135−173) | 160 (132−182) | 0.238 |
| LBBB | 80% | 86% | 0.281 |
| RBBB | 7% | 5% | 0.770 |
| IVCD | 13% | 9% | 0.432 |
| NYHA functional class median (IQR) | 3.0 (2.0−3.0) | 3.0 (2.0−3.0) | 0.502 |
| Non-ischemic etiology | 40% | 74% | <0.001 |
| Diuretics | 83% | 79% | 0.452 |
| Beta-blocker | 81% | 87% | 0.216 |
| AT-II receptor blockers | 42% | 47% | 0.383 |
| ACE inhibitors | 76% | 74% | 0.625 |
| Spironolacton | 46% | 38% | 0.253 |
| Presence of apical rocking | 34% | 76% | <0.001 |

**Endpoint**

Patients with paired echocardiograms were divided into quartiles of LVEF response to CRT based on change from baseline to follow-up echocardiograms. Two groups based on response to CRT were defined and labeled as ‘super-responders’ and ‘non-super-responders’ [11]. Super-response to CRT was defined by the highest quartile of LVEF change (n=76) and non-super-response by the lowest, second and third quartiles of LVEF change (n=221).

**Statistical analysis**

Statistical analysis was performed using SPSS statistical software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Continuous variables were expressed as mean±SD and significance of differences between independent groups were calculated using the non-parametric Mann-Whitney U-test. Categorical variables were presented as number and percentages and significance of differences between groups were calculated using the Chi-squared test or Fisher’s exact test as appropriate. Logistic regression analysis was performed to assess the univariable and multivariable predictors

super-response versus non-super-response. We computed the sensitivity and specificity of apical rocking in predicting super-response. The probability of clinical outcomes was plotted using Kaplan-Meier estimates, and groups were compared using log-rank tests. p values <0.05 were considered statistically significant in all analyses.

## RESULTS

### Baseline characteristics

Initially 347 patients with prophylactic CRT-D indication were registered in our hospital database. Paired echocardiograms from both baseline and follow-up were not available in 50 (14%) patients. Of these patients, 25 (50%) patients died before follow-up echocardiograms were performed. Therefore, these patients were excluded from analysis. The final study population consisted of 297 patients (Figure 1). Echocardiographic follow-up was performed at median 2.1 years (IQR 1.4−3.2) after device implantation. General characteristics of the study population are summarized in Tables 1 and 2. The median age was 68.7 (IQR 58−78) years with 30% female gender. Median LVEF was 24.8% (IQR 20−30%), LBBB was present in 81%, the median QRS duration was 160 ms (IQR 132−182 ms) and 49% of patients had non-ischemic aetiology. The coronary sinus leads were positioned in the lateral, posterolateral or posterior region in 83% and anterolateral or anterior in 8% of patients. Furthermore, 9% of LV leads were positioned epicardially during open-heart surgery prior to CRT-D implantation. A total of 76 patients were classified as super-responders. A higher proportion of women, patients with non-ischemic etiology and with baseline apical rocking were present in super-responders to CRT. At the follow-up, the median LVEF was 37% (IQR 20−32%) in all patients, 38% (IQR 30−43%) in non-super-responders and 49 % (IQR 45−52%) in super-responders (p<0.001) (Table 3).

### Inter- and intra-observer variability

To quantify the inter- and intra-observer variability for assessment of apical rocking, we reviewed 140 (47%) patients by three cardiologists. The inter-observer variability kappa was 0.85 and intra-observer variability kappa was 0.90 between all three cardiologists.

**Table 3.** LVEF changes and presence of apical rocking between different groups at baseline and follow-up.

| | Non-super-responders (n=221) | | Super-responder (n=76) | p value |
|---|---|---|---|---|
| | Non-responders (n=73) | Responders (n=148) | | |
| LVEF (%) at baseline median (IQR) | 25.0 (21.0−29.0) | 25.0 (21.0−31.5) | 22.0 (18.0−25.5) | <0.001 |
| LVEF (%) during follow-up median (IQR) | 24.0 (20.0−28.0) | 38.0 (30.0−43.0) | 49.0 (45.0−52.0) | <0.001 |
| LVESV decrease (ml) mean±SD | 4.3±35.8 | 31.4±37.6 | 86.5±61.6 | <0.001 |
| Presence of apical rocking | 15% | 44% | 76% | <0.001 |

The groups were defined as: Super-responders the highest quartile of LVEF change, responders the second and third quartiles of LVEF change, and non-responders the lowest quartile of LVEF change.

**Long-term outcome of super-responders**

Patients were followed for a median of 5.2 years (IQR 4.4−6.2). During this period 63 (21%) patients died (all-cause mortality). The mode of death was cardiac in 33 patients (11%) and non-cardiac or unknown in 30 patients (10%). All-cause mortality in super-responders was significantly lower compared to non-super-responders (11% vs 25%, p=0.008, Figure 2A). None of super-responders died from a cardiac cause, whereas a cumulative incidence of cardiac cause up to 20% was observed in non-super-responders (Figure 2C). During total follow-up, 21% of patients were admitted to hospital due to worsening of heart failure. Rate of hospitalization was significantly lower in super-responders compared to non-super-responders (8% vs 25%, p=0.001, Figure 2B). Appropriate CRT-D shock was significantly lower in super-responders compared to non-super-responders (1% vs 12%, p=0.006, Figure 2D). Inappropriate ICD shock did not differ between the super-responders and non-super-responders (10% vs 11%, p=0.977).

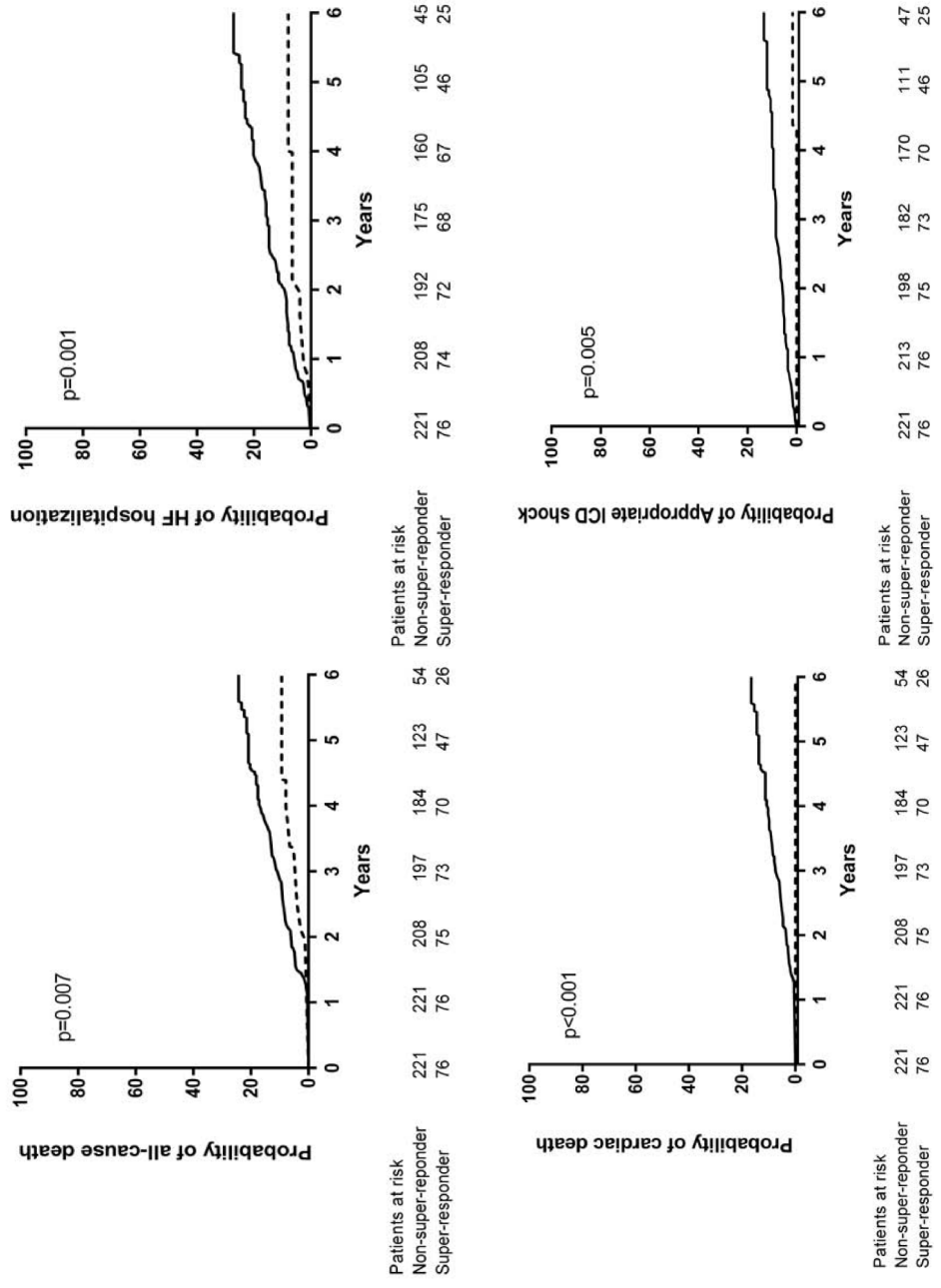


**Figure 2.** Kaplan-Meier estimates of cumulative probability of all-cause mortality (a), heart failure hospitalization (b), cardiac death (c) and appropriate ICD shocks (d) stratified by response category. ——— , non-super -responders; — — —, super-responders.

