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New insight into device therapy for chronic heart failure

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New insights into device therapy for chronic heart failure

Claudia Ypenburg

The studies described in this thesis were performed at the department of Cardiology of the Leiden University Medical Center, Leiden, the Netherlands

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New insights into device therapy for chronic heart failure

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Voor David en Finn

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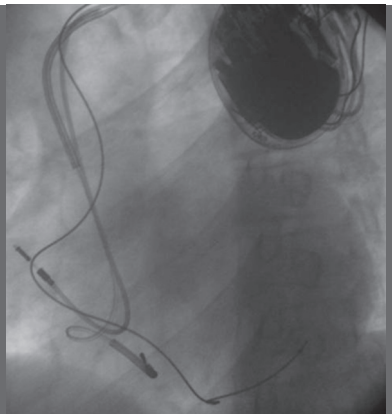
Chapter 1



General introduction and outline of the thesis

10

INTRODUCTION

Chronic heart failure - prevalence and prognosis

Heart failure is a clinical syndrome that results from a structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood (1,2). The damage to the myocardium is in the majority of patients caused by ischemic heart disease, due to a previous myocardial infarction or chronic ischemia. Other reasons include persistent overload, such as in hypertension or valvular disease, or loss of functional myocardium due to myocarditis or tachycardia. Importantly, this syndrome constitutes a major health problem worldwide. The estimated prevalence of symptomatic heart failure in Europe varies from 0.4% to 2% of the general population, with a significant increase of the prevalence with age. Currently, in the Netherlands 176.000 patients are diagnosed with heart failure with an incidence of 40.000 per year (3). Since the proportion of elderly is increasing and the incidence of hypertension, diabetes and obesity is growing, a significant rise of the prevalence of heart failure can be expected in the coming decades.

Clinical presentation of heart failure patients ranges from asymptomatic left ventricular (LV) dysfunction to a severe form with disabling resting symptoms. New York Heart Association (NYHA) classification is most often used assess the severity of heart failure symptoms (Table 1) (1,2). At present, 2% of all hospital admissions (medical and surgical) and 5% of all medical

Table 1. New York Heart Association Classification of Heart Failure

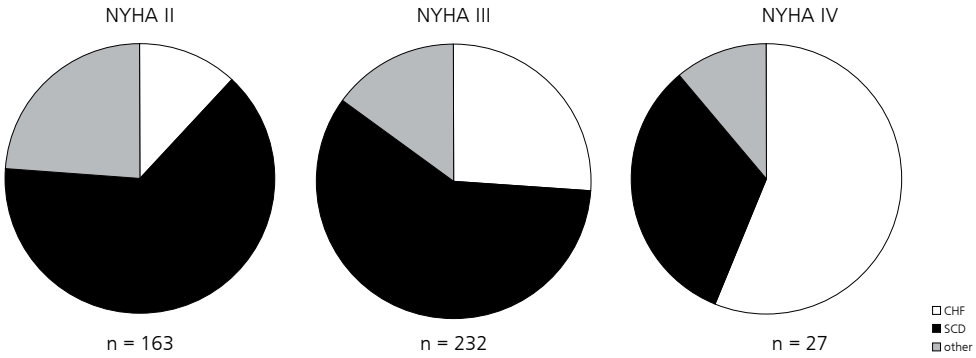
Class I	No limitation: ordinary physical exercise does not cause undue fatigue, dypnea or palpitations
Class II	Slight limitation of physical activity: comfortable at rest but ordinary activity results in fatigue, dyspnea or palpitations
Class III	Marked limitation in physical activity: comfortable at rest but less than ordinary activity results in symptoms
Class IV	Unable to carry out any physical activity without discomfort: symptoms of heart failure are present even at rest with increased discomfort with any physical activity

admissions are heart failure related (3). The prognosis of heart failure is poor; approximately 50% of patients diagnosed with heart failure die within four years, and within one year in case of severe heart failure. Although the cause of death is heart failure-related in most patients with advanced symptoms, a significant proportion will die suddenly and unexpectedly due to ventricular arrhythmias (1,2). More severe heart failure is associated with a higher overall mortality rate but with a decreasing proportion of sudden cardiac death. This was illustrated in the MERIT-HF trial in which patients in NYHA class II, III and IV showed respectively a decreasing percentage of deaths that were classified as sudden cardiac death (64, 59, and 33%, Figure 1) (4).

