CLINICAL ASPECTS OF CARDIAC RESYNCHRONIZATION THERAPY

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CLINICAL ASPECTS OF CARDIAC RESYNCHRONIZATION THERAPY

KLINISCHE ASPECTEN VAN CARDIALE RESYNCHRONISATIE THERAPIE

(met een samenvatting in het Nederlands)

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Aan mijn liefhebbende ouders,
mijn broertje en zusjes

“Do. Or do not. There is no try.”
Yoda - *The Empire Strikes Back*

CONTENTS

Chapter 1

GENERAL INTRODUCTION

Heart failure

With the ageing of the population in economically developed the prevalence of heart failure increases and consequently health care consumption and costs are rising. In economically developed countries the prevalence of HF is 1-2%, with 80% of affected patients being above the age of 65. Incidence of heart failure is 5-10 per 1000. [1] These numbers indicate heart failure affects many people, and numbers continue to rise as acute care is still improving. [2] It is now expected that 20% of the population will develop heart failure during life. [3] Of patients admitted to the hospital with the diagnosis heart failure 17-45% do not survive the first year thereafter, and more than 75% die within five years. [3] Health care costs for heart failure care are high and comprise 1-3% of the total health care costs in Europe, North and South America. These costs can be attributed mostly to hospital admissions. The average length of a hospital admission is 5-10 days and 25% and 65% of patients is readmitted within 1 month and 1 year, respectively. [2] These numbers illustrate that heart failure is an important concern for our health and health care.

Heart failure and conduction abnormalities

It has been demonstrated that 30% of patients with heart failure have ventricular conduction delay, increasing the risk of cardiovascular events even more. [4,5]
In the EuroHeart Failure survey 36% of patients hospitalized with a suspected diagnosis of heart failure showed an left ventricular ejection fraction (LVEF) of ≤ 35%, of which 41% had a broad QRS complex. [6] Of these, 34% had a left bundle branch block (LBBB) or aspecific intraventricular conduction delay (IVCD), 7% had a right bundle branch block (RBBB), and 17% had a QRS complex ≥ 150 ms. In addition, the annual incidence of LBBB in ambulatory HF patients is 10%. In case of a broad QRS complex, ventricular conduction is impaired. This can lead to dyssynchronous contraction, as different parts of the heart are not simultaneously activated; leading to mechanical discoordination and impaired cardiac efficiency.
It has been demonstrated that in isolated LBBB, LVEF is reduced by 7% each year, for RBBB this is 1%. [7] Ventricular conduction delays are a risk factor for worse prognosis. In a recent study by Haataja et al. in 6299 individuals it was demonstrated that aspecific IVCD, LBBB and incomplete RBBB had a hazard ratio of 4.25, 2.11, and 2.24 for cardiovascular mortality, while complete RBBB did not have any prognostic consequences. [8] Both LBBB, RBBB, as well as RV-pacing result in mechanical dyssynchrony, although LBBB induces the highest amount of dyssynchrony. [9-11]

Cardiac resynchronization therapy

According to current guidelines, cardiac resynchronization therapy (CRT) is a therapy for patients with NYHA ≥ II drug refractory heart failure with ventricular conduction delay. [12] Nowadays, this therapy is well-implemented in the cardiac care system. In 2013 around 2500 CRT implantations were performed in the Netherlands: 75% comprised a CRT with defibrillator (CRT-D), and 25% comprised a CRT without defibrillator (CRT-Pacemaker). [13] The first CRT implantation was already performed in 1993 at the UMCU by Dr. P. Bakker, a cardiac surgeon. Unfortunately she never published this breakthrough and the first case-report describing a CRT implantation was published in 1994 by Cazeau et al. [14] A CRT device has three cardiac leads: one right atrial lead, one right ventricular (RV) lead, and one epicardial left ventricular (LV) lead. Therefore, a CRT device can pace biventricularly, in order to resynchronize ventricular contraction. Usually, the latter is placed transvenously through the coronary sinus. If this approach fails, the LV lead is surgically positioned; either by video assisted thoracoscopy (VATS) or mini-thoracotomy. Most frequently the RV lead has a defibrillator function as well, besides its pacing abilities. The device itself is placed pre- or subpectorally. Since its introduction several studies investigated the short and long-term outcome. At the beginning of the CRT era it was a treatment for patients with severe symptoms of HF. In patients with functional class of heart failure NYHA ≥ III CRT significantly improved exercise capacity, quality of life, reduced LV volumes and increased ejection fraction. [15-17] Subsequently, large randomized showed a mortality benefit of CRT in these patients. [18,19] Despite a clinical responder rate (reduction of HF symptoms) of approximately 70% only 50-60% of CRT-patients showed a reduction of the LVESV of at least 15%. [20] One of the reasons of non-response was lack of ventricular dyssynchrony because patient inclusion was based on QRS duraction (≥120ms) but not on QRS morphology. Therefore, studies to refine inclusion criteria have been performed since then focusing on QRS duration and morphology. [21-24] The more recent published multi-center randomized trials [25] included patients with mild symptoms of heart failure and showed a significant improvement of the LV function during CRT. [26,27] According to the ESC guidelines from 2013 only patients with a typical LBBB have a class I indication. The indication for CRT in patients with non-LBBB QRS widening is based on QRS duration (>= 150 ms class IIa, < 150 ms class IIb).

Imaging and cardiac resynchronization therapy

Non-invasive cardiac imaging, especially echocardiography, has been a major player in the field of CRT, both for prediction and assessment of response. Echocardiographically assessed left ventricular volumes are frequently used to determine response to CRT. [20,27,28] In addition, echocardiographic measurements of mechanical dyssynchrony in order to predict response to CRT were evaluated. [29] Tissue Doppler Imaging (TDI) has extensively been investigated in single center studies. [30-32] However, since the PROSPECT study most of these parameters, like septal-to-lateral delay (SL-delay) and maximum difference of time to peak systolic displacement (Ts-peak), have been abandoned as this study showed high intra-and interobserver variability for these measurements and moderate predictive capacity concerning CRT response. [20] Afterwards, a growing interest in the latest echo technique of speckle tracking started to develop.

Speckle tracking has many advantages as compared to TDI. Speckle tracking is based on automated tracking of speckle patterns generated by the acoustic backscatter interference during standard grey-scale imaging. Therefore, the technique is angle independent. Moreover, it is an automated analysis which reduces analysis time, and improves measurement reproducibility. [29,33] Speckle tracking assesses the whole ventricular wall, and better discriminates between active and passive motion. [29] Systolic rebound stretch of the septum (SRSsept), is a parameter derived from longitudinal speckle tracking and it has been demonstrated to have a high predictive value concerning reverse remodeling as well as long-term outcome after CRT implantation in single center studies of our own department in the UMC Utrecht. [34,35] Moreover, our center demonstrated that this parameter maintained a linear relationship with reverse remodeling in the presence of scar. [36] SRSsept needs to be validated in other or multi-center settings.

Response to CRT

A frequent used measure of response is left ventricular end systolic volume (LVESV) decrease. [16,20] Echocardiographic response is commonly defined as ≥ 15% LVESV reduction. It is known that at least up to 30% do not demonstrate echocardiographic response to CRT and these so called non-responders demonstrate a survival rate similar to that of HF patients without CRT. [37] It is important to determine which patients respond and which do not respond and which surrogate marker could be used to assess this response. Current guidelines do not mention how to evaluate response. Therefore, definition of response varies amongst trials. Several end-points have been studied. Some studies focused on symptoms: Decrease of NYHA classification, improvement of Quality of Life (QoL) or exercise capacity. [16,38] Others analyzed reverse remodeling: Reduction of LVESV and/or improvement of LVEF. [26,27] Furthermore, also hard end-points have been investigated, like HF events, hospitalization, and mortality. [19] Response to CRT is difficult to predict and remains a challenging subject. [39,40]

In addition, increasing response rates by, for example, optimization of the left ventricular (LV) lead position, is still a focus of current research. It has been demonstrated that targeting either electrically latest activated regions or mechanically latest activated regions with the LV lead improves response rates. [41-43] Nevertheless, it is currently unknown up to which extent electrical and mechanical measurements of latest activated regions correspond and which one is best to target.

In clinical practice left ventricular end systolic volume (LVESV) decrease is frequently used as response parameter. [20,44,45] However, also other response measures have been used, such as 6 minute walk test (MWT) [46] , VO2 peak [16], NYHA [47]. Currently, no consensus consists on which parameter is the best marker of CRT response. [39,40] Yu et al. [28] demonstrated that LVESV was superior to LVEF, LV end diastolic volume (LVEDV), NYHA, 6MWT, and quality of life scores concerning discrimination between a favorable and unfavorable outcome after CRT implantation. Furthermore, it has also been shown that different response measures are not interchangeable. [48] In addition, there are more surrogate markers to explore. Also, response to CRT is usually assessed after six months of therapy. In large cohorts it has been demonstrated that reverse remodeling is a process that continues at least up to 24 months after device implantation. [49,50] However, it is unknown whether there are individual patients showing an initial response to CRT (after six months), but deteriorate thereafter. Moreover, it has been demonstrated that patients with ischemic and non-ischemic cardiomyopathy respond differently to CRT: in general, patients with ischemic cardiomyopathy show less LVESV decrease after CRT as compared to patients with non-ischemic cardiomyopathy. [26] However, CRT reduces mortality and hospital admissions due to heart failure for both groups. [51] Nevertheless, ischemic and non-ischemic disease are completely different entities and whether both etiologies have similar predictors.

Thesis outline

Chapter 3 describes the additional value of echocardiographic parameters of mechanical dyssynchrony concerning the prediction of reverse remodeling. Two models, with and without echocardiographic parameters of mechanical dyssynchrony, were tested in a CRT population on their capacity to predict reverse remodeling 6 months after device implantation. In addition, model performance was tested separately for patients with non-ischemic cardiomyopathy and ischemic cardiomyopathy. In **chapter 4** we evaluate whether electrically latest activated regions of the LV are also latest mechanically activated as both electrical delays and mechanical delays have been used in previous studies to guide LV lead positioning. To assess electrical activation delays electrical mappings were performed in the coronary sinus and its large side branches. Mechanical activation delays were evaluated by 2D speckle tracking analyses and time to peak strain was assessed.

Definition of response is still under debate. In **chapter 5** several surrogate markers of CRT response, among them change in LVESV, are investigated and their relationship to long-term outcome is assessed. In addition, we evaluate whether these surrogate outcome measures are equally appropriate for patients with ischemic and non-ischemic cardiomyopathy. In **chapter 6** we evaluate whether echocardiographic responders also show significant improved exercise capacity six months after CRT implantation. All included patients performed an exercise test pre- and 6 months post implantation and echocardiographic studies were performed at the same time points. In **chapter 7** we investigate whether echocardiographic responders are also health status responders after 6 months of CRT. We defined health status response by the Kansas City Cardiomyopathy Questionnaire (KCCQ), which is a self-report questionnaire that has been validated and shown to be sensitive to clinical change in HF patients. [52] Echocardiographic response was defined as LVESV decrease of at least 15 %. In **chapter 8** we measure echocardiographic response, by LVESV decrease, at 6 and 14 months after device implantation and assess which percentage of patients show a cross-over to another response group (either from non- to responder or the other way around) between 6 and 14 months, focusing on patients being responder at 6 months and non-responder at 14 months. Furthermore, we assess whether response rates at either six or 14 months better correspond to long-term health outcomes.

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Chapter 2

CRT INDUCED LEFT VENTRICULAR DYSSYNCHRONY: IS IT A FACT?

eLetter to the editor, European Heart Journal, Published on: 21 May 2012

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In a recent issue of this journal Auger et al.[1] claimed that cardiac resynchronisation therapy (CRT) might induce left ventricular (LV) dyssynchrony in patients without significant LV dyssynchrony at baseline and this appeared to be related to a worse long-term outcome. LV dyssynchrony was assessed by tissue Doppler imaging (TDI) (septal to lateral delay of peak systolic velocities: SL-delay) and a cut-off of 60 ms was taken to select patients from an existing cohort. In 290 patients a CRT device was implanted despite a lack of significant dyssynchrony on TDI (SL-delay < 60 ms). Two days after CRT implantation and continuous pacing patients without LV dyssynchrony at baseline were reclassified into 2 groups based on the median LV dyssynchrony present, which appeared to be 40 ms. The group showing LV dyssynchrony of > 40 ms after CRT implantation seemed to have a worse long-term outcome compared with the group showing < 40 ms LV dyssynchrony: cumulative mortality rates of 23% versus 10% at 3-year follow-up.

At first sight these results seem to correspond with the existing framework concerning dyssynchrony and CRT. However, it has been debated whether TDI is the best method to assess dyssynchrony. TDI has serious limitations as it is angle and sample dependent, cannot discriminate between passive and active contraction and has poor correlation with longitudinal contraction.[2,3] Previous studies demonstrated that the predictive value of TDI concerning prediction of CRT response was only moderate and therefore TDI could not improve patient selection for CRT. [2,4-7] Also, in LBBB it was demonstrated that although intramyocardial electrogram reported myocardial activation started in the septum, peak systolic velocities showed the opposite.[8] Suggesting that differences between peak velocities might not be the best method to assess dyssynchrony. Furthermore, reclassifying the groups post CRT implantation using a different cut-off value for the identification of LV dyssynchrony (40 ms post CRT versus a cut-off of 60 ms pre CRT) is confusing. For instance patients with an SL-delay of 58 ms pre CRT and 42 ms post CRT; are they considered to have CRT induced dyssynchrony?

In addition indicating that 50% of the patients without dyssynchrony at baseline suffer from induced dyssynchrony post CRT is a debatable outcome when the median is taken as cut-off value for the presence of dyssynchrony. Another option could have been to divide patients in 2 groups according to absolute increase and decrease of SL-delay. Moreover, a significant number of patients with right bundle branch block was included: 5 and 9% respectively in the group with and without dyssynchrony at baseline, while these did not show benefit of CRT in all randomized multi-center trials.[9-11] Furthermore, PQ intervals at baseline and AV-delays during pacing should be provided for interpretation of LV capture during biventricular pacing. In conclusion, we believe the methodology and consequently the results of this study are not optimal. Therefore, we do not support the conclusion that CRT induces LV dyssynchrony at such a high rate, based on these data. More information is needed and other dyssynchrony measurements should be taken into account to study CRT induced dyssynchrony.

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Conflict of Interest:

None declared.

Chapter 3

MEASUREMENTS OF ELECTRICAL AND MECHANICAL DYSSYNCHRONY ARE BOTH ESSENTIAL TO IMPROVE PREDICTION OF CRT RESPONSE

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Abstract

Introduction: Predicting reverse remodeling after cardiac resynchronization therapy (CRT) remains challenging and different etiologies of heart failure might hamper identification of predictors. Objective: Assess the incremental value of mechanical dyssynchrony besides electrical dyssynchrony for predicting CRT response.

Methods: 227 patients (51% ischemic) received CRT. Response was defined as ≥15% left ventricular end systolic volume decrease after six months. Prediction models were developed comprising clinical parameters and electrical dyssynchrony (Model A), subsequently complemented with mechanical dyssynchrony (Model B).Models were compared by area under the receiver-operating curve (AUC), net reclassification index (NRI) and integrated discrimination improvement (IDI) for the complete cohort, ischemic (ICM) and non-ischemic (NICM) subpopulations.

Results: Model B performed significantly better than Model A supported by AUC, NRI and IDI. Furthermore, model B significantly better predicted response for NICM than ICM.

Conclusion: Electrical dyssynchrony and mechanical dyssynchrony are essential to predict CRT response. Nevertheless, response prediction for ICM remains challenging.

Introduction

Cardiac resynchronization therapy (CRT) is a well established therapy in NYHA ≥ II heart failure (HF) patients with QRS ≥120 ms and left ventricular ejection fraction (LVEF) ≤35% [1]. CRT is applied in a heterogeneous group of HF patients; ranging from dilated to ischemic cardiomyopathy. Despite demonstrated benefits, in a substantial proportion of the population (up to 50%) the effects of CRT cannot be objectively established [2]. The beneficial effects of CRT are believed to rely to a great extent on the reversal of electrical andmechanical dyssynchrony [3]. In the guidelines, indication for CRT is based on measures of electrical dyssynchrony: QRS width and QRS complex morphology, and no measures of mechanical dyssynchrony proven to be of value are taken into account [1]. Several studies aimed to improve detection of mechanical dyssynchrony but no single criterion has been established yet in multi-center setting that successfully and reliably improves patient selection [2,4,5]. Moreover, it remains unclear to what extent mechanical dyssynchrony complements electrical dyssynchrony. This study focused on the additional value of mechanical dyssynchrony; interventricular mechanical delay (IVMD) and systolic rebound stretch of the septum (SRSsept), besides electrical dyssynchrony for prediction of volume response after CRT implantation. Secondly, we hypothesized that due to differences in underlying disease, capacity to predict volume response after CRT implantation might vary for non-ischemic (NICM) and ischemic cardiomyopathy (ICM).

Methods

Study cohort and design

For this single-center study we included 227 HF patients of the University Medical Center Utrecht (UMCU) who received a CRT-D device according to guidelines at time of enrolment or inclusion in multi-center clinical trials (e.g. MADIT-CRT) and of which prospectively planned echocardiographic and electrocardiographic data were available. Implantations were performed between August 2005 and December 2011. AV and VV timing delays were optimized invasively (dP/dtmax), echocardiographically, or based on the ECG. De novo CRT implantations were performed in 194 (86%) patients, and 33 (14%) had a pacemaker upgrade of which 32 were paced in the right ventricle, and 1 solely in the right atrium. The left ventricular (LV) lead was epicardially positioned in a lateral (74%), posterior (17%), and anterior (9%) segment of the LV free wall, determined as previously described [6]. Electrical and mechanical dyssynchrony, clinical, and laboratory data were assessed at baseline. LV volumes and ejection fraction (LVEF) were echocardiographically assessed at baseline and six months after device implantation.

The study conformed to the guiding principles of the Declaration of Helsinki and patients consented to clinical evaluation.

Clinical and laboratory data
Electronic patient files were searched to collect baseline clinical and laboratory data.

Electrical dyssynchrony
12-lead ECG recordings were acquired at baseline. QRS duration was manually assessed in lead II. Left bundle branch block (LBBB) was defined as QRS duration ≥ 120 ms with a broad notched or slurred R wave in leads I, aVL, V5 and V6 and an occasional RS pattern in V5 and V6, absent q waves in lead I, V5 and V6, R peak time of ≥ 60 ms in lead V6 (lead V5 was excluded for this criterion because of likely remodeling of the heart in the selected patient group which would change the position of V5 with respect to the heart) [7] and an rS or QS pattern in lead V1. In case of a known old anterior/lateral infarction a pathologic q in I or V6 did not exclude LBBB [7,8]. A pathologic q was defined as initial negative deflection of > 40 ms.

Echocardiography

Acquisition and analyses
Echocardiographic studies were performed using a Vivid 7 (General Electric, Milwaukee, USA). Patients were imaged in the left lateral decubitus position. At baseline, volumes, LVEF, and mechanical dyssynchrony: IVMD, and SRSsept were assessed. Both IVMD and SRSsept have been associated with LV reverse remodeling in previous studies [2,3,9–11]. Six months after device implantation volumes and LVEF were evaluated again. For speckle tracking recordings frame rates were kept between 50 and 110 frames per second. Speckle tracking analyses were performed offline.

Mechanical dyssynchrony
Interventricular mechanical delay. Doppler flows over the pulmonary and aortic valve were recorded and time from Q to onset of flow was assessed for both valves. IVMD was defined as the timing difference between opening of the aortic valve and the pulmonary valve [2].

Systolic rebound stretch of the septum. SRSsept quantifies inefficient deformation, which occurs in early activated segments, and characterizes mechanical dyssynchrony [3,4,9,12,13]. Longitudinal speckle tracking analyses were performed offline for the septal wall.

We used this method as previously described and validated [3]. SRSsept was defined as the cumulative amount of systolic (i.e. between mitral valve closure and aortic valve closure) lengthening of the septum after initial shortening.3 Fig. 1A and B demonstrates a normal longitudinal speckle tracking trace, and a curve showing SRSsept, respectively. Previously, intra- and interobserver variability of this parameter has been tested in our center [3].

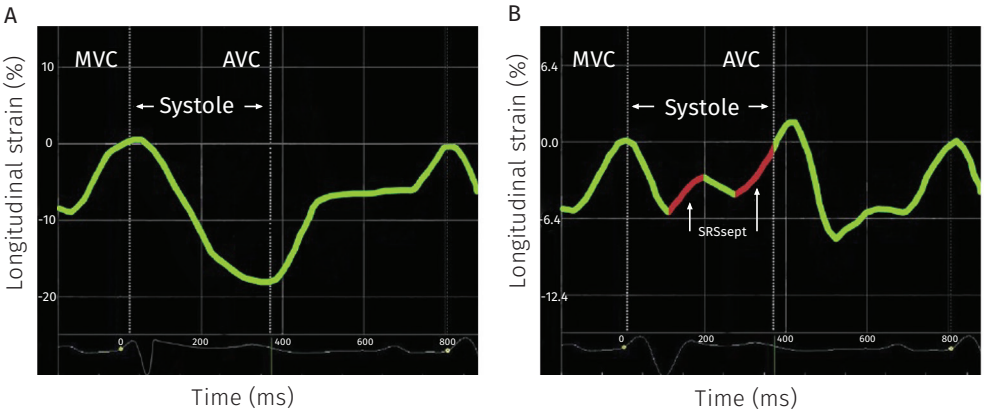

Figure 1. Longitudinal speckle tracking traces of the septal wall derived from echocardiographic 2D gray-scale images. When the speckle tracking trace is directed downwards the septal wall shortens. When the speckle tracking trace is directed upwards the septal wall stretches. Systole is defined as the time period between mitral valve closure (MVC; first dotted vertical line) and aortic valve closure (AVC; second dotted vertical line). Panel A: Trace of the septal wall demonstrating a normal septal curve. Panel B: Trace of the septal wall demonstrating systolic rebound stretch of the septum (SRSsept). SRSsept is indicated by the red lines in panel B.Systolic rebound stretch of the septum: Cumulative amount of systolic lengthening of the septum after initial shortening. In this example SRSsept is 3.0 + 4.0% = 7.0%.\

Volume assessment; outcome measures

LV volumes and LVEF were assessed according to Simpson's biplane method. Measurements were performed three times and averaged. In line with several previous studies, response to CRT was defined as relative change in left ventricular end systolic volume (LVESV) of≥15% six months after CRT implantation [2]. Consequently, non-responders were patients demonstrating <15% LVESV decrease.

Statistics

Statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL). Continuous variables are presented as mean with standard deviation (SD) when normally distributed and as median with interquartile range (IQR) in case of non-normal distribution. Assessing baseline differences between responders and non-responders was done using the Student t test in case of normally distributed variances, or Kruskal–Wallis test if otherwise. Categorical variables are summarized as frequencies and percentages and compared using Pearson's Chi-square.

Model development

Univariable and multivariable backward logistic regression analyses were performed to determine independent predictors with regard to relative change in LVESV. Brain-type natriuretic peptide (BNP), creatinine, left ventricular end diastolic volume (LVEDV) and LVESV become normally distributed after logarithmic transformation. Regression analyses were performed on log10-transformed values. SRSsept is left-skewed. Age, gender, etiology of HF, logBNP, logCreatinine, logESV, logEDV, left ventricular ejection fraction (LVEF), atrial fibrillation (AF), LBBB and QRS duration were included based on the results of previous studies, randomized trials [14–16] and differences at baseline with a p-value < 0.05 (Table 1). Variables with a feasibility of ≥90% and a p-value <0.05 in univariable analysis were included in the multivariable analyses. LogESV and logEDV, as well as LBBB and interventricular conduction delay (IVCD) showed multicollinearity by Pearson correlation >0.75. Based on univariable regression analyses, logEDV and LBBB were used for multivariable purposes. LBBB is a dichotomous variable per definition. QRS duration was used as a dichotomous variable (cut-off 150 ms), as this is applied in the guidelines. As parameters of mechanical dyssynchrony are not (yet) defined in current guidelines we chose to employ them as continuous variable as these contain more information than dichotomous. Odds ratios for continuous variables are therefore per unit of the mentioned variables. For SRSsept this is per percent point increase. For IVMD this is per ms increase. Subsequently, two separate models were created using backward logistic regression analysis. For model A conventional clinical, laboratory and parameters of electrical dyssynchrony (QRS duration and LBBB) were entered at the start. For model B conventional clinical, laboratory, electrical and additional mechanical dyssynchrony parameters (IVMD and SRSsept) were entered at the start. Assumption of normally distributed residuals was tested by checking histogram and normal probability plots of the regression unstandardized residuals and assumptions were met. Differences between two models were assessed by comparing the respective area under the receiver operating curves (AUC) C-statistics [17]. Furthermore, the incremental predictive value of mechanical dyssynchrony was assessed with the net reclassification index (NRI) as well as integrated discrimination improvement (IDI) [18]. Thereafter, we evaluated whether independent predictors for the whole study cohort performed equally well when the study population was stratified according to etiology of HF. For comparison of the model performance for NICM and ICM we used AUC. Calculation of NRI was based on the following categories of chances of becoming a responder: <0.33, 0.33–0.66, and >0.66. The IDI is independent of category choice and regards any shift in predicted chance in the right direction as a relevant change.

Results

Table 1. Patient characteristics

Clinical data	All patients (n=227)	Responders (n=115)	Non-responders (n=112)	p-value
Age, mean ± SD, (years)	65.4 ± 10,5	65.3 ± 11.1	65.4 ± 9.9	0.931
Male gender (%)	153 (67)	70 (61)	83 (74)	0.033
Ischemic cardiomyopathy (%)	115 (51)	48 (42)	67 (60)	0.006
Baseline NYHA II (%)	29 (13)	18 (16)	11 (10)	0.188
Baseline NYHA III (%)	185 (82)	94 (82)	91 (81)	0.924
Baseline ECG data				
Heart rate, mean ± SD, bpm	72 ± 14	71 ± 15	72 ± 14	0.403
Atrial fibrillation (%)	42 (19)	15 (13)	27 (24)	0.032
QRS duration, mean ± SD, ms	168 ± 24	171 ± 21	164 ± 26	0.021
QRS duration dichotomous ≥150 ms (%)	186 (82)	102 (89)	84 (75)	0.007
Left bundle branch block (%)	127 (56)	78 (68)	49 (44)	<0.001
QRS duration dichotomous ≥150 ms (%) within LBBB	114 (90)	71 (91)	43 (88)	0.554
Right bundle branch block (%)	1 (0)	0 (0)	1 (1)	0.310
Interventricular conduction delay (%)	67 (30)	20 (17)	47 (42)	<0.001
Right ventricular pacing (%)	32 (14)	17 (15)	15 (13)	0.764
Baseline medication				
Beta blocker	178 (79)	87 (76)	91 (81)	0.365
ACE inhibitor and/or Angiotensin-II receptor blocker (%)	202 (89)	101 (89)	101 (90)	0.700
Diuretics (%)	206 (91)	104 (91)	102 (91)	0.967
Baseline echocardiographic data				
Left ventricular end-systolic volume, median (IQR), ml	183 (96)	166 (94)	193 (99)	0.009
Left ventricular end-diastolic volume, median (IQR), ml	229 (103)	218 (94)	242 (105)	0.011
Left ventricular ejection fraction, mean ± SD, %	21 ± 7	22 ± 7	20 ± 7	0.043
Interventricular mechanical delay mean, ± SD, ms	46 ± 27	55 ± 26	36 ± 24	<0.001
Systolic rebound stretch of the septum, median (IQR), %	3.3 (4.4)	4.7 (4.9)	2.4 (3.6)	<0.001
Baseline laboratory data				
Brain-natriuretic peptide, median (IQR), pmol/L	119 (171)	84 (137)	138 (181)	0.002
Creatinine, median (IQR), µmol/L	109 (51)	104 (47)	113 (55)	0.005
Left Ventricular Lead position				
Lateral (%)	163 (74)	86 (78)	77 (71)	0.247
Posterior/lateral (%)	37 (17)	18 (16)	19 (17)	0.810
Anterior/lateral (%)	20 (9)	13 (12)	7 (6)	0.147

Study population

Patient characteristics are summarized in Table 1. Mean age 65.4 ± 10.5 years, 153 (67%) male, 115 (51%) ICM. For NYHA classification the distribution was as follows: NYHA I: n = 1, NYHA II: n = 29, NYHA III: n = 185, NYHA IV: n = 12. Atrial fibrillation (AF) was seen in 42 (19%) patients. In our cohort 127 (56%) had LBBB, 67 (30%) had aspecific interventricular conduction delay (IVCD), and 32 (14%) had right ventricular (RV) pacing. Echocardiographic response was seen in 115 (51%) patients. Responders less often were male (61 vs 74%, p = 0.033) or had ICM (42 vs 60%, p = 0.006) than non-responders. At baseline responders more often showed electrical dyssynchrony: LBBB (68 vs 44%, p < 0.001), and QRS duration ≥150 ms (89 vs 75%, p = 0.007), than non-responders. In addition, responders demonstrated significantly more mechanical dyssynchrony. Volumes and BNP were significantly lower in responders than non-responders and LVEF higher.