**Table 4**. Multivariate association to CRT super-response

| | Odds ratio | 95%CI | p value |
|---|---|---|---|
| Age (years) | 1.01 | 0.97−1.05 | 0.585 |
| Female | 2.14 | 1.07−4.29 | 0.032 |
| LVEF (%) baseline | 0.89 | 0.84−0.94 | <0.001 |
| QRS duration (per 10 ms) | 0.98 | 0.87−1.12 | 0.795 |
| LBBB vs non-LBBB | 0.91 | 0.33−2.49 | 0.858 |
| Non-ischemic etiology | 1.99 | 0.96−4.12 | 0.063 |
| Presence of apical rocking | 5.82 | 2.68−12.61 | <0.001 |

Adjusted for age, gender, LVEF, QRS width, LBBB/RBBB and ischemic/non-ischemic cardiomyopathy.

**Apical rocking and super-response to CRT**

Presence of apical rocking between super-responders and non-super-responders to CRT was significantly different (76% and 34%, respectively, p<0.001). Presence of apical rocking predicted super-response to CRT with a sensitivity of 76% and a specificity of 66%. The positive predictive value of apical rocking in predicting super-response response was 44% and the negative predictive value was 89% and the accuracy was 68%. In univariate analysis, female gender (OR 2.39 95%CI 1.38−4.11), LVEF at baseline (OR 0.91 95%CI 0.87−0.95), non-ischemic etiology (OR 4.15 95%CI 2.33−7.39) and apical rocking (OR 6.19 95%CI 3.40−11.25) were associated with super-response to CRT. In multivariate analysis, female gender (OR 2.14 95%CI 1.07−4.29), LVEF at baseline (OR 0.89 95%CI 0.84−0.94) and apical rocking (OR 5.82 95%CI 2.68−12.61) were associated with super-response to CRT after adjustment for age, LVEF baseline, QRS duration, LBBB vs non-LBBB, non-ischemic etiology and presence of apical rocking (Table 4).

## DISCUSSION

The present study assessed the association of apical rocking with super-response to CRT in a large cohort of patients. Apical rocking was strongly associated with super-response. Furthermore, super-responders had a lower incidence of cardiac death, heart failure hospitalization and appropriate ICD shocks.

Super-response is associated with decreased cumulative probability of HF or all-cause mortality and ICD therapy for ventricular tachycardia or ventricular fibrillation. Therefore, predicting super-response is important. Previous studies tried to find predictors of super-response. LBBB and smaller LA volume were previously identified as predictors of super-response [16,17]. The MADIT-CRT trial [11] identified female gender, no prior myocardial infarction, QRS duration $\geq$150 ms, LBBB, BMI <30 kg/m$^2$ and smaller left atrial volume index as predictors of super-response.

The present study assessed several general characteristics and apical rocking as echocardiographic parameter to predict the potential super-response and identified lower baseline LVEF, female gender and apical rocking as predictors of super-response to CRT. Although the association of higher baseline LVEF with 'normal CRT response' has been established, in current study lower baseline LVEF was associated with 'super-response to CRT'. One of the recent trials [18] demonstrated that super-responders had lower baseline LVEF compared to non-/modest-responders (22.6 vs 25.8%, p<0.001). Our results are in line with this trial. However, in MADIT-CRT trial [11] there were no significant differences in baseline LVEF between super-responders and non-super-responders. Apical rocking, as we recently published, predicted the response to CRT [14] and can be visualized in a standard echocardiographic 4-chamber view. This is in contrast to several dyssynchrony indices, which require well-trained echocardiographist and special imaging software and techniques. Previous study compared a quantitative measurement with visual assessment of apical rocking and demonstrated a comparable accuracy in predicting CRT response [13]. Therefore, we decided in this study to use only visual assessment which can be assessed easily with a good inter- and intra-observer variability. In 2007 Jansen et al. [19] described apical shuffle as an abnormal systolic septal-to-lateral motion of the left ventricle. Apical shuffle, defined as an abnormal systolic septal-to-lateral apical motion of left ventricle, has been shown to be predictive of LV reverse remodelling with sensitivity and specificity between 70−90%. The investigators, however, did not describe the pathophysiologic mechanism of apical shuffle. In recent years, the pathophysiologic mechanism of apical rocking, defined as short-lived early septal motion of the apex and a predominantly lateral motion during ejection, has been described in two separate publications [12,13]. Apical rocking is the same phenomenon as described by Jansen et al. [19]; however, they called this abnormal movement of the apex 'apical shuffle'. Septal rebound stretch (SRSsept) is another relatively new dyssynchrony parameter. Previous studies [20−22] demonstrated the strong association of SRSsept with CRT response. Septal rebound stretch reflects the amount of stretch in septum during systole and seems comparable with 'multiphasic septal motion' which has been described by Jansen et al. [19]. However, in current study we did not assess the predictive value of SRSsept on 'super-response to CRT' because we only had data on septal rebound stretch in a minority of

patients. Our study, as far as we can ascertain, is the first study to demonstrate the association between apical rocking and super-response. Although we predefined our LVEF response categories carefully, and found a strong association between apical rocking and super-response, we realize that our results should be confirmed in large multicenter trials. Although apical rocking has a strong association (OR 5.82, 95%CI 2.68−12.61) with super-response as compared to patients without apical rocking, we emphasize that even in patients with apical rocking only 44% is super-responder. This low positive predictive value of 44% is dependent on the definition of super-response and low prevalence of super-response in our cohort. The absence of apical rocking is a strong predictor of non-super-response with a negative predictive value of 89%. However, the absence of apical rocking was not our focus in the current study.

The response to CRT can change over time, particularly shortly after CRT. In our cohort echocardiographic examination after CRT implantation was performed after a mean of 2.1 years (IQR 1.4−3.2). The time from implantation to follow-up echocardiogram was comparable in both groups [in non-super-responders 2.1 years (IQR 1.4−3.3) and in super-responders 2.1 years (IQR 1.4−3.1), p=0.80)]. So, we do not think that timing of echo-cardiography caused misclassification of super-responders.

**Long-term outcome in 'super-responders' to CRT**

The cumulative probability of all-cause mortality, heart failure hospitalization, cardiac death and appropriate ICD therapy for ventricular tachycardia or ventricular fibrillation differed significantly across LVEF response categories at 6 years of follow-up, with improved event-free survival based on magnitude of response (Figure 2). In the current study we observed 11% all-cause mortality, 8% hospitalization due to heart failure and 1% appropriate ICD therapy in super-responders. None of super-responders died from cardiac causes. In MADIT-CRT [11], all-cause death occurred in 1.6% and all-cause death or appropriate CRT-D therapy in 5.2% of super-responders. However, in MADIT-CRT, follow-up was shorter (median 15 months). Another recent trial with 259 CRT patients and mean follow-up of 5.6 years showed a cardiovascular mortality of 1.5% and all-cause mortality of 6% in super-responders defined as LVEF>50% [23]. One of the largest trials with 92 super-responders (LVEF>50%) demonstrated that the survival rate was similar to that of the age- and sex-matched general population with appropriate shocks in 4.4% of patients [24] during a mean follow-up of 5.7±2.4 years. Given the good prognosis of super-responders which is demonstrated in previous studies, including the current study, we should be able to identify these patients and apical rocking may play an important role.