Furthermore, NYHA class is identified as a major determinant of heart failure outcome. Data from the SOLVD (Studies of LV Dysfunction) and the CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) trials reported that mortality rates were related with the severity of symptoms (5,6); NYHA class I patients showed mortality rates of 19% whereas NYHA class IV patients demonstrated mortality rates of 64% at 4-years follow-up. Next to clinical symptoms, echocardiographic parameters have been proposed as important determinants of heart failure outcome. A study in 605 post myocardial infarction patients demonstrated that enlargement of the LV with an end-systolic volume (ESV) >130 ml was associated with ~50%

Figure 1. Severity of heart failure and mode of death

Data from the MERIT-HF study (4) showed that with a more progressive stage of heart failure relatively more patients died from progressive pump failure than from sudden cardiac death.
CHF: congestive heart failure; SCD: sudden cardiac death.



mortality at 7-years follow-up (7). The same study also showed that systolic LV dysfunction (ejection fraction [EF] <40%) was associated with ~45% mortality at 7-years follow-up.
Beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and aldosterone antagonists have been shown to improve NYHA class, LVESV and LVEF in patients with heart failure, thereby effectively reducing morbidity and mortality (1,2). However, despite these advances in the pharmacological treatment of heart failure, prognosis remains poor. In the last decade, several non-pharmacological therapies such as implantable cardioverter-defibrillator (ICD) and biventricular pacing known as cardiac resynchronization therapy (CRT) have been proposed as an additional therapy for patients with LV dysfunction and drug-refractory heart failure.

Chronic heart failure - CRT

The clinical use of CRT began in the early 1990's in by Cazeau et al in France with the first cases of biventricular pacemaker implantation in patients with severe heart failure without a conventional indication for cardiac pacing (8). The first patient was a 54-year old man who received a four-chamber pacing system for severe congestive heart failure (NYHA class IV). The patient had ventricular dyssynchrony evidenced by left bundle branch block (LBBB) and 200 ms QRS duration on 12 leads electrocardiogram (ECG) and atrio-ventricular dyssynchrony in the form of 200 ms PR interval. An acute hemodynamic study with insertion of four temporary leads was performed prior to the implant which demonstrated a significant increase in cardiac output and decrease of pulmonary capillary wedge pressure (8). Similar data was reported at the same time by Bakker and colleagues in the Netherlands (9). In both of these early experiences, the LV lead was implanted epicardially by thoracotomy. Daubert and colleagues first described the transvenous approach through the coronary veins in 1998 (Figure 2) (10). Few years later, CRT alone or with combination with an implantable cardioverter-defibrillator (ICD) has become a largely validated treatment for heart failure patients with a moderate to severe heart failure and pre-implantation electrical dyssynchrony.

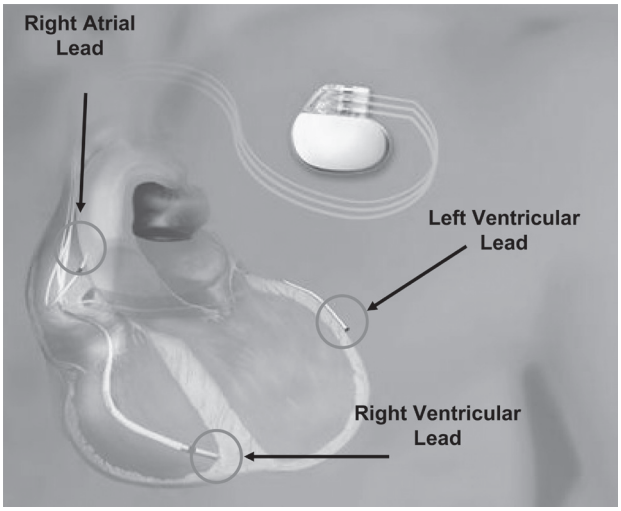


Figure 2. Position of the three pacing leads in cardiac resynchronization therapy

One lead is positioned in the right atrium (RA lead). One lead is placed in the right ventricle, usually the apex (RV lead), and the last lead will be placed on the LV (postero)lateral free wall through the coronary sinus (LV lead).