Additional value of mechanical dyssynchrony

Table 2 shows univariable and multivariable predictors for volume response for Model A and B in the whole study cohort. Solely significant univariable predictors were used for multivariable regression. After multivariable regression analysis model A comprised logBNP, QRS duration ≥150 ms, and LBBB, with a C-statistic of 0.711 (95% confidence interval (CI), 0.642–0.781). When parameters of mechanical dyssynchrony were also entered at the start, QRS duration was replaced by IVMD and SRSsept by the regression analysis and model B (termed BLISS) therefore comprised log**B**NP, **L**BBB, **I**VMD, and **S**R**S**sept, with a C-statistic of 0.767 (95% CI, 0.703–0.832) (Fig. 2). The difference in C-statistic showed a p-value of 0.06. The NRI increased significantly using the BLISS model: 28.7%, p = 0.003. And the IDI was 9.5%, p < 0.001. C-statistic for the BLISS model in NICM and ICM was 0.829 (0.751–0.907), and 0.688 (0.584–0.792), respectively (Fig. 3).

Table 2. Patient characteristics

Potential predictors	Univariable OR (95% CI)	Multivariable OR (95% CI) model A	Multivariable OR (95% CI) model B
Age[ab]	0.999 (0.974–1.024)	–	–
Male gender[ab]	0.544 (0.309–0.956)	–	–
Ischemic cardiomyopathy[ab]	0.481 (0.283–0.817)	–	–
Left bundle branch block[ab]	2.821 (1.639–4.855)	2.445 (1.374–4.350)	1.940 (1.024–3.677)
Interventricular conduction delay	0.323 (0.172–0.604)	–	–
QRS duration ≥ 150 ms[ab]	2.615 (1.275–5.364)	2.384 (1.091–5.210)	–
Atrial fibrillation[ab]	0.472 (0.236–0.945)	–	–
Log10ESV	0.113 (0.021–0.603)	–	–
Log10EDV[ab]	0.092 (0.013–0.651)	–	–
Left ventricular ejection fraction[ab]	1.039 (1.001–1.079)	–	–
Interventricular mechanical delay[b]	1.029 (1.017–1.041)	–	1.017 (1.003–1.031)
Systolic rebound stretch of the septum[b]	1.298 (1.170–1.440)	–	1.191 (1.055–1.344)
Log10BNP[ab]	0.399 (0.218–0.732)	0.359 (0.190–0.682)	0.421 (0.218–0.814)
Log10Creatinine[ab]	0.049 (0.006–0.377)	–	–

OR: Odds ratio. Multivariable odds ratios are presented solely for independent predictors after backward logistic regression.
Model A: Model with clinical, laboratory, and ECG parameters.
Model B: Model with clinical, laboratory, ECG, and echo parameters.
[a] Variables entered at step 1 in model A.
[b] Variables entered at step 1 in model B.

Discussion

The main finding of this study is that the combination of electrical and mechanical measurements of dyssynchrony (BLISS model) significantly improves response prediction after CRT implantation. The BLISS model contains easy available measurements, and BNP, LBBB, and IVMD are well-known and widespread used parameters which are easy to perform. SRSsept is a relatively new parameter, however previously our center proved this to be a very valuable measurement concerning prediction of reverse remodeling and prognosis after CRT implantation [3,9]. In addition, SRSsept has been validated in a computer model, indicating that it is a measure of intraventricular dyssynchrony with powerful predictive capacity [10,19]. Furthermore, the BLISS model appeared more applicable to non- ischemic than ischemic subjects.

Prediction of volume response in CRT patients

CRT is an electrical therapy aiming for mechanical improvements (so-called resynchronization). Measures ofelectrical dyssynchrony denote electrical conduction disturbances, but lack information on LV mechanics. Therefore, measurements of mechanical dyssynchrony might be helpful as these could distinguish between correctable and uncorrectable mechanical dyssynchrony and therefore improve response prediction in addition to ECG parameters. SRSsept provides information on both recruitable dyssynchrony as well as contractile function, possibly accounting for its powerful predictive capacity. Rebound stretch is stretch occurring after prematurely ended shortening in systole. This prematurely ended shorting is caused by opposed shortening of other LV segments which start contracting later in the cardiac cycle due to electrical conduction delay [20,21].

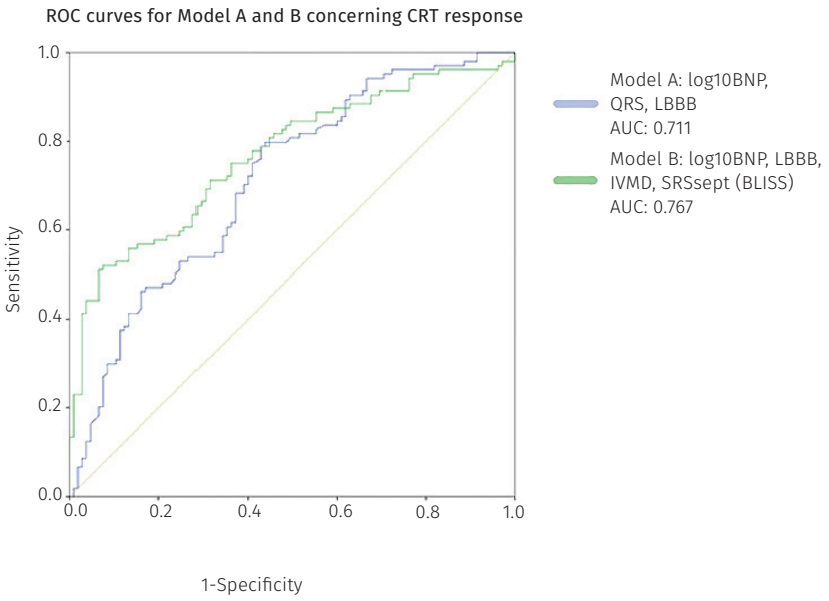

Figure 2. Areas under the receiver operating curve for Model A (blue line): 0.711 (0.642–0.781) and Model B (green line) the BLISS (logBNP, LBBB, IVMD, SRSsept): 0.767 (0.703–0.832).

These opposing powers are referred to as mechanical dyssynchrony, and can be displayed by SRSsept. On the other hand, in case of hypocontractility of either the septum or the opposing lateral wall, SRSsept is reduced, demonstrating that it also contains information on myocardial performance [19]. Several other echocardiographic parameters have been studied previously. Tissue Doppler Imaging (TDI) echo parameters showed additional value in predicting CRT response in single center studies [22,23], but failed in multi-center setting. The PROSPECT study demonstrated that dyssynchrony parameters assessed by TDI had high intra- and interobserver variability and lack of good sensitivity and specificity [2]. With speckle tracking the whole ventricular wall is taken into account, not solely a small sample in the basal wall segment. Furthermore, it better discriminates active and passive motion and is angle independent [4]. The EchoCRT study did not show CRT benefit in HF patients with QRS complex <130 ms and echocardiographic evidence of mechanical dysssynchrony [5]. Patients were randomized 1:1 to CRT-D 'ON' or CRT-D 'OFF' group. Dyssynchrony was assessed by TDI (SL-delay) and speckle tracking radial strain (anteroseptal to posterior wall). Mechanical dyssynchrony was said to be present either when SL-delay ≥ 80 ms or radial strain delay ≥ 130 ms, or both. The study was prematurely ended due to a higher mortality rate (primarily caused by cardiovascular deaths) in the CRT-D 'ON' group compared with the CRT-D 'OFF' group. In contrast to EchoCRT study, our study included HF patients with broad QRS complex and longitudinal instead of radial strain measurements were used to assess mechanical dyssynchrony. Besides superior feasibility, longitudinal strain is also less subject to out of plane motion than radial strain, which has been described previously, making longitudinal strain more reliable [24]. Furthermore, for TDI it was already shown this could not predict CRT-response [2]. Nevertheless, time-to-peak analysis using speckle tracking traces, has demonstrated to be able to predict response to CRT [25]. Therefore, in the current study, we also measured septal-to-lateral delay (SL-delay) by assessing longitudinal septal and lateral peak strain. However, as feasibility did not reach 90% (81%), we decided not to use this parameter in our analysis. Also, dyssynchronous hearts have a complex and multiphasic mechanical behavior making definitions of peaks complex [10]. IVMD and SRSsept were entered in the model together as IVMD is a measure of interventricular dyssynchrony and SRSsept a measure of intraventricular dyssynchrony and CRT aims to correct both [4].

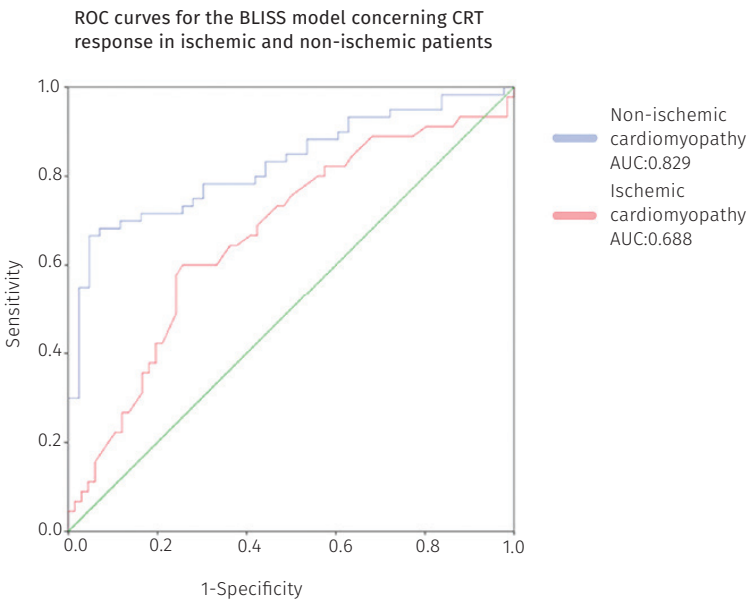

Figure 3. Areas under the receiver operating curve for the BLISS (logBNP,LBBB, IVMD, SRSsept) model in ischemic (red line): 0.688 (0.584–0.792) and non-ischemic (blue line) cardiomyopathy: 0.829 (0.751–0.907).

In line with our results, IVMD and LBBB have been identified as robust predictors concerning CRT response in several other studies [2,16]. A wide variety of LBBB definitions is currently being used in daily clinical practice and for research purposes. In 2011 Strauss et al. proposed new and stricter criteria for complete LBBB among which was a QRS duration ≥140 ms for men and ≥130 ms for women. [7] Although these criteria are interesting we did not apply them as they still need validation and we chose to enter QRS duration as an independent variable in the model. Furthermore, the precise implication of identifying patients with a complete LBBB is still unclear. The REVERSE study showed that longer QRS duration was beneficial in LBBB patients concerning CRT response [26]. However, as in our population a QRS duration of ≥150 ms significantly more often occurred in patients with high SRSsept and prolonged IVMD, this variable probably dropped out in multivariable analyses. We used QRS duration as a dichotomized variable, with a cut-off at 150 ms, as this is already used in CRT guidelines and our aim was to evaluate the additional value of parameters of mechanical dyssynchrony on top of established parameters of electrical dyssynchrony. However, using QRS duration as a continuous variable might be valuable when aiming to predict the actual amount of reverse remodeling. The REVERSE study showed that patients with a QRS duration of 140–160 ms at baseline showed a significant decrease of LVESVi, while those with a more narrow QRS complex did not show significant reverse remodeling and those with a wider QRS complex had the largest improvement in LVESVi [27].

Moreover, a meta-analysis of five large randomized controlled CRT trials which evaluated the relationship between QRS duration as a continuous variable and death or hospitalization due to HF found a significant progressive increase in benefit from CRT as QRS duration increased which had a plateau of effect beyond 180 ms [28].

Model B, containing both electrical and mechanical parameters of dyssynchrony, performed best in predicting response to CRT. As CRT aims to correct delayed activation of the LV, the additional value of mechanical dyssynchrony parameters in predicting response to CRT could suggest that they complement ECG criteria for LBBB in identifying those patients with a true LBBB. It should be noted, that even when patients with RV pacing at baseline were neglected, results remained unchanged.

In line with findings of Cappola et al. [29] our study demonstrated that lower BNP levels correspond to volume response after CRT implantation. Lower baseline BNP levels have previously been associated with decreased risk of morbidity and mortality in HF patients, as compared to patients with higher BNP levels. Lower BNP levels indicate lower loading pressures and thus less advanced heart failure [30]. However, a study of Brouwers et al. [31] reports contradictory results. They did not find an association between baseline BNP levels and reverse remodeling. A reason for the discrepancy with our data could be that their population had, on average, smaller baseline volumes and lower BNP levels at baseline as compared to our study cohort (results not shown, as we presented data with median and interquartile range). Therefore, study cohorts are possibly not comparable.

Furthermore, duration of HF might be of influence on chances of CRT response. However this relationship has never been adequately addressed as it is fairly challenging to determine the exact moment of onset of LV dysfunction. Therefore, duration of HF was unknown for our cohort. It could be argued that ICD upgrades possibly had a longer history of HF than de novo CRT implantations. Nevertheless, there was no significant difference between the number of ICD upgrades in the responder and non-responder group.

Other possible parameters which influenced CRT response were LV lead position, AF, and percentage of biventricular pacing. The focus of this study was on the predictive value of baseline variables, and both pacing percentage and lead position are not available at baseline. In addition, pacing percentages were not available for the complete study cohort, although a median pacing percentage of 99% was found for 174 patients, which seems to be appropriate.

Moreover, when AF patients were neglected, the BLISS model still appeared to be the best performing model.

Non-ischemic and ischemic cardiomyopathy

Our results demonstrate that prediction of volume response after CRT implantation is far more challenging for ICM than for NICM. Although SRSsept and IVMD have previously demonstrated to maintain a linear relation with reverse remodeling in the presence of scar, the BLISS model, based on our entire cohort, fits well to the NICM, but not the ICM subpopulation. An explanation could be that both SRSsept and IVMD showed significantly lower values in ICM than NICM. Consequently, measurement errors are relatively larger. Furthermore, univariable odds ratios for SRSsept and IVMD were lower in ICM than NICM (e.g. for SRSsept these were 1.211 and 1.361, for ICM and NICM respectively).

This indicates that especially in ICM different potential predictors have to be identified. Especially quantification of the scar tissue should be considered [32]. Magnetic Resonance Imaging (MRI) can identify regions of scar tissue, which could guide LV lead positioning into a scar free area. Furthermore, it might be helpful to assess the extensiveness of coronary artery disease in patients with ICM, as this varies from a single lesion to disseminated three-vessel disease, which might influence the potential of reverse remodeling. A model in which amount of scar tissue, extent of coronary artery disease, and LV lead position are implemented may increase predictive value. In addition, a recent meta-analysis showed that although NICM and ICM benefit in a similar way from CRT concerning major adverse cardiac events, reverse remodeling is more prominent in NICM [33]. Currently applied cut-off value of 15% could therefore misclassify a substantial proportion of ischemic responders as non-responders. Consequently, in ICM a lower cut-off value of LVESV decrease to identify responders and non-responders could be considered.

Future directions

A study should be conducted to test our results in a prospective, preferably multi-center, cohort. Currently the Center for Translational Molecular Medicine (CTMM) is running a multi-center trial to investigate the predictive value of a broad spectrum of (bio)markers concerning CRT response. This could also include the validation of our BLISS model.

Clinical implications

According to current guidelines in patients with HF and LVEF ≤35% indication for CRT is based solely on parameters of electrical dyssynchrony. However, this way of screening is bothered by a considerable proportion of patients being classified as non-responder. Additional ECG parameters (e.g. LVAT) have been evaluated to improve response prediction [34]. Due to lack of feasibility of LVAT, the additional value of this parameter is limited. Our results show that SRSsept and IVMD have both high feasibility and important additional predictive value concerning volume response in CRT patients.

Therefore we would recommend additional measurements of mechanical dyssynchrony, above assessment of electrical dyssynchrony, especially in class IIb indication for CRT (non-LBBB, QRS < 150 ms). A model that includes electrical and mechanical measurements of dyssynchrony (BLISS: logBNP, LBBB, IVMD, SRSsept) could be valuable to decide whether patients should receive ICD with or without CRT.

Study limitations

This study was a single-center retrospective study with its inherent limitations. Although we had a relative large cohort size, results of this study should be investigated in a prospective multi-center study. Furthermore, besides clinical, electrical and mechanical parameters, several other factors (might) influence CRT response: compliance to pharmacological therapy, psychological factors, physical activity, comorbidity, amount of scar tissue. However, these were beyond the scope of this study. Furthermore this study did not report changes in NYHA classification, although improvement of patients' well-being is also an important aim of CRT.

Conclusion

Both electrical dyssynchrony and mechanical dyssynchrony are important concerning prediction of CRT response. However, response prediction in ischemic subjects remains challenging and new predictors for this subgroup should be identified.

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Chapter 4

REGIONAL LEFT VENTRICULAR ELECTRICAL ACTIVATION AND PEAK CONTRACTION ARE CLOSELY RELATED IN CANDIDATES FOR CARDIAC RESYNCHRONIZATION THERAPY

Submitted

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Abstract

Background: Placing the left ventricular (LV) lead in the region of latest electrical activation or the region of latest peak contraction has both been shown to improve response to cardiac resynchronization therapy (CRT). We compared the timing of LV electrical activation and peak contraction at potential LV pacing locations in CRT candidates to investigate whether these two LV lead targeting strategies are comparable.

Methods: Twenty-eight consecutive CRT candidates underwent intra-procedural coronary venous electro-anatomic mapping using EnSite NavX. Peak contraction time of the mapped LV regions was determined using longitudinal strain derived from speckle tracking echocardiography. Electrical activation and peak contraction times were correlated on a per-patient basis and the regions of latest electrical activation and latest peak contraction were compared.

Results: Successful measurements by both techniques allowed analysis in 23 of 28 patients. There was a strong positive correlation between electrical activation and peak contraction times within each patient (R2=0.85±0.09). However, the magnitude of the electrical activation – peak contraction relationship varied greatly between patients (slope of regression line = 4.05±3.23). The regions of latest electrical activation and latest peak contraction corresponded in 19 of 23 (83%) patients and were adjacent in the other 4 patients.

Conclusion: There is a strong positive correlation between the timing of LV electrical activation and peak contraction measured at potential LV pacing locations in CRT candidates. This finding suggests that a strategy of determining the latest activated LV region based on speckle tracking echocardiography is equivalent to that based on intra-cardiac measurements of electrical activation.

Abbreviations: CRT = cardiac resynchronization therapy; LV = left ventricular; CS = coronary sinus; EAM = electro-anatomic mapping; LBBB = left bundle-branch block; IVCD = intra-ventricular conduction delay; AHA = American Heart Association; EAT = electrical activation time; ACE-i = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ms = milliseconds; LAO = left anterior oblique; RAO = right anterior oblique view; AIV = anterior inter-ventricular vein; ALV = anterolateral vein; ILV = inferolateral vein; A = anterior; AL = anterolateral; IL = inferolateral; I = inferior; L = lateral; S = septal; IS = inferoseptal; AS = anteroseptal.

Introduction

Cardiac resynchronization therapy (CRT) has become an important treatment for heart failure patients with left ventricular (LV) systolic dysfunction and evidence of LV conduction delay.[1] CRT aims to resynchronize the electrical ventricular activation by paced pre-excitation of the delayed LV lateral wall. Doing so, it restores coordinated ventricular contraction, improves LV systolic function and reverses ventricular remodeling.[2] The position of the LV lead with respect to the region of latest activation has been shown to be an important determinant of CRT response. Studies focusing on electrical activation have demonstrated that a greater delay in time from onset of the QRS complex to the locally sensed LV lead electrogram is associated with a greater likelihood of benefit from CRT.[3,4] Other studies used speckle tracking based strain measures of mechanical activation and suggest better CRT outcome when the LV lead position coincides with the segment of latest peak contraction.[5,6] The choice between targeting the region of latest electrical activation or the segment of latest peak contraction is currently a matter of debate. On the one hand, pre-clinical studies in non-failing canine hearts have previously shown that electrical and mechanical activation of the heart are closely coupled.[7-9] On the other hand, echocardiography based time-to-peak measures of mechanical dyssynchrony have recently been questioned for their ability to predict CRT response.[10,11]

Therefore, it remains unclear whether the preclinical results can be extrapolated to the dyssynchronous failing human heart. The results of two recent small-scale studies on this subject have been conflicting.[12,13] The purpose of the present study was to perform a within-patient comparison of the timing of LV electrical activation and peak contraction at potential LV pacing locations accessible via the coronary veins in patients undergoing CRT.

Methods

Study population

This study was conducted in 28 consecutive patients enrolled for CRT with a class I or IIa indication according to current European Society of Cardiology guidelines. [14] The study protocol was approved by the Maastricht University Medical Center's Institutional Review Board.

Electro-anatomic mapping

All patients underwent intra-procedural coronary venous electro-anatomic mapping (EAM) at the MUMC as described previously.[15] In brief, prior to LV lead placement, a 0.014 inch guidewire (Vision Wire, Biotronik SE & Co.KG), which permits unipolar sensing and pacing[16], was inserted into the coronary sinus (CS) and connected to an EnSite NavX system (St Jude Medical, St Paul, MN, USA) along with the surface electrocardiogram. The guidewire was manipulated to various CS branches, creating an anatomic map along with determining local electrical activation time during intrinsic ventricular activation.

Classification of coronary venous anatomy

The coronary venous anatomy was classified according to the American Heart Association (AHA) 17-segment heart model [17] by detailed evaluation of biplane coronary venous angiograms using Mortensen's o'clock technique.[18] In the left anterior oblique image, which is comparable to the short axis of the heart, the CS was divided into anterior, anterolateral, inferolateral and inferior areas, and the distribution of the branches was described similarly. The right anterior oblique image, representative of the long axis of the heart, was used to divide CS branches into basal, mid-ventricular and apical segments.

Echocardiography

Standard 2-dimensional echocardiography was performed prior to CRT implantation at the Maastricht University Medical Center using a commercial machine (Philips IE 33, Philips Medical Systems, Andover, Massachusetts, USA). Routine gray-scale cine loop images were acquired in standard apical views with a frame rate of at least 50 Hz and digitally stored for post-processing offline (Xcelera software R3.3L1).

Left ventricular end-diastolic volume, LV end-systolic volume and LV ejection , fraction were calculated using Simpson's biplane method. Speckle tracking 2-dimensional longitudinal strain analysis of the apical two-three- and four-chamber images was performed at the University Medical Center Utrecht by an experienced observer blinded to the electrical data using Cardiac Performance Analysis software version 1.2 (Tomtec Imaging Systems). The endocardial border was manually traced in end-systole. Subsequently, the speckle tracking software automatically analyzed frame-by-frame movement of the stable patterns of acoustic markers (speckles) to generate time-strain curves over the cardiac cycle of the myocardial segments. The peak contraction time of each myocardial segment was measured in milliseconds from QRS onset to peak longitudinal strain. If segmental time-strain curves showed more than one peak, the first peak was assessed. Echocardiographic images that were of insufficient quality for speckle tracking strain analysis and myocardial segments with likely scar (low amplitude longitudinal strain curves < 5.3 %, thin wall ≤ 0.5 cm, abnormal increase in acoustic reflectance, and akinetic wall motion)[19,20] were handled as missing data.

Comparison of electrical activation and peak contraction times

After classification of the coronary venous anatomy according to the AHA 17-segment heart model as described above, the electrical activation time of each myocardial segment was calculated as the average of all electrical activation times measured within a segment during mapping. To determine the peak contraction time corresponding to each mapped myocardial segment, the echocardiographic free-wall segments were relabeled to correspond to the AHA 17-segments heart model as follows (with echocardiographic labels listed first): anterior = anterior, lateral = anterolateral, posterior = inferolateral, and inferior = inferior. The electrical activation and peak contraction times of each myocardial segment were then directly compared. Pearson's correlation coefficient was computed between the electrical activation and peak contraction times observed for each patient. The segments of latest electrical activation and latest peak contraction were determined in each patient.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation. Categorical values are expressed as observed number and percentage values. Within-patient correlation between electrical activation and peak contraction times was calculated using Pearson's correlation coefficient. Statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chigaco, IL, USA) software.

Results

Patient characteristics

Twenty-eight consecutive patients enrolled for CRT underwent echocardiographic examination before the procedure and coronary venous EAM during CRT implantation. The patient characteristics are described in table 1.

Table 1. Patient characteristics (n = 28)

Age, years	71±9
Male gender (n, %)	18 (64)
Ischemic heart disease (n, %)	13 (46)
NYHA functional class (n, %)	
II	13 (46)
III	15 (54)
Echocardiography characteristics	
LV ejection fraction (%)	28±6
LV end-diastolic diameter (mm)	61±7
LV end-systolic diameter (mm)	52±7
LV end-diastolic volume (mL) 169±51	169±51
QRS (ms)[#], mean ± SD	123±38
ECG characteristics	
QRS duration (ms)	154±15
LBBB (n, %)	18 (64)
IVCD (n,%)	10 (36)
Intrinsic rhythm (n, %)	
Sinus rhythm	23 (82)
Atrial fibrillation	5 (18)
Treatment (n, %)	
Diuretics	19 (68)
ACE-i/ARB	27 (96)
Beta-blockers	24 (86)
Spironolactone	15 (54)
Digoxin	2 (7)
Amiodarone	4 (14)

LBBB = left bundle branch block, IVCD = intra-ventricular conduction delay, ACE-i = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker.

Coronary venous electro-anatomic mapping and speckle tracking strain analysis
Intra-procedural coronary venous EAM was accomplished in all 28 patients without complications. Coronary venous angiography in the 28 patients revealed a total of 96 coronary venous branches, of which 83 (86%) could be mapped. Three-dimensional electrical activation maps were generated from 62±25 unique anatomic points. Mapping time was 19±7 minutes, and fluoroscopy time during the entire procedure was 21±4 minutes. Speckle tracking longitudinal strain analysis was accomplished in 23 of 28 patients. In the other 5 patients, speckle tracking strain analysis was hampered by insufficient quality of the acquired echocardiographic images (n = 4) and frequent premature ventricular beats (n = 1). These 5 patients were excluded from further analysis.