**Clinical implications**

Identification of potential super-responders prior to implantation and during follow-up has several advantages. Super-responders have very good prognosis in terms of lower rate of heart failure hospitalization and all-cause mortality. Furthermore, the incidence of cardiac death or appropriate ICD therapy is very low. These are important issues to discus with the patients prior to implantation. In super-responders, during the follow-up when device change is necessary due to battery depletion or when high voltage RV lead shows dysfunction, downgrading from CRT-D to CRT-P can be discussed. Absence of apical rocking has a strong relation with 'non-super-response'. It may therefore be used to identify the non-super-responders who require possible more intensive monitoring during follow-up.

**Strengths and limitations**

Both the large size of the study population and the long-term clinical follow-up are probably the major strengths of the current study. For the definition of 'super-response' we used the top quartile of LVEF response based on change from baseline to follow-up, exactly the same definition as MADIT-CRT trial [11], whereas other studies used an absolute LVEF >50% as cut-off for super-response. Using changes in LVEF as definition for super-response can be difficult to interpret. A patient can show both a decrease and an increase in LVEDV and LVESV, so that the LVEF remains relatively unchanged. Therefore, non-response or response to CRT can remain unnoticed. The follow-up echocardiographic examinations were performed at median 2.1 of years (IQR 1.4−3.2), which means that all potential LV remodelling has taken place as demonstrated in a previous study [5]. However, majority of the studies performed the follow-up echocardiography at 6−12 months post-implantation. Furthermore, our data concern observations of a single center; however, with high experience in CRT. Our study focused on patients with available baseline and follow-up echocardiograms. Therefore, a proportion of patients (14%) were excluded from the analysis. These patients included those who died before follow-up echo or were lost to follow-up because of referral to their own regional hospital. Another limitation of the current study is that the Kaplan-Meier graphs started immediately after the implantation, whereas defining of response group by follow-up echocardiograms took place at mean 2.1 years. The current study population most closely resembles real life with inclusion of patients with atrial fibrillation. Visualization of apical rocking was not negatively influenced by the inclusion of patients with atrial fibrillation. Suboptimal LV lead placement or unfavorable pacemaker settings may, at least in part, have contributed to diminished improvement of LVEF and

poorer outcome after CRT. In our population, no information is available on optimization during follow-up.

## CONCLUSION

Apical rocking is independently associated with super-response to CRT. Apical rocking may therefore play an important role in identifying these patients, who seem to have a good long-term prognosis. Absence of apical rocking has a high negative predictive value for prediction of non-super-response.

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CHAPTER 11

# Summary
# and
# General discussion

SUMMARY

Cardiac resynchronization therapy improves left ventricular function, NYHA functional class, quality of life and reduces mortality and heart failure hospitalization in patients with symptomatic heart failure with reduced LVEF and wide QRS duration. Unfortunately, 30−40% of patients do not show response to CRT. Therefore, a reliable echocardiographic tool will be required to predict response to CRT and correctly identify those patients who may benefit most from this costly therapy. Since appropriate CRT corrects LV dyssynchrony, it is crucial that LV dyssynchrony is recognized. Previous studies have investigated several echocardiographic methods to evaluate LV dyssynchrony; however, it was difficult to find a response predictor with high efficacy.
Therefore, the main goals of this thesis were to study the potential role of relatively new echocardiographic methods to establish LV dyssynchrony, prediction of response and the prognosis of patients who underwent CRT implantation. In the following chapters our results are summarized.

In an overview, Chapter 1, general information on definition, prevalence, pathophysiological mechanism and pharmacological therapy of heart failure are provided. Additional value of ICD implantation on survival in heart failure patients under optimal medical therapy is also addressed. Mechanism of action of CRT in heart failure patients with wide QRS duration as well as the beneficial effects of CRT on functional class, reverse remodelling of LV, reduction in hospitalization and mortality are discussed. Several important issues such as response, super-response and non-response to CRT are explained. Finally, the manner in which these issues can be predicted by echocardiographic tools is discussed.
We evaluate device-related re-intervention within 1 year following implantation in Chapter 2. We collected the data prospectively, over a period of 2 years, from 1929 patients who had been implanted with either pacemaker, ICD or CRT devices. Almost 31% of patients underwent a CRT implantation. In total 3909 leads were implanted. To identify the lead-related complications, the database was searched on re-intervention procedures during the first year. Lead-related re-intervention was necessary in 86 (4.4%) patients. The cause of re-intervention was mainly lead dislodgement (66%), followed by malfunctioning (20%) and perforation (18%). Re-intervention was more common in men compared to women and younger patients. Coronary sinus lead dislodgement or malfunctioning was 1.4%. Right atrial lead dislodgement (1.9%) and ICD lead dislodgement (1.8%) were more common than right ventricular pacemaker lead dislodgement (0.3%). The incidence of lead malfunctioning was higher (0.8%) in ICD leads. Apical position of the right ventricular lead and lateral wall position of the right atrial lead were related to cardiac perforation.

We investigated the mechanical activation pattern of LV in pacing-induced LBBB (RV pacing) and intrinsic LBBB in order to assess the LV dyssynchrony in these patients correctly. We studied 74 patients with heart failure who had been referred for cardiac resynchronization therapy, 37 patients with chronic RV apical pacing and 37 patients with intrinsic LBBB. Echocardiographic study including 2D speckle tracking longitudinal strain and M-mode were performed at baseline in all patients. We present the results in Chapter 3. When compared to mechanical activation in intrinsic LBBB, RV pacing results less often in early basal activation and more often in early mid-septal and late lateral wall activation. Imaging techniques that only visualize the basal or mid-part of the LV may result in a serious underestimation of dyssynchrony in patients with pacing-induced LBBB. The differences in mechanical activation may have implications for the selection of potential candidates for cardiac resynchronization therapy.
LV dyssynchrony was assessed with time-based speckle tracking longitudinal and radial strain in order to predict response to CRT. In Chapter 4, we studied 138 consecutive patients with symptomatic heart failure and CRT-D implantation. Six different time-based LV dyssynchrony parameters were assessed with longitudinal and radial strain. Response to CRT was defined as a reduction in LV end-systolic volume of $\geq$15%, or survival without heart failure hospitalization. 70% were classified as echocardiographic responders and 83% as clinical responders. QRS duration and non-ischemic etiology predicted echocardiographic response to CRT. None of the speckle tracking parameters was different between echocardiographic responders and non-responders to CRT. Regarding clinical response, only the maximal delay between six segments in 4-chamber view measured with longitudinal strain was different between responders and non-responders, with 154 ms delay as the optimal cut-off value. Our conclusion was that only maximal delay between six segments in 4-chamber view as assessed with longitudinal strain was associated with clinical response to CRT.

The association between the changes in the extent of LV dyssynchrony as a result of CRT and response to CRT was investigated in a cohort of 138 patients. Time-based speckle tracking longitudinal strain was used to assess LV dyssynchrony at baseline and during follow-up. CRT response was defined as a reduction in LV end-systolic volume of $\geq$15%, and 70% were classified as responders. In Chapter 5 we present the results. In the total study group, LV dyssynchrony decreased from 196±89 ms at baseline to 180±105 ms during follow-up, p=0.01. Moreover, in responders there was a pronounced reduction in LV dyssynchrony (198±88 ms at baseline versus 154±50 ms after CRT, p<0.001), whereas in non-responders there was a significant increase (191±92 ms at baseline versus 243±160 ms after CRT, p=0.04). After adjustment for age, gender, QRS duration, baseline LVEF, LBBB/RBBB and

non-ischemic/ischemic etiology, decrease in LV dyssynchrony was significantly associated with response to CRT.