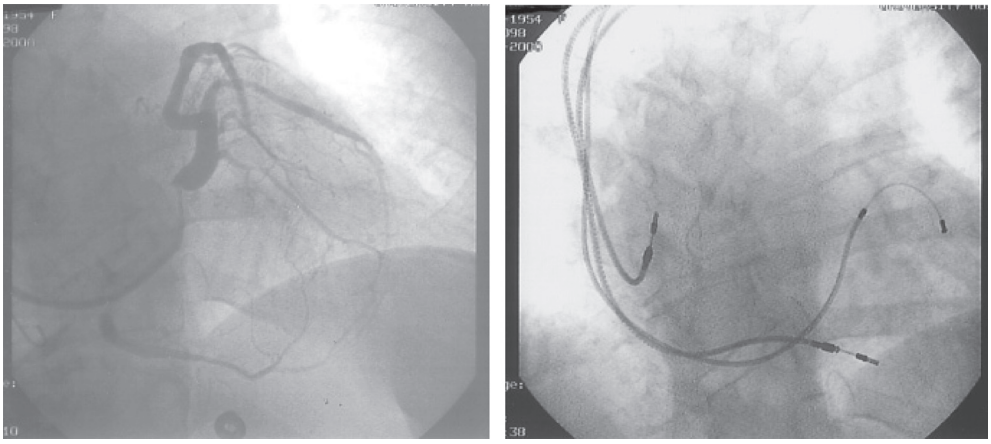
Mechanisms of CRT

In patients with heart failure, LV function is not only affected by depressed contractile function or abnormal loading conditions (or both), but also by a dyssynchronous activation of the heart, resulting in inefficient LV pumping (11). The rationale for CRT involves atrio-ventricular, inter-ventricular and intra-ventricular resynchronization, thereby improving LV pump performance and reversing the deleterious process of ventricular remodeling.

To achieve resynchronization, three different pacing leads are implanted: one lead will be inserted in the right atrium, on in the right ventricle (usually the apex) and the third one will be placed via the coronary sinus on the LV (postero)lateral free wall (Figure 3) (12). In some cases the LV pacing lead will be placed directly on the epicardial LV free wall by minimal invasive surgery. Lastly, the three leads will be connected to a biventricular device.

Figure 3. Anatomy of the coronary sinus

Left panel demonstrates a coronary sinus venogram; the LV lead is placed via the coronary sinus in a cardiac vein, preferably a lateral or postero-lateral vein in the mid part of the LV. Coronary venous anatomy varies significantly between patients. In a small percentage of cases it may not be possible to place the left ventricular lead transvenously. Standard pacing leads are placed in the right atrium and right ventricle. The right panel shows a fluoroscopy view after implantation of the three pacing leads.



Intra-ventricular resynchronization can be achieved by simultaneously stimulating the inter-ventricular septum (RV pacing lead) and the LV lateral wall (LV lacing lead) resulting in a coordinated septal and free wall contraction, and thus improved LV pumping efficiency. In addition, atrio-ventricular resynchronization allows for optimization of the AV delay between atrial and LV pacing leads. By modulating the preload, this will result in an effective LV filling period. Moreover, inter-ventricular resynchronization can be achieved via either simultaneous or sequential left and right ventricular pacing and will improve the dyssynchronous contraction between the left and right ventricle.