Relationship between left ventricular electrical activation and peak contraction
In the 23 patients with successful measurements by both coronary venous EAM and speckle tracking strain analysis, the electrical activation and peak contraction times of a total of 87 myocardial segments were measured (25 anterior (basal, n = 14; mid, n = 11) 31 anterolateral (basal, n = 18; mid, n = 14), 16 inferolateral (basal, n = 8; mid, n = 8), and 15 inferior (basal, n = 7; mid, n = 8)). All patients had at least 3 myocardial segments measured. An example of the analysis in one patient is shown in figure 1. In this patient, the CS and three side branches situated on the basal and mid anterior-, anterolateral- and inferolateral wall were mapped (figure 1A). Earliest activation was found in the mid segment of the anterior inter-ventricular vein and latest activation in the basal segment of the inferolateral vein.

Figure 1B shows the corresponding time strain curves of the mapped myocardial segments obtained by speckle tracking echocardiography. In figure 1C, the average electrical activation times of the mapped myocardial segments are displayed on the standard AHA 17-segment heart model together with the corresponding peak contraction times. In figure 1D, peak contraction time is plotted as a function of average electrical activation time. There was a strong correlation between electrical activation and peak contraction times within this patient and the segment of latest electrical activation corresponded with the segment of latest peak contraction.

A strong linear relationship between electrical activation and peak contraction times, as observed in the example shown in figure 1, was found in all patients ($R2 = 0.85 \pm 0.09$). Figure 2 shows the individual regression lines. The slope of the regression line was positive in all patients, indicating that as electrical activation time increases, the peak contraction time increases as well. However, the slope and hence the magnitude of this relationship varied greatly between patients (slope of regression line = 4.05±3.23). Also, the slope of the regression line was above unity in all but one patient, indicating that mechanical delay was generally greater than the corresponding electrical delay.

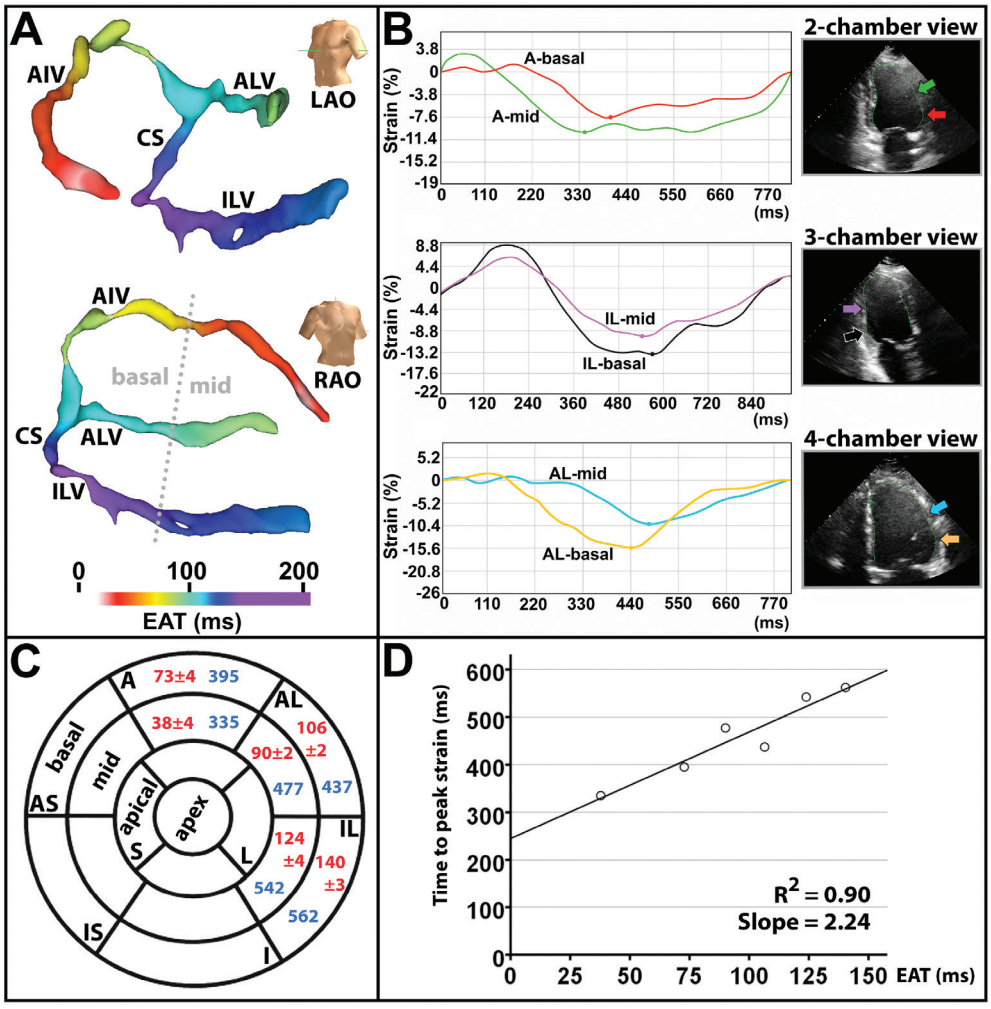

Figure 1. (A) Coronary venous electro-anatomic map of a study patient. The coronary sinus and three side branches (basal and mid segments) were mapped. Earliest activation is represented in white and red and latest activation in blue and purple. (B) Corresponding time strain curves of the mapped myocardial segments. (C) Electrical activation times (mean ± standard deviation, red numbers) of the mapped myocardial segments together with the corresponding peak contraction times (blue numbers) displayed on the standard AHA 17-segments heart model. (D) Correlation between electrical activation and peak contraction times. L/RAO = left/right anterior oblique view, CS = coronary sinus, AIV = anterior inter-ventricular vein, ALV = anterolateral vein, ILV = inferolateral vein, EAT = electrical activation time, A = anterior, AL = anterolateral, IL = inferolateral, I = inferior, L = lateral, S = septal, IS = inferoseptal, AS = anteroseptal.

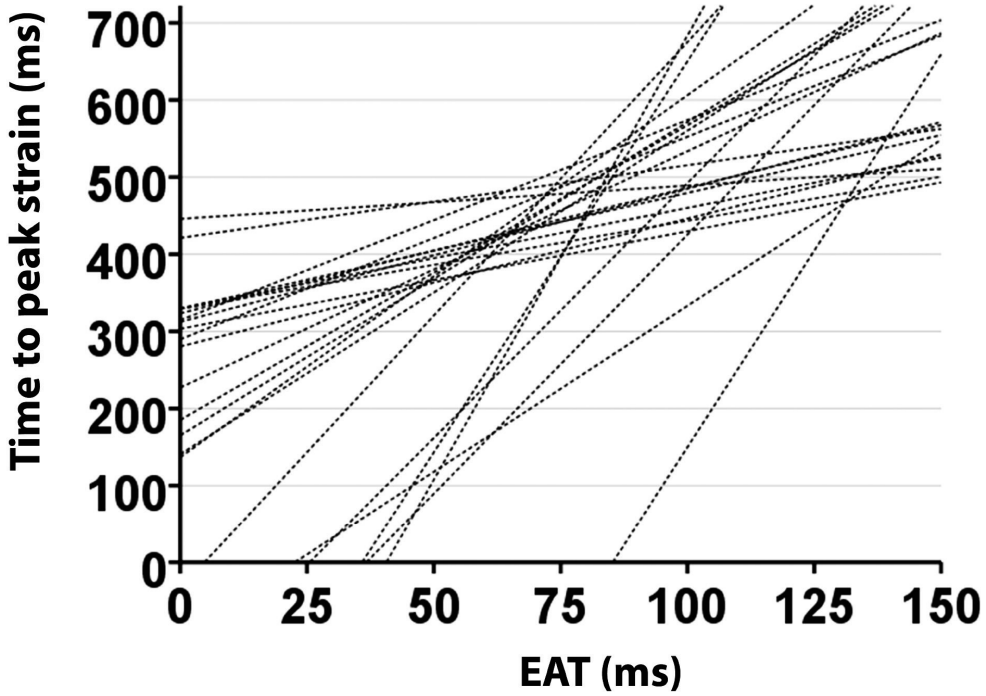

Figure 2. Individual regression lines between electrical activation and peak contraction times. The slope of the regression line varied greatly between patients, but was always positive and had a value of >1 in all but one patient.
EAT = electrical activation time, ms = milliseconds

Figure 3 shows the spatial distribution of the electrically latest activated and latest contracting segments in all patients. The segment of latest electrical activation was located anteriorly in 11 (basal, n = 10; mid, n = 1), anterolaterally in 8 (basal, n = 5; mid, n = 3), and inferolaterally in 4 (all basal). The segment of latest peak contraction was located anteriorly in 11 (all basal), anterolaterally in 8 (basal, n = 5; mid, n = 3), and inferolaterally in 4 (all basal). The myocardial segment with the largest electrical activation time also had the largest peak contraction time in 19 of 23 patients (83%). In the other 4 patients, the myocardial segments of latest electrical activation and latest peak contraction were adjacent.

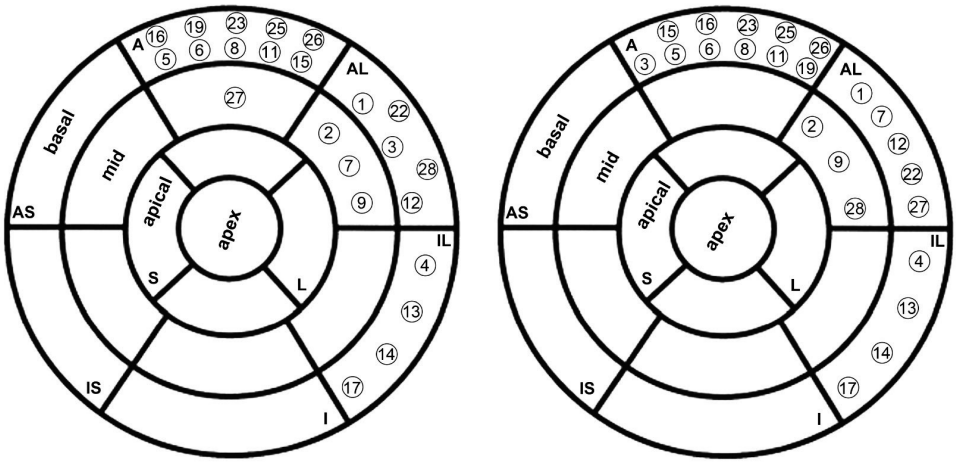

Figure 3. Distribution of the electrically latest activated (left panel) and latest contracting segments (right panel) in the 23 patients with successful measurements by both coronary venous EAM and speckle tracking echocardiography. Each circled number represents a patient. The segment with the largest electrical activation time also had the largest peak contraction time in 19 of 23 patients (83%). In 4 patients (nrs. 3, 7, 27 and 28), the segments of latest electrical activation and latest peak contraction were adjacent. A= anterior, AL = anterolateral, AS = anteroseptal, I = inferior, IL = inferolateral, IS = inferoseptal, L = lateral, S = septal.

Discussion

In the present study we investigated the relationship between the timing of regional LV electrical activation and peak contraction in dyssynchronous heart failure patients undergoing CRT implantation. We demonstrated a strong positive correlation between electrical activation and peak contraction times measured at potential LV pacing regions accessible via the coronary veins in all patients. However, the magnitude of the relationship between electrical activation and peak contraction times varied greatly between patients. The myocardial segments of latest electrical activation and latest peak contraction corresponded in 83% of patients. Our data indicate that a strategy of determining the latest activated LV region based on speckle tracking strain patterns is equivalent to that based on intra-cardiac measurements of electrical activation.

Relationship between timing of electrical activation and peak contraction

A number of animal studies have previously studied the relation between the sequence of LV electrical activation and contraction using a combination of electrical mapping techniques and strain measurements. These studies were conducted in healthy spontaneously activated or paced canine hearts and focused on the relation between timing of electrical activation and time-to-onset of contraction, rather than peak contraction. A strong linear relation between timing of electrical activation and onset of contraction was found in these studies. In addition, mechanical delay was shown to be larger than electrical delay.[7,9,21,22] While time-to-onset of contraction may be a better surrogate for mechanical activation than time-to-peak contraction, in practice, the identification of the first subtle onset of contraction can be cumbersome. Therefore, most clinical studies employed time-to-peak contraction.[5,6]

The findings of the present study are consistent with the results of a recent study by Suever et al.[13], who investigated the relation between electrical and mechanical delay times measured at potential pacing locations within the coronary veins. In this study, the mechanical contraction times were computed using cross correlation of radial displacement curves from high temporal resolution cine cardiac magnetic resonance images, while electrical activation times were derived from intra-procedural local electrograms obtained using the LV lead. Similar to our findings, they found a strong correlation between electrical and mechanical delay times within each patient. Additionally, the electrically latest activated region corresponded with the latest contracting region in 91% of patients.

Our results are also in line with a very recent study by Kroon et al[23], who used NOGA mapping derived electrograms and local strain derived from the motion of the NOGA catheter to investigate the relation between the timing of LV electrical activation and peak shortening in 10 CRT candidates. In this study, an excellent correlation was found between local electrical activation and peak shortening times in 8 out of 10 patients.

However, our findings are in contrast to the results of a previous study that had a similar design as ours. In that study by Fujiwara et al., the electrically latest activated region as determined by coronary venous EAM matched with the latest contracting region as determined by speckle tracking radial strain analysis in only 18% of patients[12], whereas we found that the regions of latest electrical activation and latest peak contraction corresponded in 83% of patients. An important methodological difference between our study and the study by Fujiwara et al. is the use of different types of strain measurements (radial vs. longitudinal). The Longitudinal strain measurements that were used in the present study have been shown to be more feasible and reproducible than radial strain measures.[24,25] Also, in contrast to Fujiwara et al., we only measured peak contraction times of LV regions accessible via the coronary veins.

In doing so, we neglected the data on mechanical activation of the septum, because this part of the LV wall is not accessible from the CS and, most importantly, is unlikely to be activated late in LBBB-like conduction abnormalities.
It was previously shown in computer simulations that septum strain patterns can be complicated and multiphasic, and can sometimes show a relatively late peak in systole, even in LBBB [26], which may lead to erroneously finding the latest peak contraction in the septum.

In the present study, the latest activated region was located on the anterior wall in 11 of 28 patients. Seven of these patients did not have a typical LBBB morphology on ECG, which may explain why the latest activated region was not located on the lateral wall as is typically the case in a LBBB activation pattern. The other 4 patients had an ischemic etiology of heart failure with myocardial scarring which may have altered the sequence of LV electrical and mechanical activation typically observed in LBBB patients.

Inter-individual variability in electrical activation – peak contraction relationship
In the present study, we found a strong linear relationship between timing of electrical activation and peak contraction within each patient. In addition, the relationship was positive in each patient, indicating that as electrical activation time increases, peak contraction time increases as well. However, the slope of the best fit line between electrical activation and peak contraction times was 4.06±3.23, which indicates that the electrical activation - peak contraction relationship varied greatly between patients and that timing differences of myocardial contraction were greater than those of electrical activation. The differences in the electrical activation – peak contraction relation between hearts may be caused by inter-individual differences in local myocardial tissue properties, such as viability, contractility and stiffness of the myocardium.[23] In computer models of LBBB, the more pronounced mechanical rather than electrical delay has been attributed to the higher mechanical load that needs to be overcome by late activated regions, which causes onset of contraction to occur relatively late.[8]

Clinical implications

In the present study, we demonstrated that there is a strong correlation between timing of electrical activation and peak contraction and that the regions of latest electrical activation and latest peak contraction largely correspond within CRT patients. These findings suggest that current targeted LV lead placement strategies which are based on either direct intra-cardiac measurements of electrical activation or speckle tracking strain echocardiography will most likely target the same myocardial region and as such can be regarded as equivalent. In this respect, the present study can be regarded as a validation of the speckle tracking approach.

This validation is not trivial, because echocardiographic measures of mechanical dyssynchrony have recently been questioned with respect to their ability to predict CRT response.[10,11,27] Proposed explanations for these disappointing results have been that the time-to-peak contraction may depend on other factors than electrical activation time alone and that there is a high variability in the way echocardiographic dyssynchrony parameters are acquired and analyzed. However, most of the problems faced with echocardiographic measures of mechanical dyssynchrony relate to difficulties in determining contraction time of the early-activated septum with its complicated, multi-phasic contraction patterns. In current practice, the LV lead is placed epicardially via the coronary veins, which only allow access to the LV free wall segments. Therefore, assessment of mechanical activation of the septum is not as important as that of the LV free wall for guiding LV lead placement. Limiting the assessment of time-to-peak contraction to the LV free wall therefore avoids most of the problems faced during echocardiographic assessment of mechanical dyssynchrony.

Limitations

The relatively small sample size is a limitation of this study. However, the study was performed on consecutive patients and the study population resembled the typical population of patients with dyssynchronous heart failure referred for CRT.

In the present study we were able to measure electrical activation and peak contraction times of an average of 3.8 myocardial segments per patient, which resulted in an obviously low sampling density. This is however inherent to the limitations of measuring epicardial electrical activation through the coronary veins, which is limited by the constraints imposed by coronary venous anatomy, and the limitations of speckle tracking echocardiography which relies on the availability of echocardiographic images with sufficient quality for reliable assessment of strain patterns.

Conclusion

The present study demonstrates that there is a strong positive correlation between the timing of LV electrical activation and peak contraction measured at potential LV pacing locations accessible via the coronary veins in patients undergoing CRT. Additionally, the regions of latest electrical activation and latest peak contraction largely correspond within CRT patients. These findings suggests that a strategy of determining the latest activated LV region based on speckle tracking echocardiography is equivalent to that based on intra-cardiac measurements of electrical activation.

Conflict of interest

Yuri Blaauw is consultant for Medtronic. Frits Prinzen received research grants from Medtronic, Boston Scientific, EBR Systems, St. Jude Medical, Biological Delivery System Cordis, MSD and Proteus Medical. Harry Crijns received grant support from St. Jude Medical and Boston Scientific, and honoraria from Medtronic and BiosenseWebster. Kevin Vernooy received research grants from Medtronic and is consultant for Medtronic.

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Chapter 5

ECHO RESPONSE AND CLINICAL OUTCOME IN CRT PATIENTS

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Abstract

Background: Change in left ventricular end-systolic volume (ΔLVESV) is the most frequently used surrogate marker in measuring response to cardiac resynchronisation therapy (CRT). We investigated whether ΔLVESV is the best measure to discriminate between a favourable and unfavourable outcome and whether this is equally applicable to non-ischaemic and ischaemic cardiomyopathy.

Methods: 205 CRT patients (age 65±12 years, 69% men) were included. At baseline and six months echocardiographic studies, exercise testing and laboratory measurements were performed. CRT response was assessed by: ΔLVESV, ΔLV ejection fraction (LVEF), Δ interventricular mechanical delay, ΔVO2 peak, ΔVE/VCO2, ΔBNP, Δcreatinine, ΔNYHA, and ΔQRS. These were correlated to the occurrence of major adverse cardiac events (MACE) between six and 24 months.

Results: MACE occurred in 19% of the patients (non-ischaemic: 13%, ischaemic: 24%). ΔLVESV remained the only surrogate marker for CRT response for the total population and patients with non-ischaemic cardiomyopathy, showing areas under the curve (AUC) of 0.69 and 0.850, respectively. For ischaemic cardiomyopathy, ΔBNP was the best surrogate marker showing an AUC of 0.66.

Conclusion: ΔLVESV is an excellent surrogate marker measuring CRT response concerning long-term outcome for non-ischaemic cardiomyopathy. ΔLVESV is not suitable for ischaemic cardiomyopathy in which measuring CRT response remains difficult.

Background

Cardiac resynchronisation therapy (CRT) reduces major adverse cardiac events (MACE), and improves exercise capacity and functional class, in drug refractory heart failure patients (NYHA ≥ II) with ventricular conduction delay.[1-3] However, the degree of CRT response varies widely and ranges from MACE rates similar to heart failure patients without CRT to rates comparable with a matched sample from the general population.[4,5] In daily clinical practice, degree of CRT response is assessed six months after CRT implantation using echocardiographic change (Δ) of left ventricular end-systolic volume (LVESV).[6] However, whether ΔLVESV is the most appropriate surrogate marker has not been extensively investigated. Furthermore, due to differences in underlying disease, response measures might not be equally appropriate for patients with non-ischaemic and ischaemic cardiomyopathy.

Two basic criteria need to be fulfilled for a variable to be a suitable surrogate marker: 1) A relation has to be demonstrated between the change of the surrogate marker over time (e.g. LVESV decrease) and the true endpoint (MACE), and 2) a pathophysiological foundation must be known to consider the surrogate marker as a main determinant of the true endpoint.[7] LVESV declines after CRT due to reverse remodelling and has been demonstrated to correlate with a favourable prognosis.[8,9] Besides change in LV volume, changes in parameters indicating LV systolic function, mechanical dyssynchrony, cardiopulmonary condition and biomarkers of overall cardiovascular function are potential surrogate markers for CRT response.[10-17]

In this study we investigated 1) several surrogate markers for CRT response, and 2) whether these surrogate markers were equally applicable for non-ischaemic and ischaemic cardiomyopathy.

Methods

Study design and cohort

This was a retrospective study in which we included 205 consecutive patients who received a CRT device (200 received a CRT defibrillator and four a CRT pacemaker) in the University Medical Center Utrecht (UMCU) between August 2005 and August 2011, with prospectively planned echocardiographic studies, cardiopulmonary exercise testing and laboratory evaluation available before implantation. It was recommended not to change device settings during the first six months. Configurations were only adjusted by exception, during regular check-up at two months. Thereafter, until the six-month point of assessment, pacing configurations remained unchanged.

Six months after device implantation, evaluation of the echocardiographic studies, cardiopulmonary exercise testing and laboratory tests was repeated. To determine the best surrogate marker for CRT response, the correlation between all potential surrogate CRT response measurements and MACE occurring between six and 24 months was assessed. We did not include MACE occurring before our six-month evaluation point, as therapy effect was quantified at six months in order to gather prognostic information for the period afterwards, not the preceding period. In addition, the effect of CRT might not yet be optimal in the preceding period, which was another reason why we chose not to include MACE occurring in the first six months to correlate to surrogate response measurements. The study was conducted in accordance with the Declaration of Helsinki.

Response to CRT was assessed six months after device implantation by 1) ΔLVESV (%), 2) Δleftventricular ejection fraction (LVEF; absolute %), 3) Δinterventricular mechanical delay (IVMD; ms), 4) ΔVO2 peak (ml/kg/min), 5) Δ percentage of predicted VO2 peak (absolute %), 6) ΔVE/VCO2 slope, 7) Δbrain natriuretic peptide (BNP; pmol/L), 8) Δcreatinine (μmol/L), ΔNYHA, and ΔQRS duration.

Echocardiography

Data were acquired using Philips IE 33 (Philips Medical Systems, Andover, Massachusetts, USA) or Vivid 7 (General Electric, Milwaukee, USA) ultrasound machines. Echocardiographic parameters were assessed using Xcelera software (R3.3L1). Volumes and ejection fraction were assessed by Simpsons' biplane method in accordance with the guidelines of the American Society of Echocardiography (ASE) and European Association of Echocardiography (EAE).[10]

Doppler flows over the pulmonary and aortic valve were recorded and time from Q to onset of flow was assessed for both valves. IVMD was defined as the time span between opening of the aortic valve and the pulmonary valve.[6] Measurements were performed on three separate beats, or five beats in case of irregular rhythms.

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing on the bicycle ergometer started with unloaded cycling for 2 minutes after which a protocol of stepwise incremental exercise was applied, starting at 25 Watt with increments of 5, 10 or 15 Watt every minute depending on the estimated maximum workload. Rotation speed was kept around 60 per minute. Prior to testing, gas and flow sensors were calibrated utilising gases with established concentrations of O_2 and CO_2. Ventilation (VE) (L/min), peak oxygen consumption (VO_2) (mL/kg/min), and carbon dioxide production (VCO_2) (L/min) were measured for each patient throughout the exercise on a breath-to-breath basis. VO2 peak and VE/VCO_2 slope were assessed. Data for the VE/VCO_2 slope were collected throughout the exercise, with exclusion of the unloaded cycling and recovery period.

VO_2 peak is the level of O_2 consumption during maximum effort and averaged over a 30-second period.[11] The VE/VCO_2 slope provides a measure of CO_2 exchange efficiency by assessing required ventilation for CO_2 elimination.[11]

Long-term follow-up and assessment of major adverse cardiac events

MACE was defined as: hospital admission for heart failure, sustained ventricular tachycardia (VT) (VT lasting >30 seconds or a VT beneath the monitoring zone leading to hospitalisation), ventricular fibrillation (VF), receiving a left ventricular assist device (LVAD), undergoing heart transplantation, death due to heart failure and appropriate implantable cardioverter defibrillator (ICD) shocks (due toVT or VF). Multicentre studies proved a CRT defibrillator was beneficial over a CRT pacemaker device concerning long-term survival, indicating that the shock function of the defibrillator prevents MACE in a heart failure population and therefore an appropriate shock was considered as an adverse cardiac event. [12]

Statistical analyses

Statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, Illinois). Continuous variables are presented as mean with standard deviation (SD) when normally distributed (mean ± SD) and as median with interquartile range (IQR) in case of non-normal distribution (median (IQR)). Distributions were checked using Q-Q plots. Categorical variables are presented as numbers and percentages.

Surrogate markers of CRT response were assessed for the total population, and the ischaemic and non-ischaemic subpopulations. Data were compared with a T-test or Mann-Whitney U test in case of nonnormal distribution. A p-value of <0.05 was considered statistically significant. Surrogate markers demonstrating a significant difference between patients with and without MACE were subsequently tested using univariable and multivariable Cox backward logistic regression analyses. Areas under the receiver-operating curve (AUC) were assessed with respect to the occurrence of MACE. Subsequently, Cox regression multivariable analyses were performed to evaluate the association between significant surrogate markers and time to first MACE. These analyses were performed for the total population, ischaemic and non-ischaemic subpopulations. Multicollinearity amongst variables was checked using variance inflation factors, and a value of >5 was considered evidence of multicollinearity. Furthermore, the relation between surrogate markers of CRT response and MACEwas calculated by the Kaplan-Meier method and compared by means of the log-rank test. A two-tailed probability value of $p<0.05$ was considered statistically significant.

Results

Baseline results

Baseline characteristics are listed in Table 1. Mean age 65±12 years, 69% (n=142) male, 52% (n=106) with ischaemic cardiomyopathy. At baseline, LVESV was 180 (87) mL, LVEF 22±7%, and IVMD 46±28 ms. Baseline VO2 peak was 14±4 ml/kg/min, predicted VO2 peak 61±19% and VE/VCO2 slope 38 (15). Baseline BNP levels were 112 (172) pmol/L and creatinine levels were 112 (52) µmol/L.

Six-month results

Six-month follow-up values are listed in Table 1. At six-month follow-up LVESV was 133 (95) ml, LVEF 29±10%, and IVMD was 15±28 ms. VO2 peak was 15±5 ml/kg/min, predicted VO2 peak 67±23% and VE/VCO2 slope 34 (11). BNP levels were 71 (107) pmol/L and creatinine levels were 115 (53) µmol/L.