Septal rebound stretch (SRSsept) is a relatively new imaging technique which uses speckle tracking longitudinal strain. It reflects an inefficient deformation of the septum during systole. In Chapter 6, we evaluate the predictive value of SRSsept on response to CRT in our cohort of 138 patients. Response to CRT was defined as a reduction in LV end-systolic volume of ≥15%, and 70% were classified as responders. Baseline SRSsept was significantly higher in responders compared to non-responders (5.1±3.2 vs 3.0±2.7, p<0.001). The optimal cut-off value for SRSsept was 4%. After both univariate (OR 3.74, 95%CI 1.72−8.10) and multivariate analyses (OR 3.71, 95%CI 1.49−9.2), a baseline SRSsept of >4% independently predicted the response to CRT.
Apical rocking is a short initial septal contraction which results in a short inward motion of the septum that pulls the apex to the septum and then the delayed activation of the lateral wall pulls the apex laterally during the ejection time while stretching of the septum takes place. Small studies suggested that it may predict CRT response. The predictive value of LV apical rocking on response to CRT in our cohort (n=137) is assessed in Chapter 7.
Echocardiographic response to CRT was defined as a reduction in LV end-systolic volume of ≥15%, and clinical response as survival without heart failure hospitalization. Apical rocking was present in 49% of patients. Apical rocking was more common in females, younger patients, and patients with non-ischemic cardiomyopathy. Echocardiographic response to CRT was observed in 69%, clinical response in 77% of patients. Apical rocking was associated with both echocardiographic response (OR 10.77, 95%CI 4.12−28.13) and clinical response to CRT (HR 2.73, 95%CI 1.26−5.91). Also, after multivariable analyses, apical rocking was associated with both echocardiographic (OR 9.97, 95%CI 3.48−28.59) and clinical response to CRT (HR 2.13, 95%CI 0.94−4.83).

The association between apical rocking and long-term clinical outcome in a large cohort of 297 patients treated with primary indication for CRT-D is evaluated in Chapter 8. Endpoint MACE (Major Adverse Cardiac Event) was defined as combined endpoint of cardiac death and/or heart failure hospitalization and/or appropriate therapy (ATP and/or ICD shocks). During a mean clinical follow-up of 5.2±1.6 years, 92 (31%) patients reached the endpoint of the study (MACE). Patients with MACE had shorter QRS duration, more ischemic cardiomyopathy and were more on Amiodarone. Apical rocking was present in 45% of the study patients. Apical rocking was significantly more common in patients without MACE compared to those with MACE (53% vs 27%, p<0.001). After multivariable analyses, baseline apical rocking was associated with MACE (HR 0.44, 95%CI 0.25−0.77).

Super-responders are patients with marked recovery of LV function and LVEF >50% as results of CRT. We determined predictors and long-term outcome of these patients, results are presented in Chapter 9. 347 patients with CRT-D as primary prevention were evaluated. Super-response was defined by LVEF ≥50% at follow-up echocardiogram. End points were major adverse cardiac events (MACE), i.e., all-cause mortality or heart failure hospitalization, cardiac death and appropriate ICD therapy. 56 (16%) patients were classified as super-responders. Female gender (OR=3.06 95%CI 1.54−6.05), non-ischemic etiology (OR=2.70 95%CI 1.29−5.68), higher LVEF at baseline (OR=1.07 95%CI 1.02−1.13) and wider QRS duration (OR=1.17 95%CI 1.04−1.32) all were predictors of super-response. Cumulative incidence of MACE at a median of 5.3 years was 18% in super-responders, 22% in responders and 51% in non-responders ($p<0.001$). None of the super-responders died from cardiac death, whereas cardiac death rate was 9% in responders and 25% in non-responders ($p<0.001$). None of the super-responders experienced appropriate ICD therapy, whereas this was 10% in responders and 21% in non-responders ($p<0.001$). In super-responders the adjusted HR for MACE was 0.37 (95%CI 0.19−0.73) and for total mortality 0.44 (95%CI 0.20−0.95). Super-response to CRT was associated with persistent excellent prognosis regarding survival and appropriate ICD therapy during long-term follow-up.

The potential association between super-responders and apical rocking in a cohort of 297 patients with primary indication for CRT-D implantation is described in Chapter 10. The definition of super-response was the top quartile of LVEF response based on change from baseline to follow-up echocardiogram after CRT. Apical rocking was present in 45% of patients. Apical rocking was significantly more common in super-responders compared to non-super-responders (76% and 34%, $p<0.001$). In univariate analysis, female gender (OR 2.39 95%CI 1.38−4.11), LVEF at baseline (OR 0.91 95%CI 0.87−0.95), non-ischemic etiology (OR 4.15 95%CI 2.33−7.39) and apical rocking (OR 6.19 95%CI 3.40−11.25) were associated with super-response to CRT. In multivariate analysis, apical rocking was still strongly associated with super-response to CRT (OR 5.82, 95%CI 2.68−12.61). Super-responders showed an excellent clinical prognosis with a very low incidence of heart failure admission, cardiac mortality and appropriate ICD therapy.

## GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Although a wide QRS complex of >120 ms is required for CRT implantation, it is not a guarantee for response to CRT. Predictive value of electrical dyssynchrony, particularly wide QRS duration, on CRT response is generally low. The major target of CRT is restoration of

mechanical dyssynchrony. It has become clear that mechanical dyssynchrony is not simply reflected by QRS duration alone. Echocardiograpy, despite its own limitations, helps to understand the complexity of LV mechanics, has proven to give a better selection of patients who will benefit from CRT, and also provides prognostic information. Measuring mechanical dyssynchrony, by one way or the other, is in general time-consuming and requires highly trained physicians. In this thesis we investigated several echocardiographic tools to assess mechanical dyssynchrony in order to predict CRT response. Our intention was to select those tools which reflect the dyssynchronous contraction caused by dyssynchronous electrical activation, without the need for complicated measurements, relatively easy to use in daily clinical practice, available in every clinic and with high positive predictive value.

***Apical rocking***, which is investigated in this thesis, has the potential to reflect the dyssynchronous contrction pattern of LBBB. It has a high positive predictive value (85−90%) on prediction of either clinical or echocardiographic response [1,2]. Furthermore, the visual assessment of apical rocking is relatively easy, reproducible and not time-consuming. It overcomes several limitations of peak velocity parameters and avoids the challenges of myocardial deformation measurements. Its potential value on the prediction of long-term outcomes has been confirmed in this thesis. Most recently, the largest trial [3] on the predictive value of apical rocking has been published, which provides much more support for our results in this thesis. In our view, apical rocking is a very suitable echocardiographic tool to assess mechanical dyssynchrony in order to predict CRT response. Therefore, using apical rocking as a firstline echocardiographic tool in every CRT candidate to predict the CRT response should be considered. However, more multicenter and large prospective registries are needed to determine its final place as dyssynchrony marker. We believe that apical rocking has the potential to be incorporated in the guidelines as a strong predictor of CRT response.

We must take into account the fact that almost 50% of CRT candidates have apical rocking at the baseline. However, in the another 50% of CRT candidates without apical rocking the prediction of CRT response is still difficult. A portion of these patients show either clinical or echocardiographic response to CRT. Therefore, we should be able to assess the mechanical dyssychrony in patients without apical rocking who still respond to CRT. For these patients we propose the assessment mechanical dyssynchrony and prediction of CRT response by Septal rebound stretch.

**Septal rebound stretch (SRSsept)**

SRSsept is based on the degree of stretch in the septal wall after the initial contraction during systole. It reflects the dyssynchronous contraction of the septum caused by typical electrical activation in LBBB. Although the measurement of SRSsept is derived from longitudinal

speckle tracking, it is not a time-based analysis. SRSsept has more advantages: it uses only the basal and mid-part of the interventricular septum as region of interest, and the central position of the septum in the ultrasound window guarantees adequate image quality. We believe that the advantages of SRSsept, especially its reproducibility, make this dyssynchrony marker suitable for further validation in multicenter and large prospective registries to determine its final role as dyssynchrony marker, especially in patients without apical rocking. As we confirmed in this thesis with the largest numbers of patients, SRSsept is a strong predictor of CRT response. Therefore, we propose assessment of SRSsept as the secondline echocardiographic tool in CRT candidates without apical rocking in order to predict CRT response. We believe that SRSsept has the potential to be incorporated in the guidelines as a strong predictor of CRT response. Unfortunately, we could not investigate the predictive value of SRSsept in patients without apical rocking due to insufficient numbers of patients with echocardiography with GE machine at baseline.
We should emphasis that in this thesis we did not compare apical rocking and SRSsept with previous dyssynchrony indices, using M-mode and tissue Doppler techniques. The reason is that these indices showed disappointing results in the prediction of CRT response in PROSPECT trial.