In addition, ventricular arrhythmias are frequently observed in patients with depressed LV function, and of more importance, the most common cause of sudden cardiac death in heart failure patients. In order to prevent sudden cardiac death the majority of CRT devices are now combined with ICD back-up in the same device (13,14).

Clinical evidence of CRT

The efficacy and safety of CRT in drug refractory heart failure patients have been widely investigated. Eight large randomized trials including ~3.800 heart failure patients have demonstrated that CRT is an effective and safe procedure for selected heart failure patients (Table 2) (15). The effects of CRT include immediate hemodynamic benefit on LV performance, but also improvement in heart failure symptoms, exercise capacity and quality of life were reported after one-three months after implantation (16-18). In addition, an improved contractile function was noted after only a few months of pacing (Figure 4). In the CARE-HF (Cardiac Resynchronization Heart Failure) trial LVEF improved from a median of 25% by 3.7% at 3 months and by 6.9% at 18 months (17). Furthermore, CRT was associated with reverse remodeling as demonstrated by significant reductions in LV volumes en mitral regurgitation jet area. In a follow-up study of the MIRACLE (Multicenter Insync Randomized Clinical Evaluation) trial these favorable changes persisted at 12 months (19). Moreover, long-term follow-up revealed less hospitalizations for heart failure and reduced mortality (Figure 5) (17,18). Based on the results of these trials, CRT is now considered a class I (level of evidence A) indication for patients with moderate-to-severe heart failure (NYHA class III or IV), QRS duration ≥120 ms, and LVEF ≤35% despite optimal medical therapy (Table 3) (2). Most patients who satisfy these criteria are also candidates for an ICD and receive a combined device, and the 2006 American College of Cardiology/ American Heart Association/ European Society of Cardiology guidelines for the management of ventricular arrhythmias and the prevention of SCD suggest a CRT-D device (biventricular pacing combined with an ICD) in this setting (20).

Many small observational studies also reported improvement in diastolic function, myocardial efficiency, RV function, pulmonary wedge pressure, mitral regurgitation, reduced frequency of atrial and ventricular arrhythmias (21-26). In addition, beneficial effects have been demonstrated in patients with a previous pacemaker, patients with paroxysmal or permanent atrial fibrillation, patients with less severe heart failure (NYHA II), patients with a narrow QRS complex.

Non-response to CRT

Despite the success of CRT as evidently demonstrated in randomized and observational studies a consistent percentage of patients failed to benefit when the above selection criteria were used, the so-called “non-responders”. The prevalence of non-responders is around 30% when

Table 2. Outcome of CRT in randomized clinical trials

All trials included patients with LVEF ≤35%, NYHA class III or IV, QRS ≥120-130 ms (except for the MUSTIC-SR who included patients with QRS >150 ms).

	No. of patients	Clinical improvement	Functional improvement
PATH-CHF (30)	41	NYHA class QOL 6MWT Less hospitalizations	
PATH-CHF II (31)	86	QOL 6MWT Peak VO2	
CONTAK-CD (32)	490	NYHA class QOL 6MWT	LVEF LV volumes
MUSTIC-SR (33,34)	58	NYHA class QOL 6MWT Peak VO2 Less hospitalizations	LV volumes MR
MIRACLE (16)	453	NYHA class QOL 6MWT	LVEF LVEDD MR
MIRACLE-ICD (35)	362	NYHA class QOL	
COMPANION (18)	1520	Reduced all-cause mortality/ hospitalization	
CARE-HF (17)	813	NYHA class QOL Reduced mortality/ morbidity	LVEF LVESV

CARE-HF: Cardiac Resynchronization-Heart Failure; CONTAK-CD: CONTAK-Cardiac Defibrillator; COMPANION: Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure; CRT: cardiac resynchronization therapy; EDD: end-diastolic dimension; EF: ejection fraction; ESV: end-systolic volume; LV: left ventricular; EDD: end-diastolic dimension; EF: ejection fraction; ESV: end-systolic volume; MIRACLE: Multicenter InSync Randomized Clinical Evaluation; MIRACLE-ICD: Multicenter InSync Implantable Cardioverter Defibrillator trial; MR: mitral regurgitation; MUSTIC: Multisite Simulation in Cardiomyopathies; NYHA: New York Heart Association; PATH-CHF: Pacing Therapies in Congestive Heart Failure trial; QOL: quality-of-life score; VO2: volume of oxygen; 6MWT: 6-minute walking test.