Long-term follow-up and major adverse cardiac events

Six patients died before six-month follow-up, one patient had undergone a heart transplant and one received an LV assist device; these patients were not included for further analyses. Of the remaining 197 patients, four patients were lost to follow-up, two died of a non-cardiac cause and one died of an unknown cause (Fig 1). Between six and 24 months 19% (36/190) experienced at least one MACE. Twenty patients had a hospital admission due to heart failure, nine had ventricular arrhythmias, and seven died due to heart failure. Of the ischaemic patients 24% (n=24) experienced a MACE versus 13% (n=12) of non-ischaemic patients (p=0.061).

Assessment of CRT response

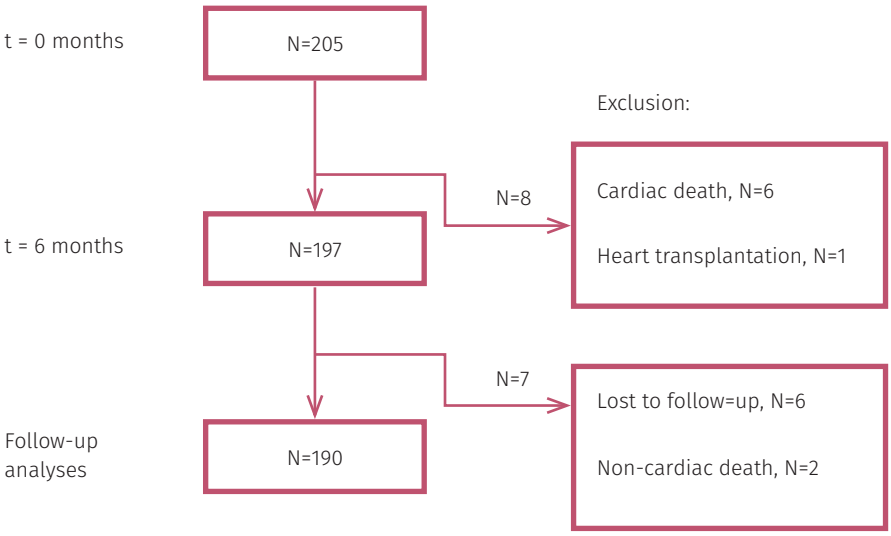
ΔLVESV, ΔLVEF, and ΔBNP differed significantly between patients with and without MACE in the total population (Table 2a). After multivariable analyses, LVESV remained the only surrogate marker for CRT response significantly correlated to the occurrence of MACE. Discriminative performance of this surrogate marker was moderate: AUC = 0.69 (Table 3 and Fig. 2). Associations between surrogate response markers and MACE differed among heart failure aetiologies (Table 2b and c and Table 3). In the non-ischaemic cardiomyopathy population results were in concordance with the total population as ΔLVESV remained the only surrogate marker for CRT response (Table 2b). Discriminative power of ΔLVESV was high in this subpopulation: AUC=0.85 (Fig. 1 and Fig. 3a). In the ischaemic cardiomyopathy population no significant correlation was found between ΔLVESV and the occurrence of MACE (Fig. 3b). In this group ΔBNP was the only independent surrogate marker for CRT response (Table 2c). Discriminative power was moderate with AUC 0.66. Concerning Fig. 2, a 15% cut-off for ΔLVESV was chosen, as this is the most often used cut-off value to discriminate between responders and non-responders.[6, 9]

Table 1. Baseline and six-month follow-up parameters

	Baseline (n=205)	Six-month FU (n=197)	P-value
Clinical			
Age, mean ± SD (years)	64.8 ± 12.4	–	
Male gender (%)	142 (69)	–	
Ischaemic cardiomyopathy (%)	106 (52%)	–	
NYHA I (%)	1 (0.5)	16 (8.3)	0.001
NYHA II (%)	26 (12.7)	104 (53.6)	0.171
NYHA III (%)	167 (81.5)	71 (36.6)	0.062
NYHA IV (%)	11 (5.3)	3 (1.5)	<0.001
ECG			
QRS duration, mean ± SD, ms	166 ± 24	153 ± 24	<0.001
Left bundle branch block (%)	116 (57)	–	
Interventricular conduction delay (%)	63 (31)	–	
Right bundle branch block (%)	1 (0.5)	–	
QRS <120 ms (%)	1 (0.5)	–	
Right ventricular pacing (%)	23 (11)	–	
Echocardiography			
LVESV, median (IQR), ml	180 (87)	133 (95)	<0.001
LVEDV, median (IQR), ml	230 (92)	182 (115)	<0.001
LVEF, mean ± SD (%)	21.6 ± 6.8	28.6 ± 10.4	<0.001
IVMD, mean ± SD (ms)	46 ± 28	15 ± 28	<0.001
Exercise test			
Peak VO2, mean ± SD (ml/kg/min)	14.0 ± 4.2	15.4 ± 4.8	<0.001
Percentage of predicted peak VO2, mean ± SD (%)	61.1 ± 18.8	67.4 ± 23.2	<0.001
VE/VCO2, median (IQR)	38 (15)	34 (11)	<0.001
Laboratory tests			
BNP, median (IQR), pmol/L	112 (172)	71 (107)	<0.001
Creatinine, median (IQR), µmol/L	112 (52)	115 (53)	0.002
Medication			
Beta-blocker (%)	157 (78)	–	
ACE-inhibitor (%)	152 (76)	–	
Diuretics (%)	180 (90)	–	

BNP: brain natriuretic peptide, FU: follow-up, IVMD: interventricular mechanical delay, LVEF: left ventricular ejection fraction, LVEDV :left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, NYHA: New York Heart Association, VO2: oxygen consumption, VE/VCO2: CO2 exchange efficiency

Figure 1. CRT therapy between 2005-2011 and prospectively planned baseline and 6 months CPX and echocardiography



CRT= cardiac resynchronization therapy,
CPX = cardiopulmonary exercise testing,
LVAD= left ventricular assist device

Discussion

For the total population, ΔLVESV was the most reliable surrogate marker for CRT response. Especially in the non-ischaemic cardiomyopathy population, this parameter showed excellent performance for discriminating between favourable and unfavourable long-term outcome. However, we demonstrated that ΔLVESV is a poor surrogate marker for CRT response in patients with ischaemic cardiomyopathy. In this group of patients ΔLVESV was unable to indicate which patients had a favourable and which had an unfavourable long-term outcome. These findings are of utmost importance as ΔLVESV is frequently chosen as outcome measure to assess response to CRT treatment regardless of aetiology. [6,13]

Surrogate markers in non-ischaemic cardiomyopathy

For non-ischaemic cardiomyopathy, ΔLVESV was the best surrogate marker in our study. The importance of change in LV volume during CRT over other surrogate markers has been demonstrated previously and seems to be in concordance with our data.(8,14) ΔLVESV was independent of change in LV systolic function, cardiopulmonary condition, mechanical dyssynchrony and cardiovascular biomarkers.

The clinical course of heart failure is determined by cardiac remodelling.[15] A decrease in LVESV implies reverse remodelling because it reflects both structural (reverse) remodelling and increased fibre shortening. LVEF, as a parameter for LV systolic function, seems less suitable as surrogate marker, probably because it is more dependent on LV end-diastolic volume and heart rate. [15] A change of mechanical dyssynchrony was not an appropriate surrogate outcome marker either. Mechanical dyssynchrony is not obligatory to be eligible for CRT implantation.[16,17] Consequently, IVMD at baseline, and its reduction, showed a wide distribution in our study cohort, making ΔIVMD an unsuitable surrogate marker.

Cardiopulmonary exercise testing parameters may take longer to improve than six months. It has been demonstrated in heart failure patients that during a training programme time to reach maximum improvement varied between 16 and 26 weeks. [18] This process probably takes even longer without training, when it is solely influenced by CRT.

Also, neither ΔBNP nor Δcreatinine could identify those with a favourable or unfavourable long-term outcome in the non-ischaemic cardiomyopathy group. ΔBNP may not be reliable due to a wide distribution and high day-to-day variability. [19] Renal function does not seem to be affected by CRT as both groups showed only minor changes in creatinine between baseline and six months. This is in line with a recent study.[20] Moreover, when stratified according to baseline renal function, patients demonstrating either an improvement or decline in renal function occurred for all disease stages and changes were therefore unpredictable. [20] Consequently, changes in renal function can probably not discriminate between favourable and unfavourable clinical outcome.

The clinical course of heart failure is determined by cardiac remodelling.[15] A decrease in LVESV implies reverse remodelling because it reflects both structural (reverse) remodelling and increased fibre shortening. LVEF, as a parameter for LV systolic function, seems less suitable as surrogate marker, probably because it is more dependent on LV end-diastolic volume and heart rate. [15] A change of mechanical dyssynchrony was not an appropriate surrogate outcome marker either. Mechanical dyssynchrony is not obligatory to be eligible for CRT implantation.[16,17] Consequently, IVMD at baseline, and its reduction, showed a wide distribution in our study cohort, making ΔIVMD an unsuitable surrogate marker.

Table 2a. Comparison of changes in echocardiographic, cardiopulmonary, and laboratory parameters between patients with and without a MACE

Potential surrogate endpoints	MACE (n=36)	Non-MACE (n=154)	P-value
Δ LVESV (%)	-9.5 ± 18.7	-23.5 ± 23.0	<0.001
Δ LVEF (absolute %)	3.5 ± 6.2	8.2 ± 9.0	<0.001
Δ IVMD (ms)	-29 ± 35	-34 ± 32	0.422
Δ QRS duration (ms)	4.0 ± 28.4	16.4 ± 26.3	0.022
Δ Peak VO2 (ml/kg/min)	0.8 ± 3.0	1.1 ± 3.1	0.684
Δ Predicted peak VO2 (absolute %)	5.7 ± 14.7	6.0 ± 14.8	0.930
Δ VE/VCO2 slope	- 2 (17)	-4 (9)	0.674
Δ BNP (pmol/L)	14.5 (125)	- 21.5 (106)	0.019
Δ Creatinine (μmol/L)	0.5 (23)	-4.8 (22)	0.375
NYHA improvement (%)	12 (38)	94 (63%)	0.009

Δ: indicates a change. BNP: brain natriuretic peptide, ICM: ischaemic cardiomyopathy, IVMD: interventricular mechanical delay, LVEF: left ventricular ejection fraction, LVESV: left ventricular end-systolic volume, MACE: major adverse cardiac events, NYHA: New York Heart Association, NICM: non-ischaemic cardiomyopathy : VO2: oxygen consumption, VE/VCO2: CO2 exchange efficiency

Table 2b. Comparison of changes in echocardiographic, cardiopulmonary, and laboratory parameters between patients with non-ischaemic cardiomyopathy with and without a MACE

Potential surrogate endpoints	MACE (n=11)	Non-MACE (n=74)	P-value
Δ LVESV (%)	-2.4 ± 11.5	-30.0 ± 24.2	<0.001
Δ LVEF (absolute %)	3.5 ± 6.2	10.9 ± 9.3	0.013
Δ IVMD (ms)	-35 ± 37	-37 ± 34	0.832
Δ QRS duration (ms)	3.6 ± 28.0	17.6 ± 28.2	0.132
Δ Peak VO2 (ml/kg/min)	2.2 ± 2.9	1.36 ± 3.5	0.615
Δ Predicted peak VO2 (absolute %)	12.4 ± 15.1	6.7 ± 16.0	0.365
Δ VE/VCO2 slope	10 (19)	3 (6)	0.049
Δ BNP (pmol/L)	-14 (360)	32 (106)	0.627
Δ Creatinine (μmol/L)	5.0 (29)	-1.5 (22)	0.159
NYHA improvement (%)	6 (60)	50 (66)	0.718

Δ: indicates a change. BNP: brain natriuretic peptide, ICM: ischaemic cardiomyopathy, IVMD: interventricular mechanical delay, LVEF: left ventricular ejection fraction, LVESV: left ventricular end-systolic volume, MACE: major adverse cardiac events, NYHA: New York Heart Association, NICM: non-ischaemic cardiomyopathy : VO2: oxygen consumption, VE/VCO2: CO2 exchange efficiency

Cardiopulmonary exercise testing parameters may take longer to improve than six months. It has been demonstrated in heart failure patients that during a training programme time to reach maximum improvement varied between 16 and 26 weeks. [18] This process probably takes even longer without training, when it is solely influenced by CRT.

Also, neither ΔBNP nor Δcreatinine could identify those with a favourable or unfavourable long-term outcome in the non-ischaemic cardiomyopathy group. ΔBNP may not be reliable due to a wide distribution and high day-to-day variability.[19] Renal function does not seem to be affected by CRT as both groups showed only minor changes in creatinine between baseline and six months. This is in line with a recent study.[20] Moreover, when stratified according to baseline renal function, patients demonstrating either an improvement or decline in renal function occurred for all disease stages and changes were therefore unpredictable.[20] Consequently, changes in renal function can probably not discriminate between favourable and unfavourable clinical outcome.

Table 2c. Comparison of changes in echocardiographic, cardiopulmonary, and laboratory parameters between patients with ischaemic cardiomyopathy with and without a MACE

Potential surrogate endpoints	MACE (n=24)	Non-MACE (n=71)	P-value
Δ LVESV (%)	-12.7 ± 20.5	-16.8 ± 19.8	0.392
Δ LVEF (absolute %)	3.5 ± 6.3	5.5 ± 7.8	0.269
Δ IVMD (ms)	-26 ± 35	-31 ± 31	0.537
Δ QRS duration (ms)	4.3 ± 29.3	15.1 ± 24.3	0.101
Δ Peak VO2 (ml/kg/min)	0.1 ± 2.8	0.8 ± 2.5	0.299
Δ Predicted peak VO2 (absolute %)	2.7 ± 13.9	5.3 ± 13.6	0.496
Δ VE/VCO2 slope	0.7 (18)	4.4 (13)	0.139
Δ BNP (pmol/L)	35 (77)	-53 (78)	0.041
Δ Creatinine (μmol/L)	-6.0 (27)	-5.0 (22)	0.673
NYHA improvement (%)	6 (27)	44 (60)	0.008

Δ: indicates a change. BNP: brain natriuretic peptide, ICM: ischaemic cardiomyopathy, IVMD: interventricular mechanical delay, LVEF: left ventricular ejection fraction, LVESV: left ventricular end-systolic volume, MACE: major adverse cardiac events, NYHA: New York Heart Association, NICM: non-ischaemic cardiomyopathy : VO2: oxygen consumption, VE/VCO2: CO2 exchange efficiency

Surrogate markers in ischaemic cardiomyopathy

A remarkable finding was that ΔLVESV in ischaemic cardiomyopathy could not distinguish patients who remained free of MACE during follow-up. Although ΔBNP was the best surrogate marker in this subpopulation, it was unsuitable for good discrimination. This implicates that ischaemic cardiomyopathy is influenced by other factors when it comes to long-term outcome. Although both aetiologies are characterised by reduced contractility and global dilatation, the disease substrate differs greatly. In ischaemic cardiomyopathy, coronary artery disease is the pathophysiological substrate and a high variety exists concerning the extent of disease, affecting prognosis, making this a very heterogeneous group. [21] Furthermore, it has been demonstrated that scar tissue is a more important determinant of long-term outcome in ischaemic cardiomyopathy than contractile reserve.[22] This is also confirmed by the current study. As BNP is mainly produced by cardiomyocytes [23], it could be hypothesised that BNP change is only possible in patients with significant amounts of myocytes left, and consequently less scar tissue. Also, presence of myocardial scar in the pacing region was another important determinant of long-term outcome in patients with ischaemic cardiomyopathy eligible for CRT. [24] In addition, in about 25% of patients disease extends beyond the coronary arteries and also affects the brain and peripheral tissues, which may affect prognosis independent of the amount of cardiac remodelling.[25] Therefore, it might be important to assess overall atherosclerotic status before CRT implantation. Importantly, these results do not imply that CRT is not beneficial for patients with ischaemic cardiomyopathy.

Table 3. Multivariable Cox regression concerning surrogate endpoints and MACE for the total population, non-ischaemic and ischaemic subpopulations

Potential surrogate endpoints		**Multivariable HR (CI)**	
	Total population	NICM	ICM
Δ LVESV (%)	0.975 (0.960-0.991)		
Δ LVEF (absolute %)	-	0.960 (0.938-0.983)	-
Δ VE/VCO2 slope	-	-	-
Δ BNP (pmol/L)	-	-	0.993 (0.988-0.998)
Δ NYHA (class)	-	-	-

Δ: indicates a change. BNP: brain natriuretic peptide, ICM: ischaemic cardiomyopathy, IVMD: interventricular mechanical delay, LVEF: left ventricular ejection fraction, LVESV: left ventricular end-systolic volume, MACE: major adverse cardiac events, NYHA: New York Heart Association, NICM: non-ischaemic cardiomyopathy : VO_2: oxygen consumption, VE/VCO_2: CO_2 exchange efficiency

Prediction of MACE

Although the present study searched for the best surrogate markers for CRT response through a correlation with MACE, prediction of MACE was not the aim. However, as the true endpoint of CRT is reduction of MACE, surrogate markers must be assessed on their capacity to discriminate between patients with high and low risk for future MACE.[8,9,14] In addition, a surrogate marker is a variable reflecting a change, for it should measure an effect of the delivered therapy.[7]

When assessing risk of MACE independent of the effect of CRT, absolute values should also be taken into account, especially in the ischaemic cardiomyopathy group. In that case, besides ΔLVESV, also creatinine levels and peak VO_2 at six months were demonstrated to be independent predictors of MACE. Both renal function and peak VO2 have prognostic value in heart failure patients.[26-28] Analysis was performed excluding appropriate ICD shocks as part of MACE. The discriminative value of ΔLVESV concerning the whole population, non-ischaemic and ischaemic cardiomyopathy subpopulations, did not significantly change (results not shown).

Limitations

This study was a retrospective single-centre study with its inherent limitations. However, our cohort comprised a rather large number of patients, and MACE after six months occurred in 19% of this cohort. MACE occurring before six months were not taken into account for this analysis, although these might show a relation with surrogate markers at six months. However, the first six months are a more instable phase as the effect of CRT might not yet be complete. In addition, the aim of the current study was to assess which surrogate marker at six months could best discriminate between patients who did and who did not encounter a MACE in the period thereafter. Moreover, LVESV and LVEF were assessed by echocardiograph. Recently De Haan et al.[29] demonstrated that eligibility to CRT depends on the imaging modality applied. This could also be true for assessment of response. This should be investigated in future research.

Conclusion

ΔLVESV is the most reliable surrogate marker for CRT response in the total population. This is attributed to the non-ischaemic cardiomyopathy subpopulation in which ΔLVESV showed an excellent correlation with long-term outcome. On the other hand, for ischaemic cardiomyopathy ΔLVESV showed a poor correlation with long-term outcome. Therefore cardiologists should be careful using volumetric response as a prognostic marker in ischaemic cardiomyopathy.

Conflict of Interest

None declared.

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Chapter 6

RELATIONSHIP BETWEEN REVERSE REMODELING AND CARDIOPULMONARY EXERCISE CAPACITY IN HEART FAILURE PATIENTS UNDERGOING CARDIAC RESYNCHRONIZATION THERAPY

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Abstract

Background: Studies on the relationship between left ventricular reverse remodeling and cardiopulmonary exercise capacity in heart failure patients undergoing cardiac resynchronization therapy (CRT) are scarce and inconclusive.

Methods and Results: Eighty-four patients with a first-time CRT-defibrillator (73% men; mean age = 65±11) underwent echocardiography and cardiopulmonary exercise testing (CPX) prior to implantation (baseline) and six months after implantation. At baseline, patients also completed a set of questionnaires measuring mental and physical health. The association between (left ventricular end-systolic volume decrease ≥15%) and a comprehensive set of CPX results was examined. Echo responders (54%) demonstrated higher peak oxygen consumption and better exercise performance than non-responders at baseline and at 6-month follow-up. Furthermore, only echo responders showed improvements in ventilatory efficiency during follow-up. Multivariable repeated measures analyses revealed that, besides reverse remodeling, New York Heart Association functional class II and good patient-reported health status prior to implantation were the most important correlates of higher average oxygen consumption during exercise, while non-ischemic etiology and smaller pre-implantation QRS width were associated with better ventilatory efficiency over time.

Conclusions: During the first six months of CRT there was a significant positive association between reverse remodeling and cardiopulmonary exercise capacity.

Introduction

Cardiac resynchronization therapy (CRT), with or without an implantable cardioverter defibrillator, is a well-established treatment in selected patients with drug-refractory heart failure (HF) and an electrical conduction delay.[1] Several large-scale randomized controlled trials have demonstrated that CRT enhances functional status, exercise capacity and quality of life, and reduces HF-related hospitalizations and mortality in these patients.[2-8] Echocardiographic measures of left ventricular reverse remodeling, including a reduction in left ventricular end-systolic volume (LVESV), are most frequently used to determine response to CRT. 9, 10 Furthermore, several large-scale randomized trials on CRT have prospectively assessed exercise capacity to evaluate treatment effects, [2,11-15] although the majority of these studies were limited to measurements of peak VO2 and 6-minute walk distance. There is a need to know whether reverse remodeling translates into improved exercise capacity, since exercise capacity determines to a large extent the health status of HF patients.[16] So far, the paucity of studies examining this relationship, found that echocardiographic responders showed enhanced exercise capacity after CRT, while non-responders did not.[17-19] Surprisingly, however, the baseline exercise capacity of these responders differed considerably across studies, with one study showing that responders had lower peak VO2 levels and cardiorespiratory reserve at time of implantation and another study showing no baseline differences in exercise capacity between echocardiographic responders and non-responders.[17,19] Hence, the current evidence on the relationship between echocardiographic CRT response and cardiopulmonary exercise capacity is inconclusive and limited by the fact that two of the three studies performed so far had a small sample size including respectively 28 and 50 patients.[17,18] Also, analyses are missing which compare the change in exercise capacity over time between echocardiographic responders and non-responders controlling for potential confounders. Importantly, none of the previous studies controlled for patient-perceived physical and mental health status and psychological functioning, while studies have shown that this may have a strong influence on exercise capacity test outcomes.[13,20-22]

Therefore, the aim of the current study was to elucidate the relationship between left ventricular reverse remodeling and cardiopulmonary exercise capacity in patients undergoing CRT treatment, by comparing echocardiographic responders (decrease in LVESV ≥15%) with non-responders on a comprehensive set of exercise capacity variables assessed at baseline and six months after implantation using univariable and multivariable repeated measures analyses, adjusting for clinical and patient-reported health factors.

Methods

Study design and participants

The study sample comprised a consecutive cohort of patients receiving a first-time CRT with defibrillator (CRT-D) in accordance with the guidelines [1] and evidence-based medicine between January 2009 and August 2011 at the University Medical Center Utrecht (UMCU), The Netherlands. Patients participated in the 'The influence of PSYchological factors on health outcomes in HEART failure patients treated with Cardiac Resynchronization Therapy' (PSYHEART-CRT) study, a prospective, single-center, observational study.[23] One day prior to implantation (baseline) and 6-month post-implantation, patients were asked to complete a set of standardized and validated questionnaires to assess patient-reported physical and mental health and psychological functioning. Pre- and 6-month post-implantation, echocardiographic studies and exercise tests were performed. Only those patients with LVESV and peak VO2 values at both time points were included in this analysis. The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Medical Ethics Committee of the UMCU. All patients received oral and written information about the study and signed a written informed consent form.

Demographic and clinical variables

Information on demographic variables including age, sex, educational level, and working and marital status, were obtained via purpose-designed questions at baseline. Information on clinical variables, including etiology (ischemic vs. non-ischemic), years since diagnosis, NYHA functional class, heart rhythm, QRS duration, left bundle branch block (LBBB), diabetes mellitus, chronic obstructive pulmonary disease (COPD), renal insufficiency (creatinine > 120 µmol/L), smoking, and cardiac medication, were extracted from patients' medical records.

Echocardiographic variables

Prior to implantation and 6-month post-implantation, patients underwent echocardiographic evaluation to assess LVESV, left ventricular end diastolic volume (LVEDV), left ventricular ejection fraction (LVEF), and diastolic function.
Patients were imaged in the left lateral decubitus position. LVESV and LVEDV were defined as the smallest and largest ventricular volume within one RR cycle, respectively, with both the mitral valve and aortic valve being closed. Subsequently, volume traces were set along the endocardial border. Papillary muscles were included in the LV cavity. Volumes were assessed according to Simpson's biplane method. Echocardiographic response to CRT was defined as a decrease in LVESV of ≥15% measured at 6-month follow-up. Diastolic function was measured in accordance with the guidelines of the American Society of Echocardiography (ASE) and European Association of Echocardiography (EAE).[24]

The grading scheme of diastolic dysfunction is mild or grade I (impaired relaxation pattern), moderate or grade II (pseudonormal LV filling), and severe or grade III (restrictive filling).

Cardiopulmonary exercise testing

CPX was performed using a bicycle ergometer until symptom limitation. Patients started with unloaded cycling for 2 minutes after which a protocol of stepwise incremental exercise was applied, starting at 25 Watt with increments of 5, 10 or 15 Watt every minute depending on estimated maximum workload. Rotation speed was kept around 60 per minute. Prior to testing, gas and flow sensors were calibrated utilizing gases with established concentrations of O2 and CO2. For each patient, VO_2 (L/min and mL/kg/min), VCO_2 (L/min), and VE (L/min) were measured throughout the exercise on a breath-to-breath basis. Peak VO2, percent-predicted peak VO2, VE/VCO_2 slope, peak workload, peak heart rate (HR), peak O_2 pulse, respiratory rate (RR) at rest/peak, HR reserve, HR at 1-minute recovery, respiratory exchange ratio (RER), and oxygen uptake efficiency slope (OUES) were assessed. Peak VO_2 is the level of oxygen consumption during peak effort and averaged over a 30-second period. [25] Percent-predicted peak VO_2 was calculated as follows: ((peak VO_2 / Wasserman predicted peak VO2) * 100).[26] The VE/VCO_2 slope provides a measure of CO_2 exchange efficiency by assessing required ventilation (VE) for CO_2 elimination.[25] Data for the VE/VCO_2 slope were collected throughout the exercise, with exclusion of the unloaded cycling and recovery period. Calculation of the VE/VCO_2 slope was executed using the slope calculation option of Excel software. Peak workload was defined as the resistance (in Watt) reached at the end of exercise. Peak HR was defined as the HR reached at peak VO_2. Peak O_2 pulse is the amount of oxygen uptake per heart beat which is calculated by dividing peak VO_2 by the HR. RR at rest, peak and 1-minute recovery is the RR during rest, during peak effort, and 1 minute after exercise cessation, respectively. The RER is the CO_2 production divided by the VO_2 consumption. OUES is defined as the efficiency of oxygen uptake and is the gradient of the linear relationship of log10VE to VO_2.

Patient-reported physical health and psychological functioning

The Kansas City Cardiomyopathy Questionnaire (KCCQ) was used to assess HF-specific physical health status.[27] The KCCQ is a 23-item, self-report questionnaire that quantifies physical limitation, symptoms, social function, and quality of life in patients with HF. In the current study, we used the Clinical Summary score (KCCQ-CS), which is derived from the physical limitation and symptoms domain. Scores are transformed into a score from 0 to 100, with higher scores representing better physical health status. The validity and reliability of the KCCQ have previously been established and the measure was shown to be highly sensitive to detect clinical change in HF patients over a 6-12 week period.[27] Poor physical health status was defined as a KCCQ-CS score < 50 points.