**Time-based dyssynchrony markers**
The majority of the dyssynchrony markers studied in the past decade are derived from the time-delays between the motions of LV walls/segments (using M-mode and tissue Doppler technique). Most of these markers suffer from limitations such as angle dependency, and are not able to differentiate between active and passive motion, and require optimal image quality. The PROSPECT study showed a limited value of these time-based dyssynchrony markers for the prediction of CRT response due to moderate sensitivity and specificity. In the post-PROSPECT era, a new imaging technique, 2D speckle tracking imaging, has been introduced. Speckle tracking measures myocardial deformation and can therefore differentiate between passive translational motion of the myocardium and active systolic contraction. Therefore, it has the potential to assess mechanical dyssynchrony better than previous markers. Speckle tracking analysis allows us to use the timing of peak strain/deformation of certain segments (time-based dyssynchrony); however, it is also possible to use the amount of defromations (SRSsept). The predictive value of time-based speckle tracking on CRT response has been investigated [4] with promising results. Moreover, time-based speckle tracking has also been used for targeting of LV lead placement and the results showed an additional value above the routine placement of LV lead [5]. However, no multicenter trials of indices derived from speckle tracking have been performed. Although previous studies showed the predictive value of time-based speckle tracking radial strain on CRT response,

recent data [6] and our data presented in this thesis could not confirm the previous findings. It seems that recognizing strain patterns is more relevant than using the peak strain for quantifying mechanical dyssynchrony. However, the problem is how to quantify the strain patterns of mechanical dyssynchrony. SRSsept can be one of the methods. Another way to quantify strain patterns is to use speckle tracking while focusing on strain patterns rather than peak strain. Quantifying the strain of the opposite walls within the LV (mechanical discoordination) can be a useful method to predict CRT response. Future studies should focus on recognizing the mechanical discoordination rather than time-based dyssynchrony to predict CRT response.

Super-responders to CRT have a good short- and long-term prognosis in terms of cardiac mortality, appropriate ICD shocks, heart failure hospitalization and a very favorable functional NYHA class after CRT. Therefore, it is very important to identify these patients prior to CRT so as to discuss the expectations from the CRT implantation. As we demonstrated in this thesis, apical rocking is independently association with super-response to CRT. Therefore, we recommend using presence/absence of apical rocking in prediction of super-response to CRT. Moreover, one can argue whether to implant CRT-P instead of CRT-D in patients who will be super-responders on the basis of their clinical characteristics and presence of apical rocking. However, randomized controlled trials are needed to compare CRT-P with CRT-D in patients who are expected to be super-responders.

Other imaging modalities to assess mechanical dyssynchrony have been introduced in the past few years. Cardiac Magnetic Resonance (CMR) has gained increasing attention for dyssynchrony assessment due to its high tissue and spatial contrast. The combination of dyssynchrony markers by CMR such as myocardial tagging and strain-coded CMR with delayed enhancement has shown to predict CRT response. Assessment of mechanical dyssynchrony by nuclear imaging has been performed with gated blood-pool ventriculography and phase analysis. However, the studies are small-scaled and with these imaging modalities the experiences are limited. CMR might be a very good alternative imaging modality to assess mechanical dyssynchrony in patients with a poor echocardiographic window.

Non-response to CRT has been an important issue in the last decade. The most important determinants of non-response to CRT are patient selection (high degree of scar burden, lack of mechanical dyssynchrony, relatively narrow QRS duration and co-morbidities), suboptimal position of LV lead and device programming. Improvements in delivery catheters, new LV leads with different curved tip and even with active fixation, enable us to reach the target region in order to minimize the non-responder rate. Another tool is multi-polar LV lead, which is able to deliver multi-point pacing in order to depolarize a large area of myocardial

tissue to increase the response rate to CRT. Multi-point pacing is currently under investigation in a large prospective randomized control trial. Hopefully these new technologies can further increase the response rate to CRT. For some of the current non-responders with persistent mechanical dyssynchrony there are new tools which enable us to reach the target region. We hope that in the future wireless endocardial pacing of the LV [7] will be available for daily use. This wireless device can reach every part of the LV and therefore it will be possible to reach the optimal pacing site.

In patients who will not benefit from CRT on the basis of comorbidities (end-stage renal failure, sever RV dysfunction, pulmonary hypertension and valvular disease), a high degree of scar tissue, or a QRS duration 120−150 ms without mechanical dyssynchrony, it may be better to implant a shock-only ICD device to prevent sudden cardiac death instead of CRT. In these patients CRT will not improve their symptoms. For these patients, new technologies are under investigation, including baroreflex modulation (8), spinal cord stimulation (SCS) and vagus nerve stimulation (VNS) [9,10].
In order to maximize the response rate in CRT patients we recommend based on the existing literature and our experience with regard to CRT in Zwolle the following approaches. (1) In all patients with LBBB or non-LBBB with a QRS duration of >150 ms, CRT should be considered, while in those with a large amount of posterolateral and/or apical scar tissue additional targeting of the LV lead is recommended to reach the target region by strain-based echocardiography or invasive measurements during implantation. (2) In patients with LVEF <35% and LBBB or non-LBBB with a QRS 120−150 ms, additional dyssynchrony assessment is recommended, especially in those with functional NYHA class III. (3) Patients with RBBB are very unlikely to show response to CRT. CRT can be considered only in those with severe symptoms and LV dyssynchrony on echocardiography.

In summary, we showed that several echocardiographic techniques have high potential in predicting response to CRT. We advice the use of apical rocking as first choice to predict CRT response. In patients without apical rocking, septal rebound stretch can also be used to predict CRT response. However, more prospectively, multicenter studies should confirm our results. Identification of patients who may be super-responders to CRT is important because of their excellent prognosis;moreover, it can potentially influence the choice of device (CRT-P instead of CRT-D) at initial implantation or during device replacement due to ERI. Finally, new device-related techniques should be developed for those patients who are non-responders with the current CRT techniques.

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CHAPTER 12

# Nederlandse samenvatting
# List of publications
# Dankwoord
# and
# Curriculum vitae

# Nederlandse samenvatting

Cardiale resynchronisatie therapie (CRT) verbetert de linker ventrikel functie, functionele NYHA klasse, kwaliteit van leven en de overleving van patiënten met systolische hartfalen en een breed QRS complex. Helaas reageert ongeveer 30−40% van de patiënten niet of onvoldoende op deze therapie, de zogenaamde “non-responders”. Daarom is het voorspellen en identificeren van patiënten die een gunstige respons zullen hebben op deze dure en invasieve therapie van cruciaal belang. CRT corrigeert de LV-dyssynchronie, daarom is het belangrijk dat LV-dyssynchronie herkend wordt. Eerdere studies hebben verschillende echocardiografische technieken onderzocht om LV-dyssynchronie te onderkennen en kwantificeren, om op die manier de kans op een CRT respons te kunnen voorspellen. Het was echter niet gemakkelijk om een krachtige en betrouwbare voorspeller voor de CRT respons te vinden.
In dit proefschrift worden verschillende onderzoeken beschreven naar relatief nieuwe echocardiografische parameters die in staat zijn LV-dyssynchronie te beoordelen om zo de respons op CRT te kunnen voorspellen..

In **hoofdstuk 1** worden definitie, prevalentie, pathofysiologisch mechanisme en de farmacologische behandeling van hartfalen toegelicht. Verder wordt de toegevoegde waarde van ICD implantatie voor de overleving van hartfalen patiënten besproken. Daarnaast worden de manier waarop CRT werkt en de gunstige effecten van CRT op functionele klasse, reverse remodeling van de LV, vermindering van de ziekenhuisopname en sterfte samengevat. Een aantal belangrijke onderwerpen zoals respons, super-respons en non-respons op CRT worden toegelicht. Tenslotte wordt het voorspellen van deze issues door middel van echocardiografische parameters besproken.

De device gerelateerde re-interventies binnen het 1e jaar na implantatie worden in **hoofdstuk 2** geëvalueerd. We hebben de gegevens van 1929 patiënten met een pacemaker, ICD of CRT implantatie prospectief verzameld. Bijna 31% van de patiënten onderging een CRT implantatie. In totaal werden 3909 leads geïmplanteerd. Lead gerelateerde re-interventie was nodig bij 86 (4,4%) van de patiënten. De oorzaak van re-interventie was vooral lead dislocatie (66%), gevolgd door lead malfunctie (20%) en perforatie (18%). Re-interventie kwam vaker voor bij mannen en jongere patiënten. De LV-lead dislocatie of malfunctie betrof 1,4%. RA-lead dislocatie (1,9%) en ICD lead dislocatie (1,8%). Dit bleek vaker voor te komen dan RV-pacemaker lead dislocatie (0,3%). De incidentie van lead malfunctie was hoger (0,8%) bij de

ICD leads. Apicale positie van de RV-lead en laterale positie van de RA-lead waren gerelateerd aan hartperforatie.