Table 3. Current CRT selection criteria

NYHA class III or IV
LVEF <35%
QRS duration >120 ms
Sinus rhythm
Optimal standard medical therapy for HF

HF: heart failure; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association

Figure 4. CRT improves LV function

Example of LV reverse remodeling after 6 months of CRT; the LV end-systolic volume decreased from 222 ml to 140 ml.

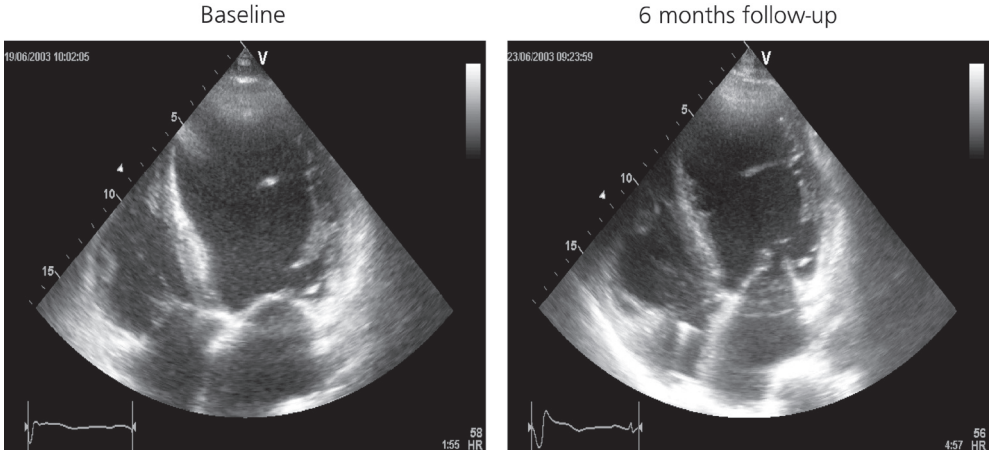
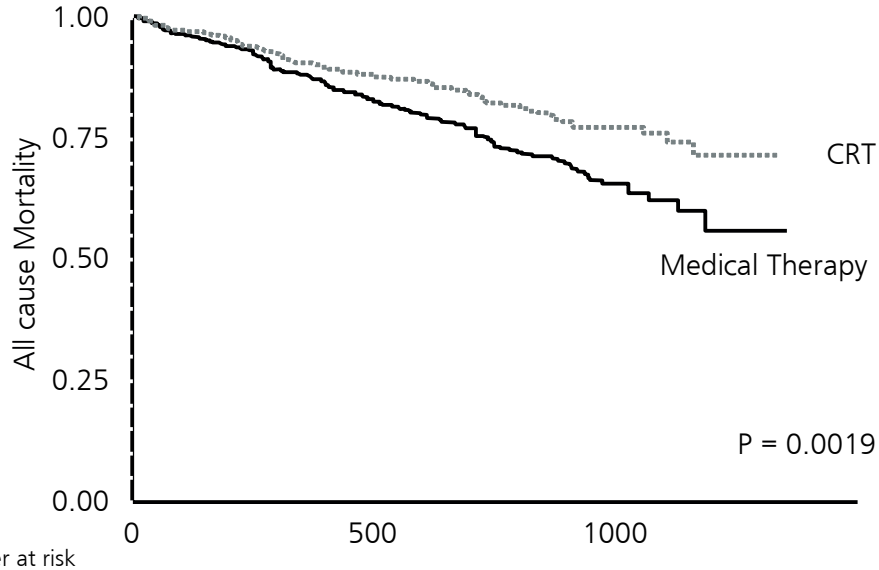


Figure 5. CRT improves survival

Kaplan-Meier curves of the time to all-cause mortality (optimal medical therapy vs. CRT without ICD) in the CARE-HF trial. Adapted from Cleland et al (17).