In order to adjust for the potentially confounding effect of patients' psychological functioning on the study end points, patients completed standardized measures on depressive and anxiety symptoms. Symptoms of depression were measured with the Patient Health Questionnaire (PHQ-9), with items mirroring the diagnostic criteria for major depressive disorder.[28] Patients were asked to rate how often each symptom had bothered them during the past 2 weeks on a scale from 0 (not at all) to 3 (nearly every day) (score range 0-27). A cut-off score of ≥ 10 was used to detect patients with clinically relevant levels of depression.[29] The PHQ-9 has good reliability and validity in medical outpatients and patients with HF.[30] The state anxiety subscale of the State-Trait Anxiety Inventory (STAI-S) was used to measure symptoms of anxiety. All items are rated on a 4-point Likert scale ranging from 1 (not at all) to 4 (very much so) (score range 20-80). Higher scores indicate higher levels of anxiety. A cut-off score of ≥ 40 was used to detect patients with clinically relevant levels of anxiety. The STAI-S has shown to be a valid and reliable measure, with Cronbach's alpha ranging from 0.87 to 0.92.[31] Patients with clinically relevant levels of anxiety (STAI-S ≥ 40) and/or depression (PHQ-9 ≥ 10) were classified as reporting 'poor psychological functioning'.

Statistical analyses

To summarize baseline demographic, clinical and patient-reported characteristics of the sample, categorical variables were presented as frequencies with percentages and continuous variables as means with standard deviations (SD) when normally distributed, and as medians with interquartile ranges (IQR) in case of a non-normal distribution. Echocardiographic responders and non-responders were compared on these variables using the Chi-square test (or Fisher's exact test if appropriate) for categorical variables and Student's t tests for independent samples for continuous variables (or Mann-Whitney U test if appropriate). Student's t tests for paired samples (or Wilcoxon signed-rank test if appropriate) were used to evaluate overall changes in echocardiographic and exercise outcomes from baseline to six months within both echocardiographic responders and non-responders. To compare the change in (percent-predicted) peak VO2, and VE/VCO2 slope from baseline to six months between echocardiographic responders and non-responders, analyses of variance (ANOVA) for repeated measures with echocardiographic response as between-subjects factor were performed. Subsequently, analyses of covariance (ANCOVA) for repeated measures were done to adjust for the potential confounding effects of age, sex, NYHA functional class III/IV, ischemic etiology, QRS duration > 150ms, poor psychological functioning, and poor patient reported physical health status. Covariates were selected a priori. All tests were two-tailed with $p \leq .05$ indicating statistical significance. Analyses were performed with SPSS 20.0 for Windows (SPPS Inc., Chicago, Illinois, USA).

Results

Baseline characteristics for the total sample and stratified by echocardiographic response

Originally, 139 CRT patients participated in the PSYHEART-CRT study, of which 84 patients had complete echocardiographic and CPX data at baseline and at six months follow-up. Excluded patients (n=55) were less likely to have a partner (73% versus 87%, p = .04) and more likely to have atrial fibrillation (36% versus 16%, p = .01). There were no other statistically significant differences in demographic and clinical baseline characteristics between in- and excluded patients.

The baseline characteristics of the total sample (N=84) and comparisons of these characteristics between the echocardiographic responder and non-responder groups are shown in Tables 1 and 2. Forty-five patients (54%) were defined as echocardiographic responders (reduction of LVESV ≥15% after six months of CRT) and 39 patients (46%) as non-responders. Responders had a significantly smaller median LVESV (143 (63) mL vs. 174 (114) mL, p = .040) and LVEDV (185 (73) mL vs. 220 (122) mL, p = .031) at the time of implantation, as compared with non-responders (Table 1). Regarding the baseline CPX results, echocardiographic responders demonstrated higher oxygen consumption (peak VO2: 16.5 ± 5.0 mL vs. 14.3 ± 3.1 mL; p = .014; percent-predicted peak VO2: 69% ± 21% vs. 59% ± 16%; p = .021), better exercise performance (peak workload: 99 ± 35 W vs. 84 ± 25 W; p = .033), and a lower RR at rest (15 ± 6 vs. 20 ± 6; p = .011) than non-responders (Table 2).

Finally, echocardiographic responders were less often prescribed aldosterone-antagonists compared with non-responders (37% vs. 64%, p < .001). This difference could be explained by non-responders more often having an ischemic HF etiology and having more severe HF symptoms (NYHA class III/IV) at time of implantation. There were no other systematic differences on demographic and clinical baseline characteristics between echocardiographic responders and non-responders (all p values > .05).

CRT, cardiac resynchronization therapy; SD, standard deviation; NYHA, New York Heart Association; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; IQR, interquartile range; LVEDV, left ventricular end diastolic volume; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme. Results are presented as n (%), unless otherwise stated. Significant results are given in bold. [a]Echocardiographic response to CRT is defined as a reduction in left ventricular end systolic volume of ≥ 15% at 6 month follow-up. [b]Primary school or lower. [c]Patients with clinically relevant levels of anxiety (STAI-S ≥ 40) or depression (PHQ-9 ≥ 10). dAs measured by the Kansas City Cardiomyopathy Questionnaire Clinical Summary score. #Number of missing values: Currently employed, 1; atrial fibrillation, 1; QRS, 1; LBBB, 4; diastolic dysfunction, 2; cardiac rehabilitation, 7.

Table 1. Baseline characteristics of the total sample and stratified by echocardiographic response to CRT[a]

	Total (n = 84)	Echo responders (n = 45)	Echo non-responders (n = 39)	P - value
Demographics				
Age, mean ± SD	65.2 ± 10.9	66.0 ± 10.9	64.4 ± 10.9	.51
Male sex	61 (73)	32 (71)	29 (74)	.74
Lower education[b]	8 (10)	4 (9)	4 (10)	1.00
Currently employed[#]	15 (18)	8 (18)	7 (18)	.94
Having a partner	73 (87)	39 (87)	34 (87)	.95
Clinical characteristics				
Ischemic etiology	46 (55)	21 (47)	25 (64)	.11
Years since diagnosis	4.55 ± 4.5	4.22 ± 4.3	4.92 ± 4.9	.49
NYHA functional class III/IV	67 (80)	34 (76)	33 (85)	.30
Atrial fibrillation[#]	13 (16)	9 (20)	4 (11)	.24
QRS (ms)[#], mean ± SD	163 ± 25	161 ± 23	165 ± 26	.43
LBBB[#]	45 (56)	24 (56)	21 (57)	.93
Diabetes mellitus	17 (20)	8 (18)	9 (23)	.55
COPD	12 (14)	8 (18)	4 (10)	.33
Renal insufficiency	30 (36)	15 (33)	15 (38)	.63
Smoking	11 (13)	5 (11)	6 (15)	.56
Cardiac rehabilitation	8 (10)	3 (7)	5 (14)	.46
Medication				
ACE-inhibitors	77 (92)	42 (93)	35 (90)	.70
Beta-blockers	68 (81)	37 (82)	31 (79)	.75
Digoxin	17 (20)	11 (24)	6 (15)	.30
Diuretics	70 (83)	36 (80)	34 (87)	.38
Aldosterone-antagonists	41 (49)	16 (37)	25 (64)	.009
Statins	53 (63)	26 (58)	27 (69)	.28

Reverse remodeling, cardiopulmonary exercise capacity, and patient-reported health during 6-month follow-up

Total study population

Six months after CRT-D implantation, significant reverse remodeling was observed in the total study population, as there was a reduction in median LVESV from 155 (70) mL to 122 (98) mL ($p < .001$) and in median LVEDV from 206 (91) mL to 174 (109) mL ($p < .001$). This resulted in a mean improvement in LVEF from 24 ± 8% to 31 ± 10% ($p < .001$). Diastolic dysfunction improved from grade 1.7 ± 0.8 to 1.4 ± 0.7 ($p < .001$). Patients showed improvements in ventilatory efficiency and exercise performance, as the mean VE/VCO2 slope decreased from 36.6 ± 9.5 to 33.2 ± 7.4 ($p < .001$) and the mean peak workload increased from 92 ± 31 W to 98 ± 36 W ($p = .005$). Furthermore, peak HR decreased from 125 ± 25 bpm to 120 ± 24 ($p = .011$), RR at peak exercise from 33 ± 7 to 31 ± 7 ($p = .002$), HR reserve from 52 ± 22 bpm to 47 ± 23 ($p = .025$), and HR at 1-minute recovery from 103 ± 19 to 98 ± 20 (p .021). There was no significant improvement in oxygen consumption (peak VO2) in the total study population. Finally, from baseline to 6-month follow-up, patients reported a significant improvement in their average physical health status score from 63.5 ± 22.5 to 78.2 ± 19.1 points ($p < .001$) and less patients reported poor physical health (7.1% versus 29.8%, $p = .008$) or poor psychological functioning (20% versus 33%, $p < .001$) (Table 2).

Echocardiographic responders vs. non-responders

Within-group analyses

Echocardiographic responders showed improvements in diastolic dysfunction (grade 1.6 ± 0.8 to 1.2 ± 0.6; $p < .001$), oxygen consumption (peak VO_2: 16.5 ± 5.0 mL/kg/min to 17.6 ± 5.2 mL/kg/min; $p = .037$; percent-predicted peak VO_2: 69% ± 21% vs. 75% ± 21%; $p = .018$), ventilatory efficiency (VE/VCO_2 slope: 37.0 ± 10.0 to 31.7 ± 5.6; $p < .001$), and exercise performance (peak workload: 99 ± 35 W to 107 ± 37; $p = .012$). Peak HR decreased from 129 ± 27 to 123 ± 22 ($p = .046$), whereas RR at rest increased from 15 ± 6 to 18 ± 5 ($p = .048$). Non-responders only showed a decrease in RR at peak exercise (33 ± 8 to 30 ± 7; $p = .006$) and HR at 1-minute recovery (104 ± 19 to 97 ± 23; $p = .007$). No improvements in diastolic function or other cardiopulmonary capacity variables at 6-month follow-up were demonstrated by non-responders (Table 2). Echocardiographic responders and non-responders both improved in their physical health status score (65.6 ± 22.1 to 81.1 ± 16.3, $p < .001$ and 61.1 ± 23.1 versus 74.7 ± 21.8, $p < .001$, respectively) and the percentage of patients reporting poor physical health status decreased, however this decrease was only significant for non-responders (35.9% versus 12.8%, $p = .047$). The percentage of patients reporting poor psychological functioning did significantly decrease in both groups: from 37.2% to 25.6% in responders ($p = .01$) and from 45.9% to 24.3% in non-responders ($p = .005$) (Table 2).

Between-group analyses

Six months after CRT-D implantation, responders had a significantly smaller median LVESV (101 (50) mL vs. 173 (109) mL; p < .001) and LVEDV (147 (54) mL vs. 227 (111) mL; p < .001), a better LVEF (36 ± 9% vs. 24 ± 8%; p < .001), and less diastolic dysfunction (grade 1.2 ± 0.6 vs. 1.7 ± 0.7; p = .001) as compared with non-responders (Table 2, between-group p-values not shown). Furthermore, at follow-up, responders demonstrated overall higher oxygen consumption (peak VO_2: 17.6 ± 5.2 mL vs. 14.2 ± 4.3 mL; p = .002; percent-predicted peak VO_2: 75% ± 21% vs. 59% ± 16%; p < .001), and a better exercise performance (peak workload: 107 ± 37 W vs. 87 ± 32 W; p = .011) than non-responders. There were no significant between-group differences in patient-reported outcomes at follow-up (Table 2, between-group p- values not shown).

Echo response and change in cardiopulmonary exercise capacity in the first six months of CRT

Figure 1 shows the change in oxygen consumption (peak VO_2, Figure 1a), percent-predicted peak VO_2 (Figure 1b) and ventilatory efficiency (VE/VCO_2 slope, Figure 1c) from baseline to 6-month follow-up for the echocardiographic responders and non-responders.

Results from the ANOVA for repeated measures showed that the time by echocardiographic response interaction effect was significant for percent-predicted peak VO_2 ($F_{(1,81)}$ = 4.33, p = .041) and VE/VCO_2 slope ($F_{(1,75)}$ = 5.24, p = .025), indicating that the change in these CPX results over six months differed between groups, with echocardiographic responders showing significant improvement over time and non-responders showing relatively stable results. For peak VO_2, the interaction effect was (borderline) non-significant ($F_{(1,82)}$= 2.36, p = .10). The main effect of echocardiographic response was significant for peak VO_2 ($F_{(1,82)}$ = 9.37, p = .003) and percent-predicted peak VO_2 ($F_{(1,81)}$ = 11.10, p = .001), meaning that responders had better average oxygen consumption over time compared with non-responders. For VE/VCO_2 slope, the main effect of echocardiographic response was not significant ($F_{(1,75)}$ = 0.47, p = .50) as responders showed worse ventilatory efficiency than non-responders at baseline and better at six months follow-up.

In multivariate analyses (ANCOVA, Table 3), the time by echocardiographic response interaction effect remained significant for VE/VCO_2 slope, for (peak) VO_2 it became borderline non-significant. Regarding the covariates, there was a significant time by sex interaction effect ($F_{(1,74)}$ = 8.62, p .004) for peak VO_2, as the average oxygen consumption improved in men (15.6 ± 4.3 to 16.8 ± 5.1, p = .008) but decreased in women (15.1 ± 4.7 to 14.2 ± 4.6, p = .07) from baseline to six months. No other significant time by covariate interaction effects were found for any of the CPX outcomes.

Looking at the main effects for the between-group factors and covariates (Table 3), baseline NYHA class II and good physical health status were the strongest associates of high peak VO_2 levels over time, followed by echocardiographic response, non-ischemic etiology and lower age. For percent-predicted peak VO_2, results showed that echocardiographic response was most strongly related to better average results over time, followed by NYHA class II and non-ischemic etiology. Non-ischemic etiology and QRS ≤ 150ms, not echocardiographic response, were significantly and independently associated with better ventilatory efficiency over time.

Discussion

Studies on the relationship between left ventricular reverse remodeling and cardiopulmonary exercise capacity in HF patients undergoing CRT treatment are scarce and the results are inconclusive. In this prospective cohort study, including 84 CRT-D patients, echocardiographic responders demonstrated higher oxygen consumption (peak VO_2) and better exercise performance (peak workload) during exercise than non-responders prior to implantation and at 6-month follow-up. Echocardiographic responders not only presented with better cardiopulmonary exercise capacity pre-implantation, they also showed overall improvement during follow-up in peak VO_2, VE/VCO_2 slope, and peak workload while non-responders did not show this improvement. Multivariable repeated measures regression analyses revealed that besides echocardiographic response, physician-rated NYHA functional class II and good patient-reported physical health status at time of implantation were the most important independent correlates of higher average oxygen consumption, while non-ischemic etiology and smaller QRS width, not echocardiographic response, were associated with better ventilatory efficiency over time.

> CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; LVEDV, left ventricular end diastolic volume; VO_2, oxygen consumption; VE, minute ventilation; VCO_2, rate of carbon dioxide elimination; W, Watts; HR, heart rate; bpm, beats per minute; RER, respiratory exchange ratio; OUES, oxygen-uptake efficiency slope. Results are presented as mean ± standard deviation. Significant results are given in bold. aEchocardiographic response to CRT is defined as a reduction in left ventricular end systolic volume of ≥ 15% at 6 month follow-up. bLVESV, LVEDV and LVEF were measured at rest. All other variables were measured during exercise. #Number of missing values: diastolic dysfunction, 3; %-predicted peak VO_2, 1; VE/VCO_2 slope, 7; peak workload, 5; peak HR, 1; O_2 pulse, 22; respiratory rate at rest, 36; respiratory rate at peak exercise, 36; heart rate reserve, 10; HR at 1 min recovery, 9.; OUES, 9. Significant between-group difference on exercise variable: *P < .05, **P < .01, ***P <.001.

Table 2. Changes in echocardiographic, exercise capacity and patient reported outcomes from baseline to 6-month follow-up for the total sample and stratified by echocardiographic response to CRT[a]

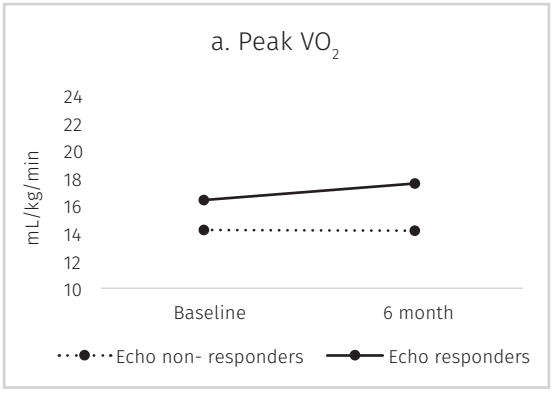
	Total (n = 84)			Echo responders (n = 45)			Echo non-responders (n = 39)		
	Baseline	6-month	P -value	Baseline	6-month	P -value	Baseline	6-month	P -value
LVEF (%)[b]	**24 ± 8**	**31 ± 10**	**<.001**	**25 ± 8**	**36 ± 9*****	**<.001**	24 ± 9	24 ± 8***	.49
LVESV (mL), median (IQR)[b]	**155 (70)**	**122 (98)**	**<.001**	**143 (63)***	**101 (50)*****	**<.001**	174 (114)*	173 (109)***	.50
LVEDV (mL), median (IQR)[b]	**206 (91)**	**174 (109)**	**<.001**	**185 (73)***	**147 (54)*****	**<.001**	220 (122)*	227 (111)***	.60
Diastolic dysfunction (grade)	**1.7 ± 0.8**	**1.4 ± 0.7**	**<.001**	**1.6 ± 0.8**	**1.2 ± 0.6****	**<.001**	1.9 ± 0.8	1.7 ± 0.7**	.11
Peak VO_2 (mL/kg/min)	15.5 ± 4.4	16.0 ± 5.1	.11	**16.5 ± 5.0***	**17.6 ± 5.2****	**.04**	14.3 ± 3.1*	14.2 ± 4.3**	.92
%-predicted peak VO_2	65 ± 19	67 ± 20	.09	**69 ± 21***	**75 ± 21*****	**.02**	59 ± 16*	59 ± 16***	.73
VE/VCO_2 slope#	**36.6 ± 9.5**	**33.2 ± 7.4**	**<.001**	**37.0 ± 10.0**	**31.7 ± 5.6**	**<.001**	36.2 ± 8.9	34.9 ± 8.8	.29
Peak workload (W)[#]	**92 ± 31**	**98 ± 36**	**.005**	**99 ± 35***	**107 ± 37***	**.01**	84 ± 25*	87 ± 32*	.21
Peak HR (bpm)[#]	**125 ± 25**	**120 ± 24**	**.011**	**129 ± 27**	**123 ± 22**	**.046**	120 ± 21	116 ± 25	.13
O_2 pulse	10.3 ± 3.3	11.1 ± 3.4	.06	10.4 ± 3.7	11.5 ± 3.5	.07	10.2 ± 2.7	10.7 ± 3.2	.41
Respiratory rate at rest	18 ± 6	19 ± 6	.12	**15 ± 6***	**18 ± 5**	**.048**	20 ± 6*	20 ± 6	.94
Respiratory rate at peak exercise	**33 ± 7**	**31 ± 7**	**.002**	34 ± 7	31 ± 7	.07	**33 ± 8**	**30 ± 7**	**.006**
Peak RER	1.15 ± 0.10	1.15 ± 0.15	.94	1.16 ± 0.11	1.16 ± 0.15	.73	1.14 ± 0.09	1.13 ± 0.14	.80
Heart rate reserve	**52 ± 22**	**47 ± 23**	**.025**	55 ± 21	52 ± 23	.28	48 ± 22	42 ± 20	.07
Heart rate at 1 min recovery	**103 ± 19**	**98 ± 20**	**.021**	102 ± 20	99 ± 18	.44	**104 ± 19**	**97 ± 23**	**.007**
OUES	1423.63 ± 668.16	1517.50 ± 518.78	.25	1477.67 ± 839.84	1565.61 ± 519.41	.53	1361.88 ± 394.00	1462.52 ± 520.06	.21
Poor psychological functioning	**33 (41.3)**	**20 (25.0)**	**<.001**	**16 (37.2)**	**11 (25.6)**	**.01**	**17 (45.9)**	**9 (24.3)**	**.005**
Physical health status	**63.5 ± 22.5**	**78.2 ± 19.1**	**<.001**	**65.6 ± 22.1**	**81.1 ± 16.3**	**<.001**	**61.1 ± 23.1**	**74.7 ± 21.8**	**<.001**
Poor physical health status	**25 (29.8)**	**6 (7.1)**	**.008**	11 (24.4)	1 (2.2)	0.24	**14 (35.9)**	**5 (12.8)**	**.047**

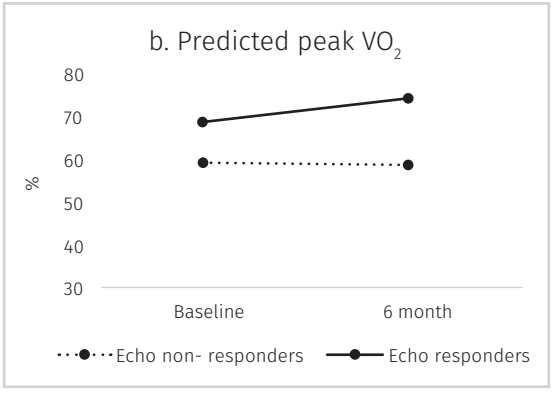
Reverse remodeling and exercise capacity

The present findings emphasize the results of previous but less comprehensive studies, showing that exercise capacity improves for echocardiographic responders to CRT but not for non-responders.[17-19,32] The exact mechanisms behind exercise capacity in HF patients is likely to be multifactorial and should be investigated in future research.[33] Yet, both diagnostic methods, i.e. echocardiography and CPX, showed improvement in cardiac function (improved LVEF and O_2 pulse, respectively) in CRT-responders. In addition, the peak workload improved in responders while their peak RER remained stable, indicating that the switch to anaerobic metabolism, and thereby lactate production, occurs later during exercise than before CRT implantation, which suggests early adaptation to improved cardiac function. In addition, their average peak VO_2 improved by 1.1 ml/kg/min, which is a relative improvement of 6.7%. This is clinically relevant as the HF-ACTION study in 1620 HF patients showed that every 6% increase in peak VO_2 over 3 months was associated with a 7% lower risk of all-cause mortality and a 4% lower risk of cardiovascular mortality or HF hospitalization in adjusted analyses.[33] Future research with longer follow-up is needed to investigate whether the improvement in exercise capacity continues over time. Echocardiographic responders in the current study already demonstrated better cardiopulmonary exercise capacity prior to implantation, which is in line with the results of a small study by Piepoli et al. (n = 44) in which echocardiographic CRT responders (increase in LVEF ≥ 20% and/or decrease in LVESV ≥15%) presented with better oxygen consumption and ventilatory efficiency at baseline when compared to non-responders.[32]

However, two other studies do not support these findings. A small study including 28 NYHA III patients found that responders (decrease in LVESV >15%) showed a flatter oxygen efficiency slope prior to implantation, as compared with non-responders.[17] However, this study focused on oxygen uptake efficiency slope during submaximal exercise testing, while in the current study peak VO_2 and VE/VCO_2 slope were examined. In addition, only 43% of the patients in the latter study had ischemic cardiomyopathy compared to 53% in the current study, and the echocardiographic responders also had larger baseline LV volumes compared with non-responders; which is completely opposite from our study and might explain the contradicting results. The second, larger study on 144 patients found no difference in oxygen consumption between responders (decrease in LVESV ≥ 10%) and non-responders prior to implantation, although it must be noted that they did not include NYHA II patients, which comprised 20% of our study cohort.[19] In our study patients with mildly symptomatic HF showed better oxygen uptake compared with NYHA class III/IV patients. Overall, the value of CPX results prior to implantation for predicting CRT induced reverse remodeling is unclear and should be investigated further in larger CRT studies.

Figure 1. Change in cardiopulmonary capacity from baseline to 6 months, stratified by echocardiographic response





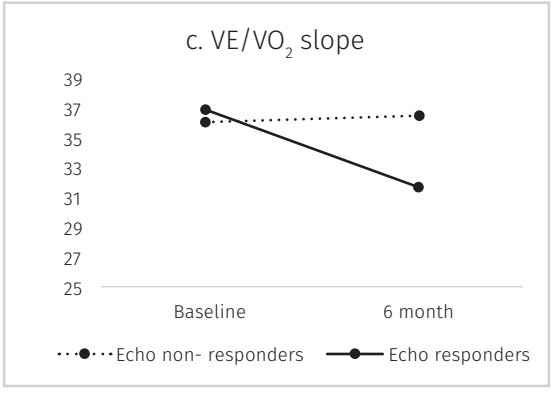


Table 1. Independent correlates of cardiopulmonary capacity during the first six months of CRT

	Peak VO_2			%-predicted peak VO_2			VE/VCO_2 slope		
	F	*p-value*	η_p^2	*F*	*p-value*	η_p^2	*F*	*p-value*	η_p^2
Time	0.12	.73	.002	0.10	.76	.001	0.32	.58	.005
Time*echocardiographic response	3.25	.08	.042	3.95	.051	.050	**6.08**	**.016**	**.083**
Echocardiographic response[a]	**7.29**	**.009**	**.090**	**6.58**	**.012**	**.081**	0.07	.79	.001
Age	**6.75**	**.011**	**.084**	-	-	-	0.11	.92	.000
Sex	1.88	.17	.025	-	-	-	0.09	.77	.001
NYHA functional class (II vs III/IV)	**8.43**	**.005**	**.102**	**5.58**	**.021**	**.069**	2.26	.14	.033
Etiology (ischemic vs non-ischemic)	**5.51**	**.022**	**.069**	**4.75**	**.032**	**.060**	**11.02**	**.001**	**.141**
QRS duration (≤150ms vs > 150ms)	1.34	.25	.018	0.12	.73	.002	**6.97**	**.010**	**.094**
Psychological functioning (poor vs good)[c]	0.00	99	.000	0.19	.67	.002	0.30	.58	.005
Physical health status (poor vs good)[d]	**8.17**	**.006**	**.099**	3.76	.06	.048	0.31	.58	.005

Results of analyses of covariance for repeated measures
VO2, oxygen consumption; VE, minute ventilation; VCO2, rate of carbon dioxide elimination; NYHA, New York Heart Association. Significant results are given in bold. aEchocardiographic response to CRT is defined as a reduction in left ventricular end-systolic volume of ≥ 15% at 6 month follow-up. bComorbidity = atrial fibrillation, chronic obstructive pulmonary disease, diabetes or renal failure. cPatients with/without clinically relevant levels of anxiety (STAI-S ≥ 40) and/or depression (PHQ-9 ≥ 10). dKansas City Cardiomyopathy Questionnaire Clinical Summary score < 50 points (poor) or ≥ 50 points (good).

Patient-reported physical health and 6-month exercise capacity
Besides reverse remodeling and physician-rated NYHA class, good patient-reported physical health status prior to implantation was an independent determinant of higher average peak VO_2 in the first six months of CRT. These results are in line with results observed in earlier CRT studies, with the KCCQ subscales being significant correlates of oxygen consumption in patients with stable HF.[21,34] Furthermore, results from the HF-ACTION trial including 2331 HF patients showed that the KCCQ physical limitation subscale had the largest, though still modest, correlation with measures of exercise capacity. However, none of the other KCCQ subscales were highly correlated with peak VO_2, [35] which corresponds with our result that patient-reported psychological functioning was not associated with exercise capacity. This suggests that the way patients perceive their own physical health status particularly determines their performance on the exercise test, which is also supported by our finding that patient-reported physical health was associated with level of oxygen consumption but not with ventilatory efficiency (VE/VCO_2 slope) over time. Ventilatory efficiency is less dependent on exercise duration and factors that might influence this, like patients' own rating of their physical capacity. [36]

Our results also showed that patients with poorer baseline health status derive the greatest health status benefit after CRT, which is in accordance with previous studies.[14,21] This might be due to a ceiling effect that limits the extent of health status improvement in patients already reporting good health status prior to implantation. The relative number of patients that report a good health status prior to implantation is probably increasing due to the expansion of the indication for CRT to include patients with mild (NYHA functional class II) HF symptoms.
In these patients, the main goal of treatment is preventing deterioration of HF. Particularly in these patients, it is essential to manage their expectations about the effects of treatment when evaluating them for CRT.