In **hoofdstuk 3** wordt het mechanische activatie patroon van de linker ventrikel bij patiënten met pacing geïnduceerde LBTB (RV-pacing) en intrinsieke LBTB geëvalueerd voor een correcte beoordeling van de LV-dyssynchronie. We onderzochten 74 patiënten met hartfalen die waren verwezen voor cardiale resynchronisatietherapie, 37 patiënten met chronische RV-apicale pacing en 37 patiënten met een intrinsieke LBTB. Als imaging techniek werden 2D speckle tracking longitudinal strain en M-mode gebruikt. We hebben vastgesteld dat vergeleken met intrinsieke LBTB, RV-pacing resulteert in minder vroege activatie van het basale septum en een meer vroegere activatie van de midseptale en laterale wand van de linker ventrikel. Beeldvormingstechnieken die alleen het basale of mid gedeelte van de LV visualiseren kunnen de dyssynchronie belangrijk onderschatten bij patiënten met pacing geïnduceerde LBTB. De verschillen in mechanische activatie kunnen gevolgen hebben voor de selectie van potentiële kandidaten voor cardiale resynchronisatietherapie

De voorspellende waarde van “time-based speckle tracking dyssynchronie” voor het beoordelen van LV-dyssynchronie wordt in **hoofdstuk 4** onderzocht. Bij 138 patiënten met symptomatisch hartfalen en een CRT-D implantatie werden zes verschillende time-based LV-dyssynchronie parameters gemeten met longitudinale en radiale strain. Respons op CRT werd gedefinieerd als een afname van het LV eind-systolisch volume met $\geq$15%, of door overleving zonder ziekenhuisopname voor hartfalen. 70% werd geclassificeerd als echocardiografische responders en 83% als klinische responders. QRS-duur en niet-ischemische etiologie waren voorspellers van een echocardiografische respons op CRT. Er was geen verschil in speckle tracking parameters tussen echocardiografische responders en non-responders. Wat betreft de klinische respons op CRT, was de maximale delay tussen zes segmenten gemeten in 4-chamber view met longitudinale strain verschillend tussen responders en niet-responders, met 154 ms delay als optimale afkapwaarde. Onze conclusie was dat alleen het maximale delay tussen de zes segmenten, gemeten in 4-chamber view met longitudinale strain, geassocieerd was met een klinische respons op CRT.

Het verband tussen de omvang van de veranderingen in LV-dyssynchronie door CRT en de respons op CRT wordt in **hoofdstuk 5** onderzocht. In een cohort van 138 patiënten werd de “time-based speckle tracking longitudinale strain” gebruikt om LV-dyssynchronie te beoordelen. CRT respons werd gedefinieerd als een afname van LV eind-systolisch volume van $\geq$15%, en 70% werd geclassificeerd als responders. In de totale studiegroep nam LV-dyssynchronie significant af, van 196±89 ms in de baseline naar 180±105 ms tijdens de

follow-up, p=0,01. Echter, bij de responders was er een duidelijke afname van de LV-dyssynchronie (198±88 ms bij baseline versus 154±50 ms na CRT, p<0,001), terwijl er bij de non-responders een significante stijging te zien was (191±92 ms bij baseline versus 243±160 ms na CRT, p=0,04). Na correctie voor leeftijd, geslacht, QRS-duur, de baseline LVEF, LBTB/RBBB en niet-ischemische/ischemische etiologie, was de afname van LV-dyssynchronie significant geassocieerd met de respons op CRT.

Septal rebound stretch (SRSsept) is een relatief nieuwe beeldvormende techniek welke gebruik maakt van speckle tracking longitudinale strain. SRSsept weerspiegelt de inefficiënte vervorming van het septum tijdens systole. We evalueerden in **hoofdstuk 6** de voorspellende waarde van SRSsept voor CRT respons bij ons cohort van 138 patiënten. Respons op CRT werd gedefinieerd als een afname van LV eind-systolisch volume van ≥15%, en 70% werd als responders geclassificieerd. Baseline SRSsept was significant hoger bij responders vergeleken met niet-responders (5,1±3,2 versus 3,0±2,7, p<0,001). De optimale cut-off waarde voor SRSsept bedroeg 4%. Na univariate (OR 3,74, 95%CI 1,72−8,10) en multivariate analyse (OR 3,71, 95%CI 1,49−9,2), bleek een baseline SRSsept van >4% een onafhankelijk voorspeller te zijn van CRT respons.

Apical rocking is een korte initiële contractie van het septum waardoor de apex naar het septum toe beweegt en vervolgens door de vertraagde activatie van de laterale wand de apex naar de laterale wand toe beweegt. Kleine studies suggereerden al dat apical rocking de CRT respons kan voorspellen. In **hoofdstuk 7** wordt de voorspellende waarde van apical rocking in ons cohort (n=137) bestudeerd. Echocardiografische respons op CRT werd gedefinieerd als een afname van het LV eind-systolisch volume van ≥15% en de klinische respons als overleving zonder ziekenhuisopname wegens hartfalen. Apical rocking was aanwezig bij 49% van de patiënten. Apical rocking kwam vaker voor bij vrouwen, jongere patiënten en bij patiënten met niet-ischemische cardiomyopathie. Een echocardiografische respons op CRT werd waargenomen bij 69% en een klinische respons in 77% van de patiënten. Apical rocking was geassocieerd met zowel de echocardiografische respons (OR 10.77, 95%CI 4,12−8,13) als de klinische respons op CRT (HR 2,73, 95%CI 1,26−5,91). Ook na multivariabele analyse, bleek apical rocking geassocieerd te zijn met zowel de echocardiografische (OR 9,97, 95%CI 3,48−28,59) als de klinische respons op CRT (HR 2,13, 95%CI 0,94−4,83).

**Hoofdstuk 8** beschrijft de associatie tussen apical rocking en de klinische uitkomsten op lange termijn in een groot cohort van 297 patiënten met primaire indicatie voor CRT-D. Het klinisch eindpunt MACE (Major Adverse Cardiac Event) werd gedefinieerd als de combinatie van cardiale sterfte en/of ziekenhuisopname wegens hartfalen en/of terechte therapie (ATP

en/of ICD schok). Tijdens de follow-up van 5,2±1,6 jaar, bereikten 92 (31%) patiënten de eindfase van het onderzoek (MACE). De groep met MACE bestond uit meer patiënten met een kortere QRS-duur, meer patiënten met ischemische cardiomyopathie en meer patiënten die amiodarone gebruikten. Apical rocking was aanwezig bij 45% van de onderzochte patiënten. Apical rocking kwam significant vaker voor bij patiënten zonder MACE vergeleken met patiënten met MACE (53% vs 27%, p<0,001). Na multivariabele analyse bleek baseline apical rocking geassocieerd met MACE (HR 0,44, 95% CI 0,25−0,77).

Super-responders zijn patiënten met een duidelijk herstel van LV functie met een LVEF >50% als resultaat van CRT. In **hoofdstuk 9** bepalen we de voorspellers en de lange termijn uitkomsten van 347 patiënten met een CRT-D als primaire preventie. Super-respons werd gedefinieerd als LVEF ≥50% tijdens de follow-up. Eindpunt was MACE, gedefinieerd als totale sterfte of ziekenhuisopname wegens hartfalen, cardiale sterfte of terechte ICD therapy. 56 (16%) patiënten werden geclassificeerd als super-responders. Vrouwelijk geslacht (OR=3,06 95%CI 1,54‑6,05), non -ischemische etiologie (OR=2,70 95%CI 1,29−5,68), een hogere LVEF bij baseline (OR=1,07 95%CI 1,02−1,13) en bredere QRS-duur (OR=1,17 95%CI 1,04−1,32) waren voorspellers van super-respons. Cumulatieve incidentie van MACE bij mediaan follow-up na 5,3 jaar was 18% in super-responders, 22% in responders en 51% in non-responders (p<0,001). Van de super-responders overleed niemand als gevolg van cardiaal lijden, terwijl cardiale sterfte 9% in responders en 25% in non-responders (p<0,001) bedroeg. Terechte ICD-therapie kwam niet voor in super-responders, terwijl 10% van de responders en 21% van de non-responders terechte ICD therapie (p<0,001) kreeg. In super-responders was de gecorrigeerde HR voor MACE 0,37 (95%CI 0,19−0,73) en voor totale sterfte 0,44 (95%CI 0,20−0,95). Super-respons op CRT bleek geassocieerd met een uitstekende prognose met betrekking tot overleving en terechte ICD-therapie gedurende lange-termijn follow-up.