Number at risk						
CRT	409	376	351	213	89	8
Medical Therapy	404	365	321	192	71	5

clinical end-points are used (e.g. improvement in NYHA class, exercise capacity) (16), but can be much higher (40-50%) when echocardiographic end-points (e.g. reduction in LV volumes, improvement in LV function) are used (27).
Previous studies have demonstrated that QRS duration does not reflect a dyssynchronous contraction within the LV (28,29). This may explain why mechanical dyssynchrony (as measured with tissue Doppler echocardiography between the septal and lateral free wall) is a better predictor of CRT response than electrical dyssynchrony (as measured by QRS duration). Presence of dyssynchrony appeared to be one of the key factors for response to CRT.
Generally, the reasons of non-response to CRT can be classified at two levels: before and after CRT device implantation. The issues before implantation include the selection of "wrong" patients, such as lack of mechanical dyssynchrony, scar tissue or placement of the LV lead at the "wrong" site. Other potential issues can be seen after device implantation such as lack of optimization of LV filling due to a prolonged atrio-ventricular interval.

OUTLINE OF THE PRESENT THESIS

The high number of non-responders requires readjustment of the current selection criteria. In addition, the exact mechanism and effects of CRT on echocardiographic and clinical parameters such as mitral regurgitation, strain and incidence of ventricular arrhythmias are currently unknown. The aim of the present thesis was to further explore these issues using varying non-invasive imaging techniques such as echocardiography, nuclear imaging, magnetic resonance imaging as well as device-based diagnostics.
In part I the issues before device implantation are presented, focusing on a better selection for CRT, including dyssynchrony, scar tissue and lead position. In Chapter 2 a novel echocardiographic technique called speckle tracking was compared to conventional color-coded tissue Doppler imaging to determine the extent of LV dyssynchrony and to predict response to CRT. Chapter 3 further extents the use of tissue Doppler imaging by demonstrating the importance of reduction in dyssynchrony after device implantation. Chapters 4-7 report on the value of viable myocardium in the LV (extent, location and contractile reserve) in order to improve LV function after CRT. Next, LV lead position was related to a dyssynchrony model in order to determine the lead position resulting in the best prognosis in Chapter 8. Lastly, Chapter 9 presents an extensive review on non-invasive imaging before CRT device implantation, particularly focusing on the various echocardiographic techniques on the assessment of LV dyssynchrony, but also including information described in chapter 2-8.
In part II, issues after device implantation were evaluated. In Chapter 10, the extent of reverse remodeling after mid-term follow-up was related to long-term prognosis after CRT device implantation. In chapter 11, the effect of CRT interruption after LV reverse remodeling was studied. Chapter 12 describes the effect of CRT on global LV strain using a novel echocardiographic technique automated function imaging. The effect of CRT on mitral regurgitation was investigated in Chapter 13 and 14 and related to the presence and reduction of LV dyssynchrony after CRT implantation. Device-based diagnostics were evaluated in chapter 15, incidence of ventricular arrhythmias in CRT patients, and Chapter 16, use of intrathoracic impedance to detect heart failure. Chapter 17 contains an extensive review on non-invasive imaging after CRT including evaluation of effects and device optimization.