Clinical implications

In our study, we found that 46% of the patients did not show significant reverse remodeling or improvement in cardiopulmonary exercise capacity after six months of CRT. Prior to implantation, these non-responders had significantly larger LV volumes, smaller LVEF values, and poorer CPX results compared with echocardiographic responders. This indicates that a subgroup of patients with particularly large LV volumes and poor exercise capacity at time of implantation may be 'beyond repair' in terms of reverse remodeling and cardiac output. Nevertheless, the patient-reported health status of non-responders did improve, suggesting that these patients might still experience benefit from CRT in their daily lives. The discrepancy between echocardiographic and patient-reported outcomes after CRT is discussed in a previous publication on the PSYHEART-CRT cohort.

[23] Our study contributes to the discussion on CRT response assessment and emphasizes that patient-reported health status provides additional information above and beyond clinical measures of disease status and should receive attention in its own right in clinical practice and research.[37,38]

Limitations

This study has some limitations. First, anaerobic threshold (AT) was not taken into account, as in HF patients this is often difficult to determine, and in 10-20% the AT cannot even be determined at all. In addition, AT measurements have a high intra- and interobserver variability (i.e. up to 10%). [39,40] However, we determined peak VO_2 and VE/VCO_2 slope, which have been demonstrated to hold valuable prognostic information in HF patients concerning the occurrence of major adverse cardiac events, and are therefore relevant and applicable parameters. Second, the current study is a single-center study and therefore the external validity of the results may be limited. Third, only CRT patients who performed CPX at baseline and 6-month post-implantation were included in the analysis, which may jeopardize the generalizability or our results. However, post-hoc analyses revealed that included patients only differed from excluded patients with respect to having a partner and their heart rhythm (sinus rhythm vs. atrial fibrillation). Finally, the current study only presents differences in mean group outcomes, as the patient sample was too small to perform latent class analyses. Future larger studies are essential to examine changes in CPX outcomes and its determinants on a more individual patient level in order to further improve the identification of patients at risk for poor outcomes after CRT. Also, it might be interesting to perform more long-term follow-ups to see whether the improvements in exercise capacity are preserved or even increase over time. Nonetheless, this study also has several strengths including the prospective study design, the examination of a large set of CPX variables, the inclusion of patient-reported health and psychological functioning, and the usage of repeated measures analyses.

Conclusion

This study showed a significant positive association between reverse remodeling and cardiopulmonary exercise capacity in the first six months of CRT. Compared with non-responders, echocardiographic responders demonstrated better exercise capacity during CPX prior to implantation, which improved even further during 6-month follow-up. Independent of echocardiographic response, good physician- and patient-rated physical functioning was related to higher oxygen consumption during exercise. Our results provide useful new insights for the discussion on the relationship between various CRT outcomes and their determinants.

Conflict of Interest

Dr. Pedersen has received moderate consultancy and speaker's fees from St. Jude Medical, Sanofi-Aventis, Medtronic, and Cameron Health BV in the past and is currently serving as a consultant for Boston Scientific. Dr. Versteeg has received consultancy and speaker's fees from St. Jude Medical, Medtronic, and Boston Scientific. There are no relationships with industry that need to be disclosed for Ms. Mastenbroek, Dr. van 't Sant, Dr. Cramer and Dr. Meine.

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Chapter 7

DISCREPANCY BETWEEN ECHOCARDIOGRAPHIC AND PATIENT-REPORTED HEALTH STATUS RESPONSE TO CARDIAC RESYNCHRONIZATION THERAPY: RESULTS OF THE PSYHEART-CRT STUDY

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Abstract

Aims: The current study examined the degree of agreement between echocardiographic and patient-reported health status response to CRT 6 months after implantation, and evaluated the differences in pre-implantation characteristics of patients with concordant and discordant echocardiographic and health status responses.

Methods and results: Consecutively implanted CRT-defibrillator patients (n=109, mean age=65.4±10.1 years, 74 men) were recruited from the University Medical Center Utrecht, The Netherlands. Prior to implantation and 6 months post-implantation, all patients underwent echocardiography and completed the Kansas City Cardiomyopathy Questionnaire (KCCQ). Echocardiographic response was defined as a relative reduction of ≥15% in LV end-systolic volume; an improvement of ≥10 points in KCCQ score indicated a health status response. In the 54 patients with discordant responses, 25 (22.9%) had an echocardiographic response but no health status response and 29 (26.6%) had a health status response but no echocardiographic response.

Patients with concordant and discordant responses differed on various pre-implantation characteristics, including sex, employment status, LV volumes, and pre-implantation KCCQ score. In multivariable analysis, pre-implantation KCCQ score [odds ratio (OR) =0.91, 95% confidence interval (CI)=0.88–0.95, P <0.001] and QRS duration (OR=1.03, 95% CI=1.01–1.06, P =0.009) were the only characteristics associated with health status response to CRT.

Conclusions: Our results show a large discrepancy between echocardiographic and patient-reported health status response to CRT. The most important predictor of health status response was the pre-implantation health status score. These results emphasize that disease-specific health status measures may have additional value over 'objective' measures of CRT response and should be incorporated in clinical practice.

Cardiac resynchronization therapy is a well-established treatment for a subgroup of patients with heart failure (HF) and an inter-/intraventricular conduction delay.[1] Large-scale trials have demonstrated that the majority of these patients benefit from CRT, yet a significant proportion of patients (10–44%) do not respond to treatment.[2] Several studies have been performed in search of (echocardiographic) predictive markers for CRT response.[2–4] Yet, the definition of response varies amongst different trials, and most trials include either clinical endpoints (e.g. survival, symptoms, and quality of life) or echocardiographic measures of LV reverse remodelling to assess CRT response.[5] The question is to what extent these CRT trials are comparable, as previous studies have reported a disagreement between clinical and echocardiographic CRT response in 25–41% of patients.[6–9] In these studies, clinical CRT response was defined as an improvement in NYHA functional class. However, NYHA class has been criticized as being predominantly a measure of general functional status, and there is only amoderate association between (physician-rated)NYHA class and patient-reported health status.[10,11]
To date, only two studies have compared change in patient-reported health status between echocardiographic responders and non-responders, and found no difference.[6,12] However, both studies used the Minnesota Living with Heart Failure questionnaire to assess health status, which may not be responsive to clinical change.[13] In addition, only group related changes in mean health status scores were examined; this approach may mask subgroups of patients that do or do not show clinically relevant health status improvement after CRT. Knowing the prevalence and pre-implantation characteristics of patients who do not report improved health status despite echocardiographic response, or vice versa, may help to enhance risk stratification for CRT and support patient-centred care. [14,15]

Hence, the objectives of the current study were (i) to examine the degree of agreement between echocardiographic and patient reported health status response to CRT in the first 6months after implantation; and (ii) to evaluate the differences in pre-implantation characteristics of patients with concordant or discordant echocardiographic and health status responses.

Methods

Study design and participants

Patients receiving a first-time CRT-defibrillator (CRT-D) implantation in accordance with the guidelines and evidence-basedmedicine [NYHA functional class≥II despite optimal pharmacological therapy (NYHA functional class II patients were only included after the publication of positive treatment results in patients with mild HF symptoms), LVEF≤35%, QRS≥120 ms] between January 2009 and August 2011 at the University Medical Center Utrecht (UMCU), The Netherlands comprised the patient sample for the current study. Patients participated in the 'The influence of PSYchological factors on health outcomes in HEART failure patients treated with Cardiac Resynchronisation Therapy' (PSYHEART-CRT), a prospective, single-centre, observational study. The PSYHEART-CRT study was primarily designed to examine whether psychological factors play a moderating role in the association between the objectively assessed CRT response (i.e. reverse remodelling) and patient-reported outcomes. Exclusion criteria were age <18 or >85 years, a history of psychiatric illness other than affective/anxiety disorders, cognitive impairments (e.g. dementia), on the waiting list for heart transplantation, and insufficient knowledge of the Dutch language. One day prior to implantation (baseline) and 6 months postimplantation, patients were asked to complete a set of standardized and validated questionnaires. Pre- and 6months post-implantation, echocardiographic studies were performed. The study was conducted in accordance with the Declaration of Helsinki, the study protocol was approved by the Medical Ethics Committee of the UMCU, and informed consent was obtained from all patients.

Demographic and clinical variables

Information on demographic variables included age, sex, marital status (single vs. having a partner), employment status (currently employed vs. unemployed), educational level (primary school or lower vs. secondary school or higher), and smoking status, which were obtained via specifically designed questions at baseline. Information on clinical variables, including HF aetiology (ischaemic vs. non-ischaemic), history of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF), NYHA functional class, QRS duration, QRS morphology [left/right bundle branch block (LBBB/RBBB), intraventricular conduction delay (IVCD), or right ventricular pacing], diabetes mellitus, COPD, renal insufficiency (creatinine >120 µmol/L), and cardiac medication, were extracted from the patients' medical records.

LBBB criteria were derived from current American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society (AHA/ACCF/HRS) recommendations: every QRS duration ≥120 ms with a broad notched or slurred R wave in leads I, aVL, V5, and V6 and an occasional RS pattern in V5 and V6 (due to displaced transition of the QRS complex), absent q wave in lead I, V5, and V6, R peak time of ≥60 ms in V6 and rS or QS pattern in lead V1. QRS duration was assessed in lead II.[16]

Echocardiography

Prior to implantation and 6 months post-implantation, patients underwent an echocardiographic evaluation to assess LV end-systolic and diastolic volumes (LVESV and LVEDV, respectively) and LVEF. Patients were imaged in the left lateral decubitus position. LVESV and LVEDV were defined as the smallest and largest ventricular volume within one RR cycle, respectively, with both the mitral valve and aortic valve being closed. Subsequently, volume traces were set along the endocardial border. Papillary muscles were included in the LV cavity. Volumes were assessed according to Simpson's biplane method. Echocardiographic response to CRT was defined by a ≥15% relative reduction in LVESV, indicating reverse remodelling. This cut-off of 15% was based on previously performed studies,[2,17] and was shown to be associated with greater longevity after CRT implantation.[18,19]

Disease-specific health status

The Kansas City Cardiomyopathy Questionnaire (KCCQ) was used to assess HF-specific health status.[13] The KCCQ is a 23- item, self-report questionnaire that quantifies physical limitation, symptoms, social function, and quality of life of patients with HF. These four health status subscales can be combined into a single overall summary score. Scores are transformed into a score from 0 to 100, with higher scores representing better health status. The validity and reliability of the KCCQ have previously been established and the measure was shown to be highly sensitive to clinical change in HF patients over a 6–12 week period. [13,20] In the current study, the absolute difference between baseline and 6-month KCCQ overall summary scores was calculated and dichotomized, where an improvement of ≥10 points indicates 'health status response'. An improvement of ≥10 points represents a moderately large difference in patient health status.[13] A previous study in CRT patients using the same cut-off showed that health status responders had a 76% lower subsequent risk of dying of any cause in the first 18months after implantation.[14] Poor health status was defined as a KCCQ score <50 points.

Statistical analyses

Characteristics of the study sample are summarized as means with standard deviations for continuous variables and frequencies with percentages for categorical variables.

Paired samples t-tests were used to evaluate overall changes in echocardiographic outcomes and health status scores from baseline to 6 months. χ 2 tests for categorical variables and independent samples t-tests for continuous variables were used to compare the characteristics of echocardiographic and/or health status responders. Univariable and multivariable regression analyses were performed to examine which pre-implantation characteristics were associated with health status response, independent of echocardiographic response. A priori based on the literature, we decided to include age, sex, echocardiographic response, baseline KCCQ score, history of VT/VF, ischaemic aetiology, co-morbidities (renal failure, diabetes, and/or COPD), pre-implantation NYHA functional class, QRS duration, LBBB, and beta-blocker use in multivariable analyses.[7,9,12,14,21] Odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) are reported. We performed sensitivity analyses using different cut-off values for echocardiographic or health status response, to see whether this would change our results. All tests were two-tailed, with P ≤0.05 indicating statistical significance. All analyses were performed with SPSS 20.0 for Windows (SPPS Inc., Chicago, IL, USA).

Results

Baseline patient characteristics

Of 139 consecutive CRT patients that consented to participate in the PSYHEART-CRT study, 30 (21.6%) were not included in analyses because of missing KCCQ data at 6-month follow-up (n=16; 9 patients died, 7 patients dropped out) ormissing echocardiographic (n=14) data. There were no systematic differences between included (n=109) and excluded (n=30) patients on demographic and clinical baseline characteristics (results not shown). However, the mean pre-implantation KCCQ score of the excluded patients was significantly lower compared with that of the 109 included patients (45.7±20.3 vs. 59.4±23.5, P =0.004). The characteristics of the total sample are shown in Table 1. Of note, only 3 (2.8%) patients received an implantable cardioverter defibrillator (ICD) shock during the 6-month follow-up.

Echocardiographic and health status response to cardiac resynchronization therapy

From implantation to 6-month follow-up, significant reverse remodelling was observed in the total study population, as there was a mean reduction in LVESV from 169.1±68.5mL to 140.1±73.7mL (P <0.001) and in LVEDV from 222.5±75.6mL to 194.8±79.7mL (P <0.001). This resulted in a mean increase in LVEF from 24.9±8.9% to 31.1±10.5% (P <0.001). Based on a relative reduction in LVESV of ≥15%, 58 (53.2%) patients were classified as echocardiographic responders. Echocardiographic responders less often used statins (51.7% vs. 72.5%, P =0.03) compared with echocardiographic non-responders; there were no other systematic differences between echocardiographic responders and non-responders on baseline characteristics (Table 1).

Table 1. Baseline characteristics of the total sample (n=109) and stratified by echo/health status response[a]

	Total	Echo responder (*n*=58)	Echo non-responder (*n*=51)	*P*-value	Health status responder (*n*=62)	Health status non-responder (*n*=62)	*P*-value
Demographics							
Age, mean (SD)	64.4 (10.1)	65.9 (10.2)	64.9 (10.1)	0.60	65.6 (12.1)	65.2 (8.5)	0.86
Male sex	74 (67.9)	37 (63.8)	37 (72.5)	0.33	**36 (58.1)**	**38 (80.9)**	**0.01**
Lower education[b]	12 (11.0)	5 (8.6)	7 (13.7)	0.40	9 (14.5)	3 (6.4)	0.18
Currently employed	22 (20.4)	13 (22.4)	9 (18.0)	0.57	**7 (11.3)**	**15 (31.9)**	**0.01**
Having a partner	89 (81.7)	46 (79.3)	43 (84.3)	0.50	50 (80.6)	39 (83.0)	0.76
Clinical factors							
History of VT/VF	18 (16.5)	8 (13.8)	10 (19.6)	0.42	12 (19.4)	6 (12.8)	0.36
Ischaemic aetiology	53 (48.6)	24 (41.4)	29 (56.9)	0.11	26 (41.9)	27 (57.4)	0.11
NYHA class III/IV	85 (78.0)	44 (75.9)	41 (80.4)	0.57	52 (83.9)	33 (70.2)	0.09
Sinus rhythm	87 (79.8)	46 (79.3)	41 (80.4)	0.89	47 (75.8)	40 (85.1)	0.23
QRS (ms), mean (SD)	161.9 (26.4)	162.4 (26.1)	161.3 (27.0)	0.82	**166.5 (27.5)**	**155.7 (23.9)**	**0.03**
Upgrade from ICD	13 (11.9)	5 (8.6)	8 (15.7)	0.26	6 (9.7)	7 (14.9)	0.41
Upgrade from pacemaker	12 (11.0)	7 (12.1)	5 (9.8)	0.71	9 (14.5)	3 (6.4)	0.18
QRS morphology							
LBBB	58 (53.2)	32 (55.2)	26 (51.0)	0.66	36 (58.1)	22 (46.8)	0.24
RBBB	1 (0.9)	1 (1.7)	0 (0)	0.35	1 (1.6)	0 (0)	0.38
IVCD	33 (30.3)	15 (25.9)	18 (35.3)	0.29	16 (25.8)	17 (36.2)	0.24
RV pacing	16 (14.7)	9 (15.5)	7 (13.7)	0.79	9 (14.5)	7 (14.9)	0.96
LVEF (%), mean (SD)	24.9 (8.9)	24.7 (8.4)	25.2 (9.6)	0.82	25.0 (9.5)	24.9 (8.3)	0.95
LVESV (mL), mean (SD)	169.1 (68.5)	161.8 (60.3)	177.4 (76.5)	0.24	178.1 (68.8)	157.3 (66.9)	0.12
LVEDV (mL), mean (SD)	222.5 (75.6)	213.8 (68.2)	232.5 (82.7)	0.20	234.7 (77.3)	206.5 (70.8)	0.06
Diabetes mellitus	23 (21.1)	9 (15.5)	14 (27.5)	0.13	15 (24.2)	8 (17.0)	0.36
COPD	17 (15.6)	10 (17.2)	7 (13.7)	0.61	12 (19.4)	5 (10.6)	0.21
Renal insufficiency	40 (36.7)	21 (36.2)	19 (37.3)	0.91	21 (33.9)	19 (40.4)	0.48
Smoking	14 (12.8)	8 (13.8)	6 (11.8)	0.75	11 (17.7)	3 (6.4)	0.08
Medication							
ACE inhibitors/ARBs	98 (89.9)	52 (91.4)	45 (88.2)	0.59	54 (87.1)	44 (93.6)	0.26
Beta-blockers	86 (78.9)	47 (81.0)	39 (76.5)	0.56	49 (79.0)	37 (78.7)	0.97
Digoxin	20 (18.3)	14 (14.1)	6 (11.8)	0.10	13 (21.0)	7 (14.9)	0.42
Diuretics	92 (84.4)	48 (82.8)	44 (86.3)	0.61	51 (82.3)	41 (87.2)	0.48
Statins	**67 (61.5)**	**30 (51.7)**	**37 (72.5)**	**0.03**	37 (59.7)	30 (63.8)	0.66
KCCQ score, mean (SD)	59.4 (23.5)	61.8 (22.6)	56.6 (24.5)	0.25	**48.2 (21.1)**	**74.1 (17.9)**	**<0.001**
Poor KCCQ (<50 points)	34 (31.2)	15 (25.9)	19 (37.3)	0.20	**30 (48.4)**	**4 (8.5)**	**<0.001**

There was a significant improvement in patient-reported health status as measured with the KCCQ overall summary score from 59.4±23.5 to 74.6±20.6 points in the total study sample (P <0.001). Based on an improvement of ≥10 points, 62 (56.8%) patients were classified as health status responders. Of note, only 38 (62.3%) of the health status responders also improved according to their NYHA functional class. Health status responders were more likely to be female (41.9% vs. 19.1%, P =0.01), less often employed (11.3% vs. 31.9%, p=0.01), and had a longer pre-implantation QRS duration (166.5±27.5 vs. 155.74±23.9, P =0.03) as compared with health status non-responders. In addition, the mean baseline KCCQ score of the health status responders was significantly lower (48.2±21.1 vs. 74.1±17.9 points, P <0.001) compared with that of the non-responders. Of the responders, 48.5% had a poor baseline KCCQ score (<50 points) compared with 8.5% of the health status non-responders (p<0.001) (Table 1).

Agreement between echocardiographic and health status response

The agreement between echocardiographic and health status response was 50.5%; 33 patients (30.3%) were full responders and 22 patients (20.2%) were full non-responders (Figure 1). In the 54 patients with discordant responses, 25 (22.9%) had an echocardiographic response but no health status response, and 29 (26.6%) had a health status response but no echocardiographic response.

The baseline characteristics of the four subgroups stratified by echocardiographic/health status response are shown in Table 2. In the subgroup of echocardiographic responders, patients without a health status response were more likely to be employed (36.0% vs. 12.1%, P =0.03), and to have smaller pre-implantation LV volumes (LVESV, 142.2±38.3mL vs. 176.7±69.6mL, P =0.02; LVEDV, 189.4±42.0mL vs. 232.21±78.3mL, P =0.01) and a higher KCCQ baseline score (74.3±19.4 vs. 43.5±21.4, P <0.001) compared with patients with a concordant health status response. In the subgroup of echocardiographic non-responders, patients with a health status response were more often female (41.4% vs. 9.1%, P =0.01) and had a lower KCCQ baseline score (52.4±20.3 vs. 73.9±16.5, P <0.001) compared with the concordant health status non-responders. Logistic regression analysis confirmed that echocardiographic response was not associated with health status response (OR 1.06, 95% CI 0.37–3.34, P =0.86).

< Results are presented as n (%), unless otherwise stated. Significant results are given in bold. ICD, implantable cardioverter defribrillator; IVCD, intraventricular conduction delay; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; RBBB, right bundle branch block RV; RV, right ventricular; VT/VF, ventricular tachycardia/fibrillation.
[a]Echocardiographic response is defined as a reduction in LV end-ystolic volume of ≥15% and health response is defined as an improvement of ≥10 points on the Kansas City Cardiomyopathy Questionnaire, at 6-month follow-up. [b]Primary school or lower.

Results of the multivariable logistic regression analysis (Table 3) showed that the pre-implantation KCCQ score (OR 0.91, 95% CI 0.88–0.95, P <0.001) and QRS duration (OR 1.03, 95% CI 1.01–1.06, P =0.009) were the only pre-implantation patient characteristics associated with health status response, independent of echocardiographic response.

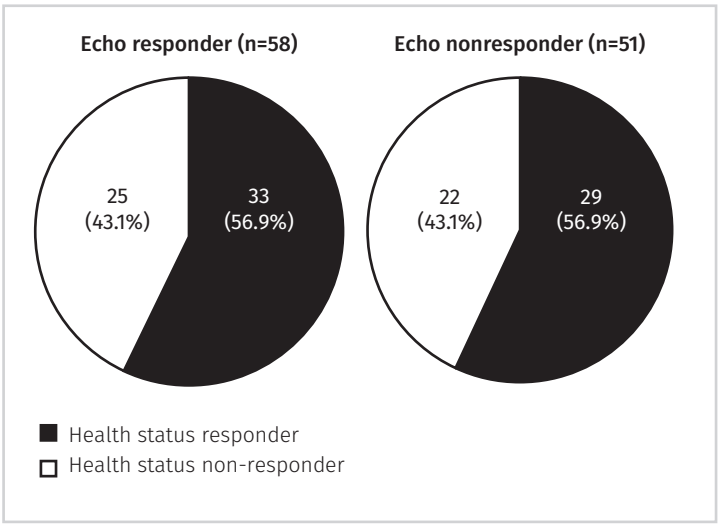

Figure 1. Concordance between echocardiographic and health status response to CRT. Echocardiographic response is defined as a reduction in LV end-systolic volume of ≥15% and health status response is defined as an improvement of ≥ 10 points on the Kansas City Cardiomyopathy Questionnaire, at 6-month follow-up.

Sensitivity analyses

We performed sensitivity analyses using different cut-off values to define echocardiographic and health status response. Of all patients, 64 (58.1%) showed a relative reduction in LVESV of ≥10%, and 47 (43.1%) of ≥20%. Regarding health status, 69 (63.3%) of the patients improved by ≥5 points on the KCCQ and 42 (38.5%) improved by ≥20 points. Using these different cut-off values, the discrepancy between the echocardiographic and health status response was confirmed, showing a poor agreement ranging between 50.5% and 56.0% and no significant associations between echocardiographic and health status responses in logistic regression analyses.

Discussion

The current study in 109 patients showed a large discrepancy between echocardiographic (i.e. ≥15% reduction in LVESV) and patient-reported health status (i.e. ≥10 points improvement in KCCQ overall summary score) response to CRT 6 months after implantation, with half of the patients (n=54) showing discordant responses. Patients with concordant and discordant responses differed on various pre-implantation characteristics, including sex, employment status, LV volumes, and pre-implantation KCCQ score. In multivariable analysis, a lower pre-implantation KCCQ score and longer QRS duration were the only characteristics associated with health status response to CRT.