In **hoofdstuk 10** wordt de mogelijke associatie beschreven tussen super-responders en apical rocking in een cohort van 297 patiënten met primaire indicatie voor CRT-D implantatie. Super-respons was gedefinieerd als het hoogste kwartiel van LVEF gebaseerd op veranderingen ten opzichte van baseline. Apical rocking was aanwezig in 45% van de patiënten. Apical rocking kwam significant vaker voor bij super-responders vergeleken met non-super-responders (76% en 34%, p<0,001). In univariate analyse waren vrouwelijk geslacht (OR 2.39 95%CI 1,38−4,11), LVEF in baseline (OR 0.91 95%CI 0,87−0,95), non-ischemische etiologie (OR 4.15 95%CI 2,33−7,39) en apical rocking (OR 6.19 95%CI 3,40−11,25) geassocieerd met super-respons op CRT. In multivariate analyse was apical rocking nog steeds sterk geassocieerd met super-respons op CRT (OR 5,82, 95%CI

2,68−12,61). Super-responders hadden een uitstekende prognose met een zeer lage incidentie van ziekenhuisopname wegens hartfalen, cardiale sterfte en terechte ICD-therapie.

## ALGEMENE DISCUSSIE EN TOEKOMSTPERSPECTIEVEN

Hoewel een breed QRS complex van >120 ms een belangrijke voorwaarde is voor CRT implantatie, is het geen garantie voor CRT respons. De voorspellende waarde van elektrische dyssynchronie, zeker als alleen naar QRS duur wordt gekeken, voor CRT respons is over het algemeen laag. Het belangrijkste doel van CRT is het herstel van de mechanische dyssynchronie. Het is duidelijk dat mechanische dyssynchronie niet alleen weerspiegeld wordt door QRS-duur. Hoewel echocardiografie beperkingen heeft, helpt het ons de complexiteit van de linker ventrikel mechanica te begrijpen. Er is aangetoond dat echocardiografie beter in staat is patiënten te selecteren voor wie CRT een gunstige uitkomst zal hebben, en daarbij verschaft echocardiografie ook prognostische informatie. Het meten van mechanische dyssynchronie is in het algemeen tijdrovend, vereist zeer getrainde cardiologen en er is geen eenduidige gevalideerde methode voorhanden. In dit proefschrift onderzochten we verschillende nieuwe echocardiografische technieken om mechanische dyssynchronie te evalueren, om daarmee de respons op CRT te kunnen voorspellen. Onze intentie was om echocardiografische methoden te gebruiken die mechanische dyssynchronie makkelijk zichtbaar konden maken, zonder ingewikkelde metingen, zodat de methode relatief eenvoudig toepasbaar zou zijn in de dagelijkse klinische praktijk, en beschikbaar kan zijn in elke kliniek. Daarnaast diende de methode een hoge positief voorspellende waarde hebben.

***Apical rocking***, dat werd onderzocht in dit proefschrift, heeft de potentie om het dyssynchrone contractie patroon van LBTB te laten zien en heeft een hoge positieve voorspellende waarde (85−90%) voor zowel de klinische als de echocardiografische respons op CRT [1,2]. Bovendien is de visuele beoordeling van apical rocking relatief eenvoudig, reproduceerbaar en niet tijdrovend. De potentiële waarde voor het voorspellen van de lange-termijn resultaten werd bevestigd in dit proefschrift. Onlangs is de grootste trial [3] over de voorspellende waarde van apical rocking gepubliceerd, hetgeen de resultaten in dit proefschrift verder ondersteunt. Naar onze mening is apical rocking een zeer geschikte echocardiografische methode om mechanische dyssynchronie te evalueren en daarmee CRT respons te voorspellen. Daarom wordt apical rocking door ons als eerste echocardiografisch instrument bij elke CRT kandidaat aanbevolen om CRT respons te voorspellen. Er zijn echter meer multicenter en grote prospectieve registers nodig om de definitieve plaats van apical

rocking als dyssynchronie marker te bepalen. Wij zijn van mening dat de apical rocking de potentie heeft om in de richtlijnen opgenomen te worden als een sterke voorspeller van CRT respons.

Een van de beperkingen van apical rocking is dat slechts bij 50% van de potentiele CRT kandidaten aanwezig is op het baseline echo. De andere 50% van de CRT kandidaten heeft geen apical rocking en is de voorspelling van CRT respons nog steeds moeilijk. Een deel van deze patiënten vertonen ook een klinische of een echocardiografische respons op CRT. Het is daarom van klinisch belang om ook mechanische dyssychronie bij deze patiënten te beoordelen. Voor deze patiënten wordt het bepalen van Septal rebound stretch als dyssynchronie marker aanbevolen.

***Septal rebound stretch*** **(**SRSsept) is gebaseerd op de hoeveelheid rek in de septale wand na de aanvankelijke contractie tijdens systole. Het weerspiegelt de dyssynchrone samentrekking van het septum veroorzaakt door typische elektrische activatie in LBTB. Hoewel de meting van SRSsept is afgeleid van longitudinale speckle tracking, is het niet time-based. Daarnaast heeft SRSsept het voordeel dat het mid en basale deel van het septum als "region of interest" gebruikt. . Deze centrale positie van het septum in het echo venster is vaak een garantie voor voldoende beeldkwaliteit en goede reproduceerbaarheid hetgeen van cruciaal belang is voor het beoordelen van dyssynchronie. Wij zijn van mening dat de voordelen van SRSsept, maken dat deze dyssynchronie marker geschikt is voor verdere bestudering en validatie in multicenter prospectief onderzoek om zo zijn definitieve plaats als dyssynchronie marker te bepalen. Wij zijn van mening dat SRSsept ook de potentie heeft om in de richtlijnen te worden opgenomen als een sterke voorspeller van CRT respons.
In dit proefschrift, hebben we bevestigd in een relatief groot patienten cohort dat SRSsept een sterke voorspeller is van CRT respons. Daarom stellen wij voor om SRSsept als 2e echocardiografische instrument te gebruiken bij CRT kandidaten zonder apical rocking om CRT respons te voorspellen. We benadrukken dat in dit proefschrift apical rocking en SRSsept niet zijn vergeleken met eerdere dyssynchronie indices zoals M-mode en tissue Doppler technieken. De reden hiervoor is dat deze indices in de PROSPECT trial teleurstellende resultaten lieten zien bij het voorspellen van een CRT respons.

**Time-based dissynchronie markers**: Over de afgelopen 10 jaar zijn de meeste dyssynchronie markers gebaseerd op de "time delay" tussen verschillende wanden/segmenten van de LV, en is dit delay gemeten met M-mode of tissue Doppler techniek. De meeste van deze markers hebben beperkingen zoals hoek afhankelijkheid en moeite om onderscheid te maken tussen actieve en passieve motion. De PROSPECT studie toonde een beperkte waarde

van deze op tijd gebaseerde dyssynchronie markers bij het voorspellen van CRT respons. In het post-PROSTPECT tijdperk, is er een nieuwe beeldvormingstechniek, 2D speckle tracking-imaging, geïntroduceerd. Speckle tracking meet myocardiale deformatie en kan daarom onderscheid maken tussen de passieve beweging van de hartspier en de actieve systolische contractie. Daarom heeft speckle tracking de potentie mechanische dyssynchronie beter te herkennen dan de vorige markers. Met speckle tracking kunnen we naar de timing van piekstrain/deformatie van segmenten kijken (time-based dyssynchrony), maar het is ook mogelijk om de hoeveelheid deformatie te meten (SRSsept). De voorspellende waarde van time-based speckle tracking op CRT respons is onderzocht [4] met veelbelovende resultaten. Daarnaast is de toegevoegde waarde van time-based speckle tracking bij het bepalen van de juiste positie van de LV-lead boven de routinematige implantatie van de LV-lead aangetoond [5]. Er zijn echter nog geen multicenter studies die de voorspellende waarde van time-based speckle-tracking voor CRT respons hebben aangetoond. Hoewel eerdere studies de voorspellende waarde van time-based speckle-tracking radiale strain op CRT respons hebben aangetoond, konden recente data [6] en onze data in dit proefschrift dit niet bevestigen. Het lijkt erop dat het herkennen van strain-patronen meer relevant is dan het gebruik van de piek-strain voor het kwantificeren van mechanische dyssynchronie. De vraag blijft, hoe kunnen we op basis van strain-patronen de mate van mechanische dyssynchronie betrouwbaar vaststellen? SRSsept is één van de methoden die ons kan helpen strain-patronen kwantificeren. Een andere manier om strain-patronen te kwantificeren is het gehele strain-patroon te gebruiken in plaats van piek-strain. Het hierbij kwantificeren van de strain van de tegenover elkaar liggende wanden in de LV (mechanische discoördination) kan een bruikbare methode zijn om een CRT respons te voorspellen. Toekomstig onderzoeken moeten zich daarom richten op het herkennen van de mechanische discoördination in plaats van time-based dyssynchronie.