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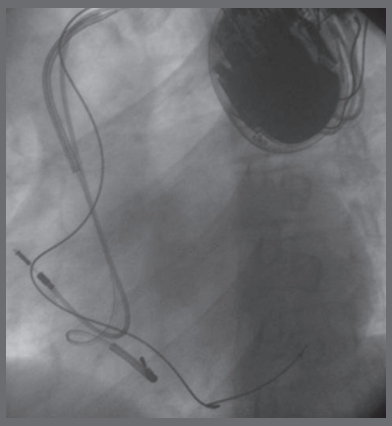
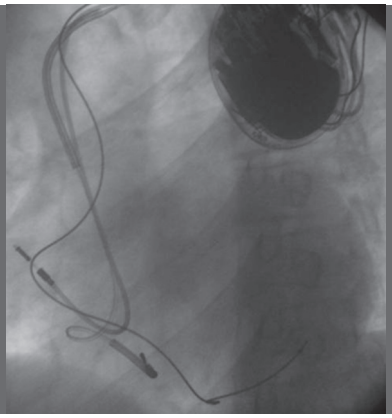


Part I

ISSUES BEFORE DEVICE IMPLANTATION

Chapter 2



Assessment of left ventricular dyssynchrony by speckle tracking strain imaging: comparison between longitudinal, circumferential and radial strain in cardiac resynchronization therapy patients

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ABSTRACT

Introduction Different echocardiographic techniques have been proposed for the assessment of left ventricular (LV) dyssynchrony. The novel 2D speckle tracking strain analysis technique can provide information on radial (RS), circumferential (CS) and longitudinal strain (LS). Aim of the study was to assess the usefulness of each type of strain for LV dyssynchrony assessment and their predictive value for a positive response after cardiac resynchronization therapy (CRT). Furthermore, changes in extent of LV dyssynchrony for each type of strain were evaluated during follow-up.

Methods In 161 patients, 2D echocardiography was performed at baseline and after 6 months of CRT. Extent of LV dyssynchrony was calculated for each type of strain. Response to CRT was defined as a decrease in LV end-systolic volume ≥15% at follow-up.

Results At follow-up, 88 patients (55%) were classified as responders. Differences in baseline LV dyssynchrony between responders and non-responders were only noted for RS (251±138 ms vs. 94±65 ms; P<0.001), whereas no differences were noted for CS and LS. A cut-off value of ≥130 ms for RS was able to predict response to CRT with a sensitivity of 83% and a specificity of 80%. In addition, a significant decrease in extent of LV dyssynchrony measured with RS (from 251±138 ms to 98±92 ms; P<0.001) was demonstrated only in responders.

Conclusions Speckle tracking radial strain analysis constitutes the best method to identify potential responders to CRT. Reduction in LV dyssynchrony after CRT was only noted in responders.

INTRODUCTION

By stimulating the right ventricle and the postero-lateral wall of the left ventricle (LV), cardiac resynchronization therapy (CRT) has been shown to decrease LV volumes, increase LV systolic function and improve clinical status in patients with end-stage heart failure (1). However, in previous studies, the percentage of non-responders is more than 30% when response to CRT is defined by echocardiographic criteria (e.g. LV reverse remodeling) (2). The lack of mechanical LV dyssynchrony has been suggested as one of the reasons for non-response to CRT (3).
In recent years various imaging techniques have been tested for their ability to quantify LV dyssynchrony and for their predictive value for response to CRT, including magnetic resonance imaging, nuclear imaging and echocardiography (3-7). Most experience has been obtained with echocardiography using color-coded tissue Doppler imaging (TDI) by measuring peak systolic velocities in different segments of the LV. Several studies in CRT patients proved that TDI was highly predictive for response to CRT and event-free survival at 1-year follow-up (3, 5, 8, 9).
Speckle tracking strain analysis is a novel method based on gray-scale 2-dimensional (2D) images, which permits the assessment of myocardial deformation in two dimensions. Using apical and parasternal short-axis views, three different patterns of myocardial deformation can be assessed; radial strain (RS) represents the myocardial thickening in a short-axis plane; circumferential strain (CS) represents myocardial shortening in a short-axis plane; and longitudinal strain (LS) represents the myocardial shortening in the long-axis plane (10). To date, few studies used either RS, CS or LS to asses LV dyssynchrony, and it is currently unclear which type of strain used for LV dyssynchrony assessment best predicts response to CRT (11-14). Furthermore, data on changes in LV dyssynchrony after CRT according to the different strain types are scarce.
Therefore, using 2D speckle tracking echocardiography, the aims of the present study were: 1) to determine which type of strain for assessment of LV dyssynchrony best predicts echocardiographic response after 6 months of CRT and, 2) to evaluate changes in LV dyssynchrony as derived from RS, CS and LS, after 6 months of CRT. In addition, the predictive value of the strain parameters was compared to the established value of TDI (3).