Our results are in agreement with those of two previous studies showing that echocardiographic responders and non-responders did not differ in their health status improvement after CRT.[6,12] However, this is the first study that used a validated cut-off score to determine health status response and hence assessed the clinically relevant effect of CRT as experienced by individual patients. The agreement between echocardiographic and health status response in the current study was 50.5%, which is lower than the concordance rate of 70–76% found in studies comparing echocardiographic response with improvement in NYHA functional class.[6-8] This suggests that the NYHA functional class which a physician decides to assign to a patient might be influenced by 'objective' measures of response indicating LV reverse remodelling. Taken together with our finding that only 38 (62.3%) of the health status responders also improved according to their NYHA functional class, these results support previous findings that NYHA functional class should not be used as the sole measure reflecting changes in the severity of symptoms and functional limitations in HF patients.[10.22]

In the group of echocardiographic responders, patients that did not report improved health status were characterized by small preimplantation LV volumes, being employed, and high KCCQ baseline scores. This could indicate that the 15% LVESV relative reduction used to demonstrate echocardiographic response might be too small to be beneficial for patients that already have relatively small LV volumes and report a good health status prior to implantation. In addition, echocardiographic non-responders who did report health status improvement were more likely to be female and to have a poor health status at baseline. In these patients, a placebo effect might be present in the first months after implantation as they receive treatment and attention from their physician. This effect is also seen in single-/double-blinded randomized controlled trials where the CRT device was randomly switched 'on' or 'off'. Results of these trials showed that patients with their CRT device switched 'off' did report an improvement in functional status and quality of life, although this improvement was significantly smaller than in the CRT 'on' group.[23,24]

Table 2. Baseline characteristics of concordant/discordant response subgroups (*n*=109)[a]

	Echo responder (*n*=58)			Echo non-responder (*n*=51)		
	Health status responder (*n*=33)	**Health status non-responder (*n*=25)**	***P*-value**	**Health status responder (*n*=29)**	**Health status non-responder (*n*=22)**	***P*-value**
Demographics						
Age, mean (SD)	66.6 (8.5)	64.9 (12.3)	0.55	64.3 (8.3)	65.6 (12.1)	0.67
Male sex	19 (57.6)	18 (72.0)	0.26	**17 (58.6)**	**20 (90.9)**	**0.01**
Lower education[b]	5 (15.2)	0 (0)	0.06	4 (13.8)	3 (13.6)	0.99
Currently employed	**4 (12.1)**	**9 (36.0)**	**0.03**	3 (10.7)	6 (27.3)	0.16
Having a partner	25 (75.8)	21 (84.0)	0.44	25 (86.2)	18 (81.8)	0.67
Clinical factors						
History of VT/VF	4 (12.1)	4 (16.0)	0.72	7 (27.6)	2 (9.1)	0.16
Ischaemic aetiology	12 (36.4)	12 (48.0)	0.23	14 (48.3)	15 (68.2)	0.16
NYHA class III/IV	27 (81.8)	17 (68.0)	0.22	25 (86.2)	16 (72.7)	0.30
Sinus rhythm	26 (78.8)	20 (80.0)	0.91	21 (72.4)	20 (90.9)	0.16
QRS (ms), mean (SD)	167.4 (25.1)	155.8 (26.4)	0.09	165.5 (30.3)	155.7 (21.3)	0.18
Upgrade from ICD	3 (9.1)	2 (8.0)	0.88	3 (10.3)	5 (22.7)	0.23
Upgrade from pacemaker	5 (15.2)	2 (8.0)	0.40	4 (13.8)	1 (4.5)	0.25
QRS morphology						
LBBB	21 (63.6)	11 (44.0)	0.14	15 (51.7)	11 (50.0)	0.90
RBBB	1 (3.0)	0 (0)	0.38	0	0	-
IVCD	7 (21.2)	8 (32.0)	0.35	9 (31.0)	9 (40.9)	0.47
RV pacing	4 (12.1)	5 (20.0)	0.41	5 (17.2)	2 (9.1)	0.40
LVEF (%), mean (SD)	24.7 (8.9)	249 (7.9)	0.93	25.4 (10.2)	24.9 (8.9)	0.86
LVESV (mL), mean (SD)	**176.7 (69.6)**	142.2 (38.3)	0.02	179.6 (69.1)	174.4 (86.9)	0.81
LVEDV (mL), mean (SD)	**232.31 (78.3)**	189.4 (42.0)	0.01	237.4 (77.5)	225.9 (90.7)	0.63
Diabetes mellitus	7 (21.2)	2 (8.0)	0.17	8 (27.6)	6 (27.3)	0.98
COPD	6 (18.2)	4 (16.0)	0.99	6 (20.7)	1 (4.5)	0.12
Renal insufficiency	11 (33.3)	10 (40.0)	0.60	10 (34.5)	9 (40.9)	0.64
Smoking	6 (18.2)	2 (8.0)	0.45	5 (17.2)	1 (4.5)	0.22
Medication						
ACE inhibitors/ARBs	30 (90.9)	23 (92.0)	0.63	24 (82.8)	21 (95.9)	0.17
Beta-blockers	27 (81.8)	20 (80.0)	0.99	22 (75.9)	17 (77.3)	0.91
Digoxin	9 (27.3)	5 (20.0)	0.52	4 (13.8)	2 (9.1)	0.69
Diuretics	26 (78.8)	22 (88.0)	0.49	25 (86.2)	19 (86.4)	0.99
Statins	16 (48.5)	14 (56.0)	0.57	21 (72.4)	16 (72.7)	0.99
KCCQ score, mean (SD)	**43.5 (21.4)**	**74.3 (19.4)**	**< 0.001**	**52.4 (20.3)**	**73.9 (16.5)**	**< 0.001**
Poor KCCQ (<50 points)	**13 (39.4%)**	**2 (8.0%)**	**< 0.001**	**17 (58.6%)**	**2 (9.1%)**	**< 0.001**

In the current study, only a longer QRS duration and lower KCCQ score prior to implantation were independently associated with health status response. Previous trials show conflicting results regarding the association between pre-implantation QRS duration and (clinical) response to CRT, with some studies showing an increase in quality of life and functional status only in patients with QRS prolongation >150 ms [24] and others showing important clinical benefit among patients with narrow QRS intervals (<120 ms). [25] A recently published meta-analysis on the association between QRS duration and CRT response, evaluating 6 randomized clinical trials and 38 observational studies, showed that QRS width was larger for both clinical and remodelling responders, which underlines the concept of a larger QRS width at baseline being beneficial for response, which was also found in our study.[26] None of the other clinical factors was associated with health status response in uni- and multivariable analyses. These results are in agreement with previous studies showing that objective measures of disease status are not associated with patient-perceived symptoms, function, and quality of life.[10,15,27] As emphasized in a report from the National Heart, Lung, and Blood Institute in the USA, studies are warranted that examine the determinants of patient-reported outcomes, including the potential moderating role of psychosocial factors (e.g. depressive and anxiety symptoms and personality traits).[28]

Our results also showed that patients with poorer baseline health status derive the greatest health status benefit after CRT, which is in accordance with previous studies.[14,21] This might be due to a ceiling effect that limits the extent of health status improvement in patients already reporting good health status prior to implantation. The relative number of patients that report a good health status prior to implantation is probably increasing due to the expansion of the indication for CRT to include patients with mild (NYHA functional class II) HF symptoms. In these patients, the main goal of treatment is preventing deterioration of HF. Particularly in these patients, it is essential to manage their expectations about the effects of treatment when evaluating them for CRT. As recently stated by the AHA, a full discussion of prognosis after HF treatment should include not only the risks of death but also the expected effect on symptoms, functional capacity, and quality of life. [29,30] This might be facilitated by assessing patient-reported health status with a disease-specific questionnaire as this provides important information about the effects patients may or may not experience in their daily lives after CRT. [30]

< Results are presented as n (%), unless otherwise stated. Significant results are given in bold.
ICD, implantable cardioverter defribrillator; IVCD, intraventricular conduction delay; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; RBBB, right bundle branch block RV; RV, right ventricular; VT/VF, ventricular tachycardia/fibrillation.
aEchocardiographic response is defined as a reduction in LV end-ystolic volume of ≥15% and health response is defined as an improvement of ≥10 points on the Kansas City Cardiomyopathy Questionnaire, at 6-month follow-up. bPrimary school or lower.

In addition, serial health status assessments offer important supplements to traditional physician-rated measures (e.g. echocardiography) to gain insight into the burden of disease and treatment on patients. When patients continue to report poor health status despite (substantial) echocardiographic improvement after CRT, this might indicate that these patients need secondary (psychological) intervention to improve their well-being. This may even result in reduced mortality and morbidity after CRT, as poor patient-reported health status has been associated with adverse prognosis in HF patients.[31]

The limitations of the current study should be acknowledged. First, our patient sample was relatively small, and we had to combine patients with stable and deteriorated LVESV or health status into one group of non-responders. Hence, we could not perform any subanalyses comparing improved, stable, and deteriorated patients. Also, this study was underpowered to perform multivariable analyses on the subgroups with concordant/discordant CRT response. Secondly, the 30 excluded patients had a lower mean KCCQ score prior to implantation compared with the patients included in the analyses. This potential attrition bias, in which dropouts show worse scores on baseline self-report questionnaires compared with patients completing a study, has been shown before and may jeopardize the generalizability of our results.[32] Thirdly, other factors that have also been related to CRT response such as lead position, percentage of biventricular pacing, and echocardiographic (strain) dyssynchrony measures were not addressed as the goal of this study was not to predict echocardiographic CRT response. Future studies with larger patient samples are needed to confirm our results. The present study also has several strengths.

First, we used the KCCQ to assess health status, which is a HF-specific measure previously shown to be highly responsive to clinical change.20 A mean difference over time of .5 points on the KCCQ overall summary score is considered a small, but clinically relevant change and has been associated with an 11% change in the adjusted hazard ratio of hospitalization and cardiovascular death.[20,33] Also, we examined proportions of patients showing health status response using a cut-off instead of mean group changes. This method is more relevant for clinical practice, as this reflects changes in individual patients rather than group changes.[34]

Table 3. Correlates of health status response: adjusted analysis[a]

	OR	95% CI	*P*-value
Echocardiographic response	1.06	0.37-3.34	0.86
Age	1.02	0.97-1.09	0.49
Male sex	0.59	0.16-2.09	0.41
KCCQ baseline score	**0.91**	**0.88-0.95**	**<0.001**
History of VT/VF	2.87	0.66-12.55	0.16
Ischaemic aetiology	2.10	0.59-7.43	0.25
NYHA class III/IV	0.38	0.09-1.60	0.19
QRS duration	**1.03**	**1.01-1.06**	**0.009**
LBBB	1.85	0.61-5.62	0.28
Co-morbidities[b]	0.90	0.27-3.00	0.86
Beta-blockers	3.68	0.82-16.43	0.09

Significant results are given in bold.
CI, confidence interfal; KCCQ, Kansas City Cardiomyopathy Questionnaire; OR, odds ratio; VT/VF, ventricular tachycardia/fibrillation.
[a]Echocardiographic response is defined as a reduction in LV end-systolic volume of ≥10 points on the Kansas City Cardiomyopathy Questionnaire, at 6-month follow-up.
[b]COPD, renal failure, and/or diabetes mellitus.

In conclusion, this study shows a large discrepancy between echocardiographic and patient-reported health status response to CRT. The most important predictor of health status response was the patients ?f pre-implantation health status score. These results emphasize that disease-specific health status measures have additional value over 'objective'?measures of CRT response and should be incorporated into clinical practice, as they may provide both HF patients and clinicians with important information about the (expected) effects of an intervention such as CRT. As outlined in a recent scientific statement of the AHA, additional research is needed to better understand the determinants of patient health status and to develop effective strategies to incorporate health status measures in clinical practice.[30]

Conflict of Interest

None declared.

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Chapter 8

VOLUMETRIC RESPONSE BEYOND SIX MONTHS OF CARDIAC RESYNCHRONIZATION THERAPY AND CLINICAL OUTCOME

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Abstract

Aims: Response to cardiac resynchronization therapy (CRT) is often assessed six months after implantation. Our objective was to assess the number of patients changing from responder to non-responder between six and 14 months, so-called late non-responders, and compare them to patients who were responder both at six and 14 months, so-called stable responders. Furthermore, we assessed predictive values of six and 14-month response concerning clinical outcome.

Methods: 105 patients eligible for CRT were enrolled. Clinical, laboratory, ECG, and echocardiographic parameters and patient-reported health status (Kansas City Cardiomyopathy Questionnaire [KCCQ]) were assessed before, and six and 14 months after implantation. Response was defined as ≥ 15% LVESV decrease as compared to baseline. Major adverse cardiac events (MACE) were registered until 24 months after implantation. Predictive values of six and 14-month response for MACE were examined.

Results: In total, 75 (71%) patients were six-month responders of which 12 (16%) patients became late non-responder. At baseline, late non-responders more often had ischemic cardiomyopathy and atrial fibrillation, higher BNP and less dyssynchrony compared to stable responders. At six months, late non-responders showed significantly less LVESV decrease, and higher creatinine levels. Mean KCCQ scores of late non-responders were lower than those of stable responders at every time point, with the difference being significant at 14 months. The 14 months response was a better predictor of MACE than six months response.

Conclusions: The assessment of treatment outcomes after six months of CRT could be premature and response rates beyond might better correlate to long-term clinical outcome.

Introduction

Cardiac resynchronization therapy (CRT) is an established treatment for patients with congestive heart failure (CHF) and a wide QRS complex.[1] A common measure for determining a patient's response to CRT is the decrease in left ventricular end systolic volume (LVESV) six months after device implantation.[2] Patients demonstrating ≥ 15% LVESV decrease are classified as responder; otherwise they are classified as non-responder.[2,3] In multi-center studies it has previously been demonstrated that this reverse remodeling is a process which continues until 18–24 months after device implantation.[4,5]
Due to continuous reverse remodeling, initial non-responders (<15% LVESV decrease) may become responders at a later time (late responders), while initial responders (≥15% LVESV) may later become non-responders due to, possibly, diminishing beneficial effects of CRT over time.

At present, many studies and clinicians evaluate CRT response within six months after device implantation and focus on pre-implantation factors predicting this response. However, limited data are available concerning the prevalence and predictors of long-term changes in response to CRT. Therefore, in the current study we assessed the number and characteristics of patients whose response at 14 months differed from their response at six months. Our main focus was on late non-responders as we hypothesize that these might have a worse prognosis than (late and stable) responders and should therefore be identified. Hence, we also examined the correlation of 14 months response with health outcomes, including patient-reported health status and major adverse cardiac events (MACE).

Methods

Study design and cohort

This was a prospective, single center study designed to study the influence of PSYchological factors on health outcomes in HEART failure patients treated with CRT (PSYHEART-CRT). Patients eligible to CRT, according to applicable guidelines and evidence-based medicine at time of inclusion, were enrolled between January 2009 and August 2011 at the University Medical Center Utrecht (UMCU).

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the local Medical Ethics Committee of the UMCU (protocol number 08–246) and patients signed informed consent. A more extensive description has been published previously.[6]

Echocardiography

Echocardiographic studies were performed prior to implantation (baseline), and six and 14 months after device implantation. Data were acquired using Philips IE 33 (Philips Medical Systems, Andover, Massachusetts, USA) or Vivid 7 (General Electric, Milwaukee, USA) ultrasound machines. Apart from speckle tracking analysis, echocardiographic parameters were assessed offline using Xcelera software (R3.3L1). Speckle tracking was performed for studies on the Vivid 7 and analyzed using EchoPac software (version 11.2, revision 1.1). Volumes and other measurements were assessed by one observer and in accordance with the guidelines of the American Society of Echocardiography (ASE) and European Association of Echocardiography (EAE).[7] Measurements were performed on three separate beats, or five beats in case of irregular rhythms.

Mitral regurgitation at baseline and after six months was visually assessed and extracted from echocardiographic records.

Volume response

LVESV was assessed by Simpsons' biplane method. Volume changes were assessed between baseline and six months FU, baseline and 14 months FU and between six and 14 months FU.

Response to CRT was defined as relative decrease in LVESV of ≥15%, which has been shown to predict clinical outcome up to five years after CRT implantation.[8] Non-responders were patients demonstrating <15% LVESV decrease, or who died due to heart failure or received a left ventricular assist device (LVAD). Response rates were assessed at six and 14 months after CRT implantation.
Patients who were responder at both six and 14-month follow-up (FU) were termed 'stable responders'. Six-month responders turning into non-responders at 14 months were termed 'late non-responders'. Six-month non-responders, turning into responders at 14 months were termed 'late responders'. Six and 14-month non-responders were termed 'stable non-responders'.

Dyssynchrony measurements

Doppler flows over the pulmonary and aortic valve were recorded and time from Q to onset of flow was assessed for both valves.[2] Interventricular mechanical delay (IVMD) was defined as the time span between the opening of the aortic valve and the pulmonary valve. ΔIVMD was assessed between baseline and six months FU.

Systolic rebound stretch of the septum (SRSsept) was evaluated using speckle tracking by evaluation of longitudinal septal strain, as previously described.[3,9] Frame rates were kept between 50–110 frames per second. Systole was defined as the period from mitral valve closure up to aortic valve closure as assessed by pulsed Doppler waves over the mitral and aortic valve, respectively. ΔSRSsept was assessed between baseline and six months FU.

Demographic, clinical, ECG, and laboratory variables

Demographic, clinical, ECG, and laboratory variables were extracted from patients' medical records, as described previously.[6] Definition of left bundle branch block (LBBB) was conform current American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society (AHA/ACCF/HRS) recommendations.[10] Pacing percentages were derived through device interrogation.

Patient-reported health status

At baseline and at six and 14-month FU, patients completed the Kansas City Cardiomyopathy Questionnaire (KCCQ) to assess CHF-specific health status.[11] The KCCQ is a 23-item, selfreport questionnaire that quantifies physical limitation, symptoms, social function and quality of life of patients with CHF. These four health status subscales can be combined into a single overall summary score. Scores are transformed into a score ranging from 0 to 100 with higher scores representing better health status. The validity and reliability of the KCCQ have previously been established and this method has been shown to be highly sensitive to clinical change in CHF patients.[11]

Major adverse cardiac events

MACE cases were defined as hospitalization due to heart failure, LVAD implantation, heart transplantation or death due to heart failure. Assessment took place for up to 24 months after CRT implantation.

Statistical analyses

Statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, Illinois). Continuous variables are presented as mean with standard deviation (SD) when normally distributed and as median with interquartile range (IQR) in case of non-normal distribution. Categorical variables are presented as numbers and percentages. Differences at baseline and at six months FU between stable responders and late non-responders were assessed.

Categorical variables were compared using Pearson's Chi-square and continuous variables were assessed using students T-tests or Mann-Whitney U, as appropriate. Related samples of continuous variables were assessed using students T-tests or Friedman's two-way analysis of variance by ranks test. Related samples of categorical variables were assessed with McNemar. Furthermore, the correlation between response rates, at six and 14 months, and MACE was assessed and compared with Pearson's Chi-square and net reclassification index (NRI).[12] The NRI is a measure demonstrating the improvement in risk prediction from (in this case) 14 months response rates over six months response rates. Calculation of NRI was based on the following categories of chances of becoming a responder: <0.33, 0.33–0.66, and >0.66. To measure the correlation between response rates and MACE, solely patients with six and 14-month echocardiographic studies were taken into account. Non-responders by other definition than <15% LVESV decrease; either receiving an LVAD or death due to heart failure, were excluded for this analysis.

A sensitivity analysis was performed for a subsample thereby excluding patients with atrial fibrillation (AF) as this is associated with reduced CRT response. [13–15]

Results

Of 139 patients that consented to participate in the study, 12 lacked a baseline echocardiographic study, 11 cases had insufficient image quality, nine were lost to follow-up, two died of non-cardiac cause. Six months after CRT implantation 71% (n = 75) patients were responders and 29% (n = 30) were non-responders. Of these responders 84% (n = 63) were stable responders and 16% (n = 12) became late non-responders, as shown in Fig 1. Fig 2 demonstrates the evolution of LVESV for late non-responders. Of the six-month non-responders, 80% (n = 24) were stable non-responders and 20% (n = 6) became late responders.

At baseline, six and 14 months FU, 15 patients demonstrated AF at least during one assessment. Of these, three had permanent AF, six had persistent AF (for which one a His-ablation was performed), and three had paroxysmal AF. Three patients had AF solely at baseline, and device interrogation did not show AF anymore during follow-up. If all patients with AF were neglected, crossover from response to late non-response still occurred in 12% of the six-month responders.

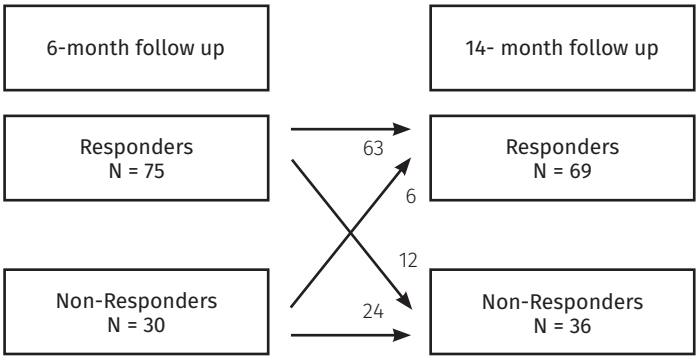

Figure 1. Flow chart of responders and non-responders
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Six-month responders

Baseline characteristics of the 75 six-month responders, stratified by stable responders and late non-responders, are shown in Table 1. New York Heart Association (NYHA) functional classification did not differ significantly between stable responders and late non-responders and the majority (77%) was in NYHA class II. LBBB was present in 59% of the patients, interventricular conduction delay (IVCD) in 27%. Fourteen percent of patients were paced in the right ventricle (RV). Mean left ventricular ejection fraction (LVEF) was 25±9%. These numbers did not differ significantly between stable responders and late non-responders.

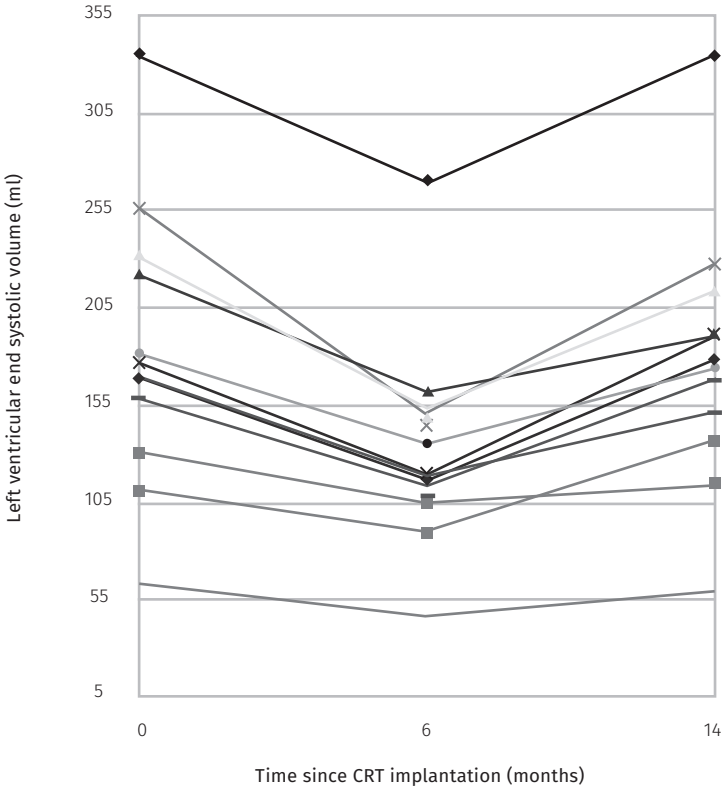

Figure 2. Baseline data of six-month responders, and stratified by late non-responders and stable responders.
doi:10.1371/journal.pone.0124323.g001

Table 1. Baseline data of six-month responders, and stratified by late non-responders and stable responders.

	All six-month responders (n=75)	Late non-responders (n=12)	Stable responders (n=63)
Baseline clinical data			
Age, yeras, means ± SD	65.4 ± 10.5	70.6 ± 7.0	64.6 ± 11.0
Male (%)	50 (67)	11 (92)*	39 (62)*
NYHA II (%)	15 (20)	1 (8.5)	14 (22)
NYHA III (%)	58 (77)	10 (83)	48 (76)
NYHA IV (%)	2 (3)	1 (8.5)	1 (2)
Ischemic cardiomyopathy, (%)	33 (44)	10 (83)*	23 (37)*
Baseline ECG data			
QRS duration, ms, mean ± SD	165 ± 25	160 ± 26	166 ± 25
LBBB (5)	44 (59)	6 (50)	38 (60)
IVCD (%)	20 (27)	4 (33)	16 (25)
RBBB (%)	1 (1)	0 (0)	1 (2)
RV pacing (%)	10 (13)	2 (17)	8 (13)
Atrial fibrillation (%)	11 (15)	4 (33)	7 (11)*
Baseline Medication			
Ace inhibitor/AT2-antagonist (%)	65 (89)	10 (83)	55 (89)
Diuretics (%)	59 (81)	10 (83)	49 (80)
Beta-blocker (%)	58 (77)	9 (75)	49 (80)
Baseline laboratory data			
Creatinine, µmol/L, median (IQR)	112 (33)	119 (33)	106 (45)
BNP, pmol/L, median (IQR)	52 (84)	113 (341)*	65 (101)*
Baseline echocardiographic data			
LVEF, %, mean ± SD	25 ± 9	24 ± 10	24 ± 8
LVESV, ml, median (IQR)	166 (65)	171 (92)	160 (64)
IVMD, ms, mean ± SD	44 ± 28	21 ± 14#	46 ± 28#
SRSsept, %, median (IQR)	4.31 (3.89)	0.57 (2.8)#	4.52 (3.7)#
Tapse, cm, mean ± SD	1.8 ± 0.5	1.5 ± 0.3*	1.9 ± 0.5*
RV peak systolic velocity, cm/sec, median (IQR)	10.0 (4.15)	8.5 (1.9)	10.3 (4.1)
LA volume, ml/m^2, median (IQR)	43.4 (20.2)	49.7 (20.9)	43.2 (20.8)
RA area, cm^2, median (IQR)	15 (8)	19 (7)*	15 (7)*
E/E', median (IQR)	13 (9)	15 (11)	13 (8)
Moderate or severe mitral regurgitation, n (%)	5 (7)	1 (8)	4 (6)

Stable responders versus late non-responders

Baseline. As shown in Table 1, late non-responders were more often male (92% vs 62%) and more likely to have ischemic cardiomyopathy (ICM; 83% vs 37%) as compared to stableresponders. Elapsed time between last myocardial infarction and last invasive treatment (percutaneous coronary intervention (PCI) or coronary artery bypass surgery) for coronary artery disease did not differ significantly between stable responders and late non-responders with ICM (7±7 years; results not shown). Late non-responders more often showed AF compared to stable responders. Furthermore, late non-responders showed significantly lower IVMD and SRSsept, and higher B-type natriuretic peptide (BNP) levels compared to stable responders.

If patients with AF at baseline were excluded from the analysis, baseline differences between late non-responders and stable responders did not change, except for RV peak systolic velocity which appeared to be significantly lower in non-responders.

Six-month follow-up. An overview of the six-month FU data of stable responders and late non-responders is provided in Table 2. Late non-responders showed significantly higher LVESV at six months than stable responders (117 ml vs 88 ml), and significantly lower LVEF (29% vs 35%). Absolute LVESV decrease in the first six months of CRT did not differ significantly between both groups. However, relative LVESV decrease was significantly lower for late non-responders than for stable responders. Creatinine and BNP levels were higher in late nonresponders than stable responders. In addition, late non-responders had a lower biventricular pacing percentage and occurrence of AF was significantly higher as compared to stable responders after six months.

< p-value between late non-responders and stable responders:
* = $p < 0.05$,
# = $p < 0.001$
ACE: angiotensin-converting enzyme, BNP: B-type natriuretic peptide, IQR: Interquartile range, IVCD: Interventricular conduction delay, IVMD: Interventricular mechanical delay, LA: Left atrium, LBBB: Left bundle branch block, LVEDV: left ventricular end diastolic volume, LVEF: left ventricular ejection fraction, LVESV: left ventricular end systolic volume, NYHA: New York Heart Association, RA: Right atrium, RBBB: Right bundle branch block, RV: Right ventricle, SRS_{sept}: Systolic Rebound Stretch of the Septum
doi:10.1371/journal.pone.0124323.t001

Table 2. Six-month follow-up date of the late non-responders and stable responders.

	Late non-responder (n=12)	Stable responders (n=63)
Six-month FU clinical data		
NYHA I (%)	0 (0)	7 (11)
NYHA II (%)	7 (58)	40 (64)
NYHA III (%)	5 (42)	16 (25)
Pacing percentage, %, median (IQR)	96 (7)*	99 (5)*
Six-month FU ECG data		
Stimulated QRS duration, ms, mean ± SD	147 ± 23	144 ± 20
Left to right axis shift (%)	6 (5)	32 (53)
Atrial fibrillation (%)	3 (25)*	4 (8)*
Six-month FU medication		
ACE inhibitor/AT2 antagonist (%)	10 (83)	52 (88)
Diuretics (%)	10 (83)	44 (74)
Beta-blocker (%)	9 (75)	50 (85)
Statines (%)	10 (83)*	28 (48)*
Six-month FU laboratory data		
Creatinine, µmol/L, median (IQR)	133 (88)*	107 (40)*
ΔCreatinine, µmol/L, median (IQR)	13 (33)	4 (22)
BNP, pmol/L, median (IQR)	152 (237)*	42 (66)*
ΔBNP, pmol/L, median (IQR)	15 (303)	-13 (65)
Six-month FU echocardiographic data		
LVEF, %, mean ± SD	29 ± 7*	35 ± 9*
Absolute ΔLVEF, %, mean ± SD	5.0 ± 9.4*	10.7 ± 6.0*
LVESV, ml, median (IQR)	117 (46)	88 (61)*
Relative ΔLVESV, %, median (IQR)	-28 (11)*	-39 (25)*
IVMD, ms, mean ± SD	3 ± 32*	20 ± 23
Absolute ΔIVMD, ms, mean ± SD	-18 ± 34	-26 ± 29
SRSsept, %, median (IQR)	0.03 (0.16)*	0.31 (1.38)*
Absolute ΔSRSsept, %, median (IQR)	-0.38 (2.78)*	-3.41 (4.69)*
Tapse, cm, mean ± SD	1.6 ± 0.4	1.8 ± 0.5
RV peak, systolic velocity, cm/sec, median (IQR)	9.1 ± 1.4	9.5 ± 4.3
LA volume, m/m^2, median (IQR)	52 (32)*	36 (18)*
RA area, cm^2, median (IQR)	16 (9)	15 (6)
E/E', median (IQR)	14 (6)	12 (11)
Moderate or severe mitral regurgitation, n (%)	0 (0)	1 (2)

If patients with AF at six months were disregarded in the analyses, six-month results showed only minor changes. Differences between late non-responders and stable responders did not differ, except for pacing percentage, ΔLVEF and SRSsept which did not show a significant difference anymore between late non-responders and stable responders.