Om de respons in CRT kandidaten te maximaliseren adviseren we op basis van de bestaande literetuur en onze ervaringen met betrekking tot CRT implantatie in Zwolle bij patienten met hartfalen de volgende benaderingen. (1) Bij alle patiënten met een LBTB of non-LBTB en een QRS duur van >150 ms moet CRT worden overwogen; Indien deze patiënten een groot posterolateraal en/of apicale litteken hebben, dan wordt “targeting van de LV-lead” aanbevolen middels echocardiografie of invasieve metingen tijdens de implantatie. (2) Bij patiënten met LBTB of non-LBTB en een QRS duur van 120-150 ms wordt extra dyssynchronie beoordeling aanbevolen, vooral bij patiënten met functionele NYHA klasse III. (3) Het is zeer onwaarschijnlijk dat RBTB patiënten een respons op CRT laten zien. CRT kan alleen worden overwogen indien ze ernstige symptomen van hartfalen hebben en er echografisch aanwijzingen zijn LV-dyssynchronie.

Super-responders hebben een goede prognose, zeer lage cardiale sterfte, terechte ICD-shocks, ziekenhuisopname wegens hartfalen en een zeer gunstige functionele NYHA klasse na CRT. Daarom is het erg belangrijk dat deze patiënten herkend worden, mede om de verwachtingen van de CRT te bespreken. We hebben in dit proefschrift aangetoond dat apical rocking onafhankelijk is geassocieerd met een super-respons op CRT. Dit zou mogelijk consequenties kunnen hebben voor de keuze van het te implanteren device. Er zou een voorkeur voor het implanteren van een CRT-P in plaats van een CRT-D kunnen zijn bij patiënten die een grote kans hebben om super-responders te worden gebaseerd op hun klinische kenmerken en aanwezigheid van apical rocking. Echter, er zijn gerandomiseerde en gecontroleerde studies nodig om CRT-P met CRT-D te vergelijken bij patiënten die naar verwachting super-responders zullen zijn.
In de afgelopen jaren zijn er andere beeldvormende modaliteiten geïntroduceerd om mechanische dyssynchronie te beoordelen. Cardiac Magnetic Resonance (CMR) heeft veel aandacht gekregen voor het evalueren van dyssynchronie vanwege de hoge weefsel en spatiele resolutie van deze modaliteit. De combinatie van myocardiale tagging en strain-coded CMR met late-enhancement lijkt een goede voorspeller te zijn van CRT respons. Evaluatie van mechanische dyssynchronie door nucleaire beeldvorming werd uitgevoerd met gated blood-pool ventriculografie en fase analyse. Echter, deze studies zijn kleinschalig en de ervaring met deze beeldvormende modaliteiten is beperkt. CMR zou een goed alternatief kunnen zijn voor patiënten die echocardiografisch nauwelijks opneembaar zijn.

In de afgelopen decennium is non-respons op CRT is een belangrijk issue geweest. De belangrijkste determinanten van non-respons op CRT zijn selectie van patiënten (hoge mate van littekenvorming, het ontbreken van mechanische dyssynchronie, relatief smalle QRS duur en co-morbiditeit), suboptimale positie van de LV-lead en niet optimale programmering van het apparaat. De nieuwe ontwikkelingen rond het implanteren van LV-leads, zoals diverse katheters en binnen sheaths, nieuwe LV-leads met verschillende bochten aan de tip en zelfs met actieve fixatie, stellen ons in staat via de zijtakken van de sinus coronarius beter de “target region” te bereiken om zo de non-responder rate te minimaliseren. Een andere positieve ontwikkeling is de multipolaire LV-lead die ons niet alleen in staat stelt om in een groter segment de LV te stimuleren maar het ook mogelijk maakt multi-point te pacen. Hierbij wordt gelijktijdig op 2 posities/electroden de LV gedepolariseerd met als doel sneller een groot gebied van de linker kamer te activeren. Er zijn voorzichtige aanwijzingen dat de respons rate op de CRT toeneemt bij het gebruik van quadripolaire leads en bij multi-point pacing. Multi-point pacing wordt momenteel onderzocht in een grote prospectief en gerandomiseerde studie. Hopelijk kunnen deze nieuwe technologieën bijdragen aan een toename van de respons rate op CRT. Voor een aantal van de huidige non-responders met

persisterende mechanische dyssynchronie bestaan er nieuwe technieken die ons in staat stellen de “target region” te bereiken. Hopelijk is draadloze endocardiale pacing van de LV [7] in de toekomst beschikbaar voor dagelijks gebruik. Dit draadloos apparaat kan elk deel van de LV bereiken en maakt het mogelijk een optimale stimulatie site te vinden.
Bij patiënten die niet zullen profiteren van CRT wegens co-morbiditeit (eindstadium nierfalen, ernstige RV dysfunctie, pulmonale hypertensie en hartklepafwijkingen), hoge mate van littekenweefsel, QRS-duur 120−150 ms zonder mechanische dyssynchronie, kan het beter zijn een shock-only ICD ter preventie van plotse hartdood te implanteren in plaats van CRT. Bij deze patiënten zal de CRT de symptomen niet verbeteren en kan soms zelfs een verslechtering tot gevolg hebben. Om de symptomen bij deze patiënten te verbeteren kunnen nieuwe technologieën zoals baroreflex modulatie [8], spinal cord stimulation (SCS) en nervus vagus stimulatie (NVS) [9,10] overwogen worden.

Samenvattend, hebben we aangetoond dat verschillende echocardiografische technieken een hoge potentie hebben voor het voorspellen van een respons op CRT. Wij adviseren het gebruik van apical rocking als eerste keuze om CRT respons te voorspellen. Bij patiënten zonder apical rocking, kan septal rebound stretch worden gebruikt om CRT respons te kunnen voorspellen. Echter, er zijn meer prospectieve, multicenter studies nodig om onze resultaten te bevestigen. Identificatie van super-responders kan belangrijke klinische implicaties hebben vanwege hun uitstekende prognose. Super-respons kan de device keuze (CRT-P in plaats van CRT-D) bij initiële implantatie of tijdens vervanging van het device door ERI beïnvloeden. Tenslote moeten nieuwe device gerelateerde technieken ontwikkeld worden voor patiënten die niet reageren op de huidige CRT technieken.

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# Curriculum vitae

The author was born on 24 November 1974 in Herat (Afghanistan). He attended secondary school in Herat (1986−1990). In 1990 he fled the country with his family because of the civil war, and went to Iran. In 1991, he moved from Iran to The Netherlands. Between 1991−1995 he learned the Dutch language, followed the higher laboratory education at the High School of Amsterdam and 1 year of medicine at the University of Antwerpen (Belgium). In 1995 he moved back to Amsterdam and started the study of Medicine at the University of Amsterdam, graduating in September 2002. After graduation, he started working as a resident of cardiology at the Isala klinieken, location Weezenlanden. He started his cardiology training in 2004 at the Isala klinieken (supervisor Dr. J.C.A. Hoorntje), which he completed in July 2010. In 2010, he started the fellowship Device Implantation, and successfully completed the curriculum of the European training programme in cardiac pacing and Implantable cardiac defibrillators in 2012. Alongside his fellowship, he joined Dr. P.P.M. Delnoy and Dr. J.P. Ottervanger in the research of echocardiographic markers of mechanical dyssynchrony to predict the response to cardiac resynchronization therapy, which resulted in this thesis.
He is married with Somayeh, and they have two children, Arsalan and Sogand. His hobby is playing volleyball and he is interested in news and politics.