Patient-reported health status. In total, 91% (68/75) of the six-month responders completed the KCCQ three times; at baseline, and at six and 14-month FU. At each assessment, the nine late non-responders reported a lower mean health status score than the 59 stable responders (i.e., 48.3±26.7 versus 58.5±22.3, p = 0.22 at baseline; 60.5±23.5 versus 75.9±21.7, p = 0.05 at six-month FU; and 52.9±29.0 versus 75.8±21.2, p = 0.006 at 14-month FU). This difference was statistically significant at 14 months FU only. In addition, the stable responders reported significantly increased KCCQ scores from baseline to six months FU (p<0.001), while this increase did not occur for the late non-responder group.

Major adverse cardiac events. Of the total population, 24% (26/105) suffered a MACE within two years after CRT implantation. For six-month responders, late non-responders and stable responders the prevalence of patients suffering a MACE were: 19% (14/75), 58% (7/12) and 11% (7/63), respectively. Table 3 demonstrates the distribution within the groups of six and 14-month responders and non-responders. The NRI increased significantly for the response rates at 14 months compared to response rates at six months: 38.1%, p = 0.009.

< p-value between late non-responders and stable responders:
* = p < 0.05,
# = p <0.001
ACE: angiotensin-converting enzyme, BNP: B-type natriuretic peptide, IQR: Interquartile range, IVCD: Interventricular conduction delay, IVMD: Interventricular mechanical delay, LA: Left atrium, LBBB: Left bundle branch block, LVEDV: left ventricular end diastolic volume, LVEF: left ventricular ejection fraction, LVESV: left ventricular end systolic volume, NYHA: New York Heart Association, RA: Right atrium, RBBB: Right bundle branch block, RV: Right ventricle, SRS_{sept}: Systolic Rebound Stretch of the Septum
doi:10.1371/journal.pone.0124323.t002

Table 3. MACE between 14-24 months after implantation in 6 and 14-month responders and non-responders.

	Six-month responders (n=75)	Six-month non-responders (n=23)	P-value
MACE (%)	14 (19)	5 (22)	0.774
No MACE (%)	61 (81)	18 (78)	
	14-month responders (n-69)	**14-month non-responders (n=29)**	**P-value**
MACE (%)	7 (10)	12 (41)	<0.001
No MACE (%)	62 (90)	17 (59)	

MACE: Major adverse cardiac events
doi:10.1371/journal.pone.0124323.t003

Discussion

The main finding of this study was that 16% of the six-month responders turned into non-responders after 14 months of CRT. Furthermore, we found that 14-months response rates correlated significantly better with patient-reported health status and occurrence of MACE compared to six months response rates, indicating that the change from responder to non-responder has important consequences for prognosis.

Baseline characteristics of late non-responders

Although late non-responders and stable responders were both eligible to CRT according to the guidelines, significant differences between these groups were already present prior to implantation. Pre-implantation BNP was lower in stable responders, whereas volumes did not differ significantly between late non-responders and stable responders. Lower BNP levels are associated with more reverse remodeling and better prognosis, as high BNP indicates high wall stress associated with dilated myocardium.[16,17] In addition, most late non-responders had ICM, which has been associated with less reverse remodeling.[18] This could be attributed to the presence of denser scar tissue in patients with ICM, which is unable to undergo reverse remodeling. However, progression of cardiovascular disease could also contribute to the (late) non-response. Cutlip et al.[19] demonstrated in 1228 patients who underwent PCI that the cumulative event rate (re-stenosis and new stenosis) five years after the intervention was 45% with an annual hazard rate of 8%, indicative of the progressive character of the disease. Since in our ICM patients, mean time since last coronary intervention was more than five years, it could be hypothesized that their coronary artery disease has progressed significantly. Furthermore, late non-responders showed significantly less mechanical dyssynchrony at baseline than stable responders, which has previously been associated with non-response and worse survival rates.[2,3]

In the current study, besides IVMD, SRSsept was used to define mechanical dyssynchrony. Our center previously demonstrated that this parameter is a good predictor of volumetric response to CRT as well as clinical outcome.[3,20] In addition, Chan et al.[9] recently demonstrated in their cohort of CRT patients that SRSsept had important additional value for the identification of CRT responders. CRT aims for the correction of dyssynchrony, thereby improving ventricular functioning and reducing heart failure symptoms. Consequently, patients with underlying dyssynchrony are more likely to respond to CRT.[3,21] However, current guidelines do not support mechanical dyssynchrony measurements concerning indication setting for CRT and eligibility for CRT is based on LVEF and measurements of electrical dyssynchrony. Nevertheless, our study did not show significant differences concerning QRS duration or the presence of LBBB between stable responders and late non-responders; implicating that according to current guidelines they were equally suitable to receive a CRT device and a priori would have similar chances of becoming a responder.
Finally, a relatively high share of late non-responders suffered from AF as compared with stable responders. AF is associated with reduced CRT response; however the mechanism remains unclear as AF could be the result of more advanced heart failure, whereas, at the same time, it can reduce biventricular capture. [13] Both advanced heart failure and decreased biventricular capture have been associated with non-response.[14,15]

Six-month characteristics of late non-responders

Late non-responders demonstrated significantly lower volume reductions and BNP did not reduce during the first six months of CRT. This indicates that they had less benefit from CRT compared with stable responders. It has been demonstrated that less reverse remodeling is correlated with an increase in MACE.[22] Moreover, late non-responders showed significantly higher creatinine levels at six months FU. Cardiac and renal functions influence each other and even mild renal insufficiency diminishes prognosis.[23,24] This decline in prognosis arises from many unfavorable changes occurring in patients suffering from renal failure including the activated Renin Angiotensin System, inducing cardiac remodeling.[25] Fung et al. demonstrated that decline in renal function after CRT implantation correlated with higher mortality rates. [26] They stated that the decline in renal function is probably due to the natural course of this disease and that patients with renal failure might require more intensive monitoring and more aggressive treatment. Moreover, in case of renal failure, patients may not tolerate maximum doses of essential medication, which might contribute to reduced reverse remodeling.[27]

Late non-responders showed larger average left atrial volumes, more often demonstrated AF and pacing percentages were significantly lower at six months, the three of which could very well be correlated. In general, patients with AF showed a significantly lower median pacing percentage; 90% vs 99%. At 14 months, late non-responders still more often demonstrated AF than stable responders (33% vs 10%, p = 0.028), whereas median pacing percentages no longer differed significantly; 98% vs 99%, (p = 0.34). Consequently, difference in pacing percentages at six months probably may not contribute to the response conversion in late non-responders, as this improved thereafter. This might implicate a merely modest role for AF concerning the occurrence of late non-response. Especially considering the fact that crossover from response to non-response still occurred in 12% when AF patients were not taken into account. However, the difference in AF burden complicates the interpretation of the influence of AF on late non-response. In addition, the results of this subanalysis have to be interpreted with even more caution as without AF patients sample size is compressed even further. Moreover, despite lower volume reductions, a lack of BNP reduction, higher creatinine levels, higher frequency of AF, and lower pacing percentages, the late non-responders did show relevant reverse remodeling at six months.

Response and health outcomes

At baseline, and six and 14 months FU, late non-responders reported lower health status than stable responders, but the difference was significant at 14 months only. This finding suggests that the correlation between volume response and patient-reported health status increases after six months of CRT.[6] At 14 months, late non-responders on average scored 23 points lower on the KCCQ than stable responders, which is a difference of major importance for patients' daily lives and their prognosis.[28] In addition, response rates at 14 months significantly improved the prediction of MACE for, at least, two years after CRT compared to six months response rates. These results indicate that response assessment after six months of CRT might be a premature moment to assess the long-term treatment effect, especially considering the fact late non-responders had a worse prognosis than stable responders.

Clinical implications

In daily practice the effect of CRT is usually assessed six months after device implantation. However, the high number of late non-responders found in our study indicates that the long term effect of CRT is not yet visible after six months, leading to premature and possibly incorrect conclusions about patients' response to treatment. Patients should be monitored closely after six months of CRT. Our recommendation would be to repeat ECG, echocardiography, laboratory measurements, and health status reports beyond the first year after CRT implantation, in order to be able to consider other interventions in case of deterioration, thereby improving prognosis and preventing early MACE.

Limitations

This is a single-center study in a real-world setting with its inherent limitations. Twelve patients lacked a baseline echocardiographic study and 11 patients had insufficient image quality. In addition, the study is underpowered for multivariable analysis; however, the main focus of this paper was to assess the prevalence of late non-responders. Nevertheless, we would encourage investigating these findings in a larger cohort, in order to confirm our results and to investigate the independent determinants of late (non)response. Moreover, the amount of biventricular pacing was estimated based on the pacing percentage provided by the device. Furthermore, during AF, biventricular pacing could be overestimated because of pseudo-fusion between intrinsic conduction and pacing. Finally, our follow-up period was 14 months, as this was the time point patients came into the clinic for their regular check-up. Yet, as previously addressed, it has been shown that reverse remodeling can continue even thereafter; until 24 months after CRT implantation. [4,5] Therefore, it would be interesting to investigate how response rates develop beyond 14 months of CRT. On the other hand, longer follow-up periods have inherently higher mortality rates causing patients to be lost for analysis.

Conclusion

We demonstrated that 16% of six-month volume responders changes into non-responders after more than 1 year of CRT. Furthermore, 14-month response had a stronger correlation with health outcomes (i.e., patient-reported health status and MACE) than six-month response, indicating that the crossover from responder to non-responder represents a relevant change in patients' health. This knowledge is essential for daily clinical practice as well as for future research projects on CRT as it indicates that the assessment of treatment outcomes after six months of CRT might be premature.

Author Contributions:

Conceived and designed the experiments: HVMM PD. Performed the experiments: HV MM. Analyzed the data: JS AF IH TM MHM. Contributed reagents/materials/analysis tools: TM JS HV MHM WE. Wrote the paper: JS AF IH TM WE MC MHM MM PD HV.

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Chapter 9

GENERAL DISCUSSION

This thesis addresses clinical aspects of cardiac resynchronization therapy (CRT). Prediction and assessment of (volumetric) response were investigated as well as clinical outcome. We analyzed the additional value of echocardiographic parameters of mechanical dyssynchrony as predictors of CRT response besides the generally used electrocardiographic parameters like left bundle branch block (LBBB) and QRS duration and assessed whether latest electrically activated segments also start contracting the latest. Furthermore, we evaluated whether echocardiographic response is accompanied by improved health status and exercise capacity. We also explored whether echocardiographic volumetric response differs at different points in time (i.e. after six and 14 months), and which parameter is best to use as a surrogate outcome marker. Furthermore, it was investigated whether these predictors and surrogate outcome measures are equally applicable for patients with ischemic and non-ischemic cardiomyopathy (ICM and NICM, respectively).

Echocardiography pre CRT & prediction of CRT response

Current guidelines solely comprise electrical measurements of dyssynchrony (QRS duration and morphology), and do not incorporate parameters of mechanical dyssynchrony.[1] As CRT aims for the correction of mechanical problems, the incorporation of parameters of mechanical dyssynchrony was explored in this thesis and it was demonstrated that the addition of interventricular mechanical delay (IVMD) and systolic rebound stretch of the septum (SRSsept) resulted in a model (BLISS), which significantly improved the prediction of reverse remodeling in a cohort of 227 patients (**chapter 3**). In the same chapter we demonstrated that the BLISS model performs significantly better for patients with NICM than for patients with ICM. Although etiology has been previously identified as a predictor for CRT response, prediction models have never been directly compared on their ability to predict response for ICM compared to NICM. Patients with ICM are much more heterogeneous than the NICM group, as location and magnitude of scarred areas differ as well as number of affected coronary arteries.
Therefore, it could be argued to compose separate prediction models for patients with NICM and ICM. For the latter group extend of coronary artery disease and fibrotic area is important to assess before CRT implantation is considered, as this holds information on amount and location of scarred tissue as well as prognosis, in addition the implanter needs to avoid scar tissue for LV lead placement.[2,3]

Moreover, besides improvement in response prediction, improvement of response rates should also be aimed for. For example by optimization of left ventricular (LV) lead position. It has been demonstrated that targeting electrically latest regions or mechanically latest regions improves response to CRT. [4,5] Nevertheless, to our knowledge, it has never been investigated whether timing of electrical activation corresponds to timing of mechanical activation in a population eligible to CRT. In **chapter 4** we demonstrate that latest electrically activated regions show a high correlation with latest mechanically activated regions. Electrical mappings were performed in the coronary sinus and its large side branches, as this is where the LV lead is positioned when transvenous access is possible. Mechanical activation was evaluated by 2D speckle tracking analyses and time to peak strain was assessed. It could be debated whether timing of peak strain is truly the best measure of mechanical activation. Maybe onset of shortening is could be a good alternative. [6] Time to electrical activation is also measured as time to onset of electrical activity in a certain region. Therefore, a comparison with onset of mechanical contraction instead of peak contraction could be better.
However, in practice, the identification of the first subtle onset of contraction can be challenging. In addition, mechanical activation probably occurs before start of shortening as a myocardial segment starts contracting when LV pressure is overcome. Therefore, although our data suggest electrically latest activated segments are also the regions of the heart which are latest mechanically activated, more studies are needed to confirm these findings.

Echocardiography post CRT & clinical outcome

In **chapter 5** we demonstrate that change in LVESV is not a suitable surrogate marker for patients with ICM as this echocardiographic measurement is unable to discriminate between patients with a favorable and with an unfavorable long-term prognosis. Therefore, future studies should focus on other surrogate markers for patients with ICM. Nevertheless, for patients with NICM, change in LVESV was an excellent surrogate outcome marker. These results do not indicate that CRT is only beneficial for patients with NICM and not for patients with ICM, they merely show that change in LVESV is not a suitable surrogate marker in this subpopulation. In meta-analyses of both randomized clinical trials (RCTs) and observational studies it was shown that, according to the pooled analyses of RCTs, both ICM and NICM have a survival benefit of CRT, although the pooled analysis of the observational studies demonstrated that patients with ICM had less survival benefit. [7]
Moreover, this meta-analysis demonstrated that functional improvement of the left ventricle was more prominent in patients with NICM as compared to patients with ICM. This could implicate that the measurement error in ICM regarding LVESV is relatively larger, which might be an explanation for the fact that change in LVESV was not a suitable surrogate outcome marker in ICM. Besides this, it has been demonstrated that survival of patients with ICM depends mostly on scar burden. [3]

Therefore, magnetic resonance imaging (MRI) as the current gold standard for infarct and fibrosis determination, might be considered before CRT implantation, not only for prognostic purposes, but also for the identification of a suitable area for the LV lead, as the presence of scar in the pacing region is another important determinant of long-term outcome.[8]
In addition, coronary artery disease is a progressive disease, also influencing event rate. [9] This might also explain why (solely) reverse echocardiographic volumetric remodeling is not suitable to predict outcome in patients with ICM. Furthermore, in 25% of patients disease extends beyond the coronary arteries, which may affect prognosis as well. [10]

Furthermore, in **chapter 6** we investigated whether significant reverse remodeling also improves exercise capacity. We found that echocardiographic responders also improved their exercise capacity, whereas none of the echocardiographic non-responders did. Also, we showed how patients perceive their own physical health status influences their performance on the exercise test. Furthermore, we demonstrated that the perceived health status of so called non-responders could improve, suggesting that these patients might still experience benefit from CRT in their daily lives, although no 'objective' improvement in echocardiographic volumes was found. On the other hand in **chapter 7** we found that only 57% of patients demonstrating significant reverse remodeling also show improved health status, whereas 53% of the patients demonstrating a positive health status response, did not show significant reverse remodeling. Patients demonstrating an echocardiographic response without a health status response on average showed a lower end systolic volume at baseline and more often were employed than patients with a concordant response. This could indicate that in patients with low baseline LV volumes, a 15% LVESV reduction is not enough to experience an increased quality of life. Patients demonstrating a positive health status response without an echocardiographic response more often were female and had lower baseline health status scores. The latter might indicate that in lower health scores, there is more room for improvement, and the experienced increase in health status is better.
The results suggest that when patients demonstrate significant reverse remodeling and do not yet experience improved health status or exercise capacity, this might improve when, for example, rehabilitation (physical training program and/or psychological support) is offered.

Subsequently, in **chapter 8** we demonstrated that 14-month response rates (based on presence of reverse remodeling) correspond significantly better with long-term outcome than six months response rates. This could partly be explained by the fact that the complete effect of CRT is probably not visible yet after 6 months and might be more reliably assessed after 14 months. It has been demonstrated previously that the process of reverse remodeling after CRT implantation continues up to 18-24 months. [11,12]

It would be interesting to conduct a study with response assessment at more points in time, in order to evaluate the best time span to measure response. In current guidelines no definite statement is made on how response to CRT should be expressed and at which time interval this should be performed.

In addition, we showed that 16% of the initial cohort changes from a responder at six months to a non-responder at 14 months. Due to limited patient numbers we were unable to perform multivariable analysis. Nevertheless, these so-called late non-responders were mostly male patients with ICM and showed only minimal presence of mechanical dyssynchrony at baseline. However, there were no differences in parameters of electrical dyssynchrony at baseline: QRS duration and morphology were similar among late non-responders and stable responders. The latter group comprised patients who were responder at both six and 14 months. These findings also support the addition of parameters of mechanical dyssynchrony to CRT guidelines, as they indeed seem to identify long-term CRT responders.

Clinical decision making

In case of insufficient echocardiographic windows, it could be recommended to perform an MRI prior to CRT implantation to assess LV volumes, function and scar tissue. First, MRI is nowadays the gold standard for the assessment of LV volumes and function. [13] Although assessment of LV volumes and function after CRT implantation might be disturbed by artifacts caused by the device and intracardiac leads, it is becoming feasible with the latest MRI conditional CRT systems (only with 1.5 Tesla). The use of MRI to assess the extent of (reverse) remodeling might lead to more reliable assessment of the effect of CRT. In addition, MRI can localize and quantify scar tissue, which is important for prognosis as well as determination of the LV lead location. Furthermore, we demonstrated that measurements of mechanical dyssynchrony could aid the prediction of reverse remodeling, therefore we would recommend to take some of these measures (e.g. IVMD and SRSsept) into account when screening patients on their eligibility for CRT. Moreover, as CRT also aims for clinical improvement, assessment of patient perceived health status before and after implantation is important to evaluate whether this goal is reached, particularly since we showed that echocardiographic response differs from health status response and we demonstrated that echocardiographic non-responders might still show a significant improvement of their health status.
In addition patient perceived health status holds much more information than NYHA classification, assigned by the physician. [14,15] Lastly, we would recommend to assess LV volumes and EF every 6 months up to at least 24 months after implantation in order to assess ongoing (non-)response.

Future perspectives

Cardiac resynchronization therapy is a dynamic area of research. Currently, it is still under debate which patients benefit from CRT and it remains difficult to predict response. Important challenges are the lack of good predictive and surrogate markers for response, which might partly be attributed to the fact that patients eligible to CRT comprise a very heterogeneous group. A first step could possibly be to distinguish between patients with NICM from ICM in future studies and perform specific research on both different patient groups as these are two complete different entities. This might aid the search for reliable predictors and surrogate markers, as these could be etiology dependent. Moreover, current guidelines do not state a preferred modality for the assessment of objective and subjective effects of CRT. Most studies use echocardiographic imaging to assess the objective effect of CRT on the LV and NYHA class to assess clinical improvement. [16-20] However, good image quality is sometimes difficult to achieve, especially in case of (severely) dilated hearts, bothering assessment of images in very ill patients. This effects both the evaluation of LV function as well as assessment of predictive markers. In clinical practice, besides 2D echocardiography, also MRI, SPECT or 3D echocardiography might be used. As there is disagreement between different modalities and vendors concerning the quantification of ventricular function and other measurements, applying different modalities might also hamper prediction and assessment of response. Therefore, it is of utmost importance to standardize the mode of assessment and to aim for optimal image quality in future (multi-center) studies. Furthermore, we should also focus on (improved) patient perceived health status, not NYHA classification assigned by the physician.[14,15]

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NEDERLANDSE SAMENVATTING

Hartfalen is een syndroom waarbij de pompfunctie van het hart tekort schiet; het hart kan onvoldoende bloed rondpompen om aan de zuurstofvraag van (perifere) weefsels te voldoen. Als gevolg hiervan ontstaan symptomen als kortademigheid, dikke enkels, gewichtstoename en moeheid. Met het ouder worden van de bevolking neemt ook het aantal patiënten met hartfalen toe. Op dit moment komt hartfalen voor bij 1-2% van onze bevolking, waarvan 80% een leeftijd heeft boven de 65 jaar. Zolang de zorg voor acute patiënten (met name de zorg voor patiënten met een hartinfarct) verbetert, zal ook het aantal gevallen van hartfalen blijven toenemen. Naar schatting zal 20% van de huidige populatie hartfalen ontwikkelen gedurende zijn of haar leven. Deze aantallen geven aan dat hartfalen een belangrijk gezondheidsprobleem is en blijft. Hartfalen heeft een relatief slechte prognose; 75% van de patiënten overlijdt binnen 5 jaar na het stellen van de initiële diagnose. De zorgkosten voor hartfalen stijgen met toename van de prevalentie en beslaan op dit moment 1-3% van de totale kosten van de gezondheidszorg en worden met name veroorzaakt door (veelvuldige) ziekenhuisopnames.

Bij hartfalen kan er een probleem zijn met de systolische of diastolische functie van het hart. De systole van het hart is de fase waarin het hart samenknijpt en het bloed vanuit de linker kamer de lichaamsslagader in wordt gepompt en vanuit de rechter kamer de longslagaders in wordt gepompt. De diastole van het hart is de fase waarin het hart weer ontspant en de linker en rechter kamer zich kunnen vullen met bloed vanuit de boezems. Bij systolisch hartfalen zit het probleem in de pompfunctie van het hart door een verminderde knijpkracht en bij diastolisch hartfalen is er een probleem met de vulling van het hart door stijfheid van de linker kamer. Het doel van hartfalen therapie is het verminderen van symptomen, verbeteren van de prognose en ziekenhuisopnames te voorkomen en reduceren.

In 30% van de patiënten met hartfalen komt geleidingsvertraging binnen het hart voor, vaak veroorzaakt dit zogenoemde ‘asynchronie’ tussen de linker en rechter kamer; de rechter kamer knijpt samen voordat de linker kamer dit doet.
Deze asynchronie kan de pompfunctie van het hart verder verslechteren en zodoende de symptomen van hartfalen verergeren. In deze patiëntengroep is cardiale resynchronisatie therapie (CRT) soms een optie; indien symptomen aanhouden ondanks optimale medicamenteuze therapie en de pompfunctie (de systolische functie) slecht blijft. Echter, tot op heden blijft het lastig te voorspellen welke van deze patiënten goed reageren op deze therapie en welke niet. CRT is een pacemaker met draden in de rechter en linker kamer en soms nog een draad in de rechter boezem. Daarom kan een CRT pacemaker een elektrisch signaal afgeven in beide kamers en op deze manier zorgen dat beide kamers weer tegelijk samentrekken; dit heet resynchronisatie.

Deel 1: Echocardiografie vooraf aan CRT implantatie en voorspellen van CRT response

In deel één van dit proefschrift worden vraagstukken besproken die van belang zijn vooraf aan implantatie van een CRT pacemaker om response te optimaliseren. Er bestaat geen eenduidige definitie voor CRT response in de richtlijnen. Een veel gebruikte maat is de afname van het eind systolisch volume (ESV) 6 maanden na CRT implantatie. In de huidige richtlijnen over CRT worden alleen elektrocardiografische (ECG) kenmerken van geleidingsvertraging meegenomen als het gaat om indicatiestelling voor een CRT pacemaker. Wij laten in hoofdstuk 3 zien dat wanneer echocardiografische parameters (metingen die kunnen aantonen of er mechanische asynchronie is) worden toegevoegd aan ECG parameters, response op CRT significant beter te voorspellen is dan wanneer enkel ECG parameters worden meegenomen.

Naast het voorspellen van response, is ook het verbeteren van de response van belang. Tot nu toe is het zo dat ongeveer 30% van de patiënten bij wie een CRT pacemaker wordt geïmplanteerd geen ESV afname te zien is. Een oorzaak van deze zogeheten non-response kan zijn de locatie van de linker kamer draad zijn. Als deze niet op de optimale plaats ligt, is er minder response te verwachten. De voorkeurslocatie voor de linker kamer draad is het laatst geactiveerde gebied in de linker kamer. Dit is het gebied waar het elektrisch signaal het laatste aankomt. Echter, tot op heden is er geen consensus over de methode welke gebruikt dient te worden om het laatst geactiveerde gebied te bepalen. Sommige studies gebruiken elektrische mappings en meten dus in de linker kamer waar het elektrisch signaal het laatst wordt opgevangen, andere studies bepalen het laatst geactiveerde gebied op basis van (echocardiografische) contractiepatronen, wat minder invasief is. In hoofdstuk 4 laten we zien dat er een hoge correlatie bestaat tussen elektrisch en mechanisch laatst geactiveerde gebieden, dat wil zeggen: vaak zijn de elektrisch laatst geactiveerde gebieden ook de gebieden die het laatst gaan samentrekken. In theorie zou dit kunnen betekenen dat beide methodes gebruikt kunnen worden om het laatst geactiveerde gebied te bepalen, echter hier dient nog meer onderzoek naar gedaan te worden.

Deel 2: Echocardiografie na CRT implantatie en klinische uitkomst

ESV afname 6 maanden na CRT implantatie wordt frequent gebruikt als uitkomstmaat voor CRT response. Wij tonen aan in hoofdstuk 5 dat ESV een goede maat is om onderscheid te maken tussen patiënten die een goede en een slechte klinische uitkomst hebben op langere termijn voor patiënten met een niet-ischemische cardiomyopathie.
Echter, voor patiënten met een ischemische cardiomyopathie is dit geen goede maat; daar kan afname van ESV geen onderscheid maken tussen patiënten met een goede en een slechte klinische uitkomst. Waarschijnlijk komt dat doordat in deze patiëntengroep andere factoren (zoals kransslagvatlijden) een veel belangrijker rol spelen voor wat betreft de prognose op de langere termijn.

In hoofdstuk 6 hebben we wel aangetoond dat patiënten die ESV afname laten zien ook een betere inspanningscapaciteit hebben na CRT implantatie. Aan de andere kant zagen we dat patiënten die geen significante afname van ESV lieten zien geen van allen verbeterden qua inspanningscapaciteit, hoewel zij tegelijkertijd wel een toename van levenskwaliteit konden hebben. Dit toont aan dat alleen objectieve parameters ter bepaling van CRT response niet altijd afdoende zijn en ook niet het complete effect van CRT weergeven. Dit vonden wij ook in hoofdstuk 7, waarbij we lieten zien dat slechts 57% van de patiënten met een significante afname van het ESV hun levenskwaliteit als beter beoordeelden ten opzichte van voor CRT implantatie. Terwijl 53% van de patiënten die een verbetering van hun levenskwaliteit rapporteerden geen significante afname van hun ESV hadden.

Tot slot hebben we in hoofdstuk 8 gekeken naar ESV afname op langere termijn. Hierbij bleek dat 16% van de patiënten die ESV afname laten zien 6 maanden na CRT implantatie, na 14 maanden toch toename van hun ESV hadden en dus in tweede instantie geen responder bleken te zijn. Deze groep noemen we late non-responders. Late non-response kwam in ons cohort vooral voor bij mannen met een ischemische cardiomyopathie die voor implantatie weinig tekenen van asynchronie hadden.

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Tot slot: Mijn paranimfen: **Rosemarijn** en **Joost**!

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