METHODS

Population and study protocol

One-hundred sixty-one consecutive patients who were scheduled for CRT were included in the present study. The current selection criteria used for CRT included: drug-refractory symptomatic heart failure, with patients in New York Heart Association (NYHA) functional class III or IV, and depressed LV ejection fraction (EF, ≤35%) with wide QRS complex (>120 ms) (15). The study protocol included evaluation of clinical status and transthoracic echocardiography before CRT implantation with follow-up evaluation after 6 months of CRT.

Device implantation

The coronary sinus was cannulated with the use of a guiding balloon catheter and a venogram was obtained. Thereafter, the LV pacing lead (Easytrak 4512-80, Guidant Corporation, St. Paul, Minnesota; or Attain-SD 4189, Medtronic Inc., Minneapolis, Minnesota) was inserted into the coronary sinus, and positioned in a lateral or posterolateral vein. The right atrial and ventricular leads were traditionally positioned and all leads were connected to a dual-chamber biventricular implantable cardioverter-defibrillator (Contak CD or TR, Guidant Corporation; or Insync III or CD, Medtronic Inc.).

Clinical follow-up

Clinical status was evaluated at baseline and after 6 months of follow-up. Assessed parameters included NYHA class, quality-of-life score according to the Minnesota Living with Heart Failure questionnaire (16), and 6-minute walking distance (17).

Echocardiography

Baseline and follow-up echocardiographic studies were performed with the patient in the left lateral decubitus position using commercially available equipment (Vingmed Vivid-7, General Electric Vingmed, Milwaukee, Wisconsin, USA). Data acquisition was performed with a 3.5-MHz transducer at a depth of 16 cm in the parasternal and apical views (standard 2- and 4-chamber images). Standard 2D images were obtained during breath hold and stored in cineloop format from 3 consecutive beats. LV diameters were obtained from the M-mode images acquired from the parasternal long-axis view. LV end-diastolic (EDV) and end-systolic volume (ESV) were measured from the apical 2- and 4-chamber views and the LVEF was calculated using the Simpson's rule (18). Furthermore, LV volumes were indexed to the body surface area. LV diastolic function was evaluated by the mitral inflow pattern obtained by pulsed-wave Doppler echocardiography, and classified as normal filling, abnormal relaxation, pseudonormal filling or restrictive filling pattern (19).

In addition, conventional color-coded TDI was performed to determine LV dyssynchrony (EchoPac 6.1, GE Medical Systems, Horten, Norway) (3). The sector width and the depth were adjusted to obtain the highest frame rate (100-120 frames/s) and pulse repetition frequencies between 500 Hz to 1KHz were used resulting in aliasing velocities between 16 and 32 cm/s. The extent of LV dyssynchrony was calculated as the maximum time delay between peak systolic velocities of basal septal, lateral, anterior and inferior LV segments (3).

Speckle tracking strain analysis

For speckle tracking analysis, standard gray-scale 2D images were acquired in the 2- and 4-chamber apical views as well as the parasternal short-axis views at the level of the papillary muscles. Special care was taken to avoid oblique views from the mid-level short-axis images and to obtain images with the most circular geometry possible. All the images were recorded with a frame rate of at least 30 fps to allow for reliable operation of the software (EchoPac 6.1, GE Medical Systems, Horten, Norway) (14).

From an end-systolic single frame, a region of interest was traced on the endocardial cavity interface by a point-and-click approach. Then, an automated tracking algorithm followed the endocardium from this single frame throughout the cardiac cycle. Further adjustment of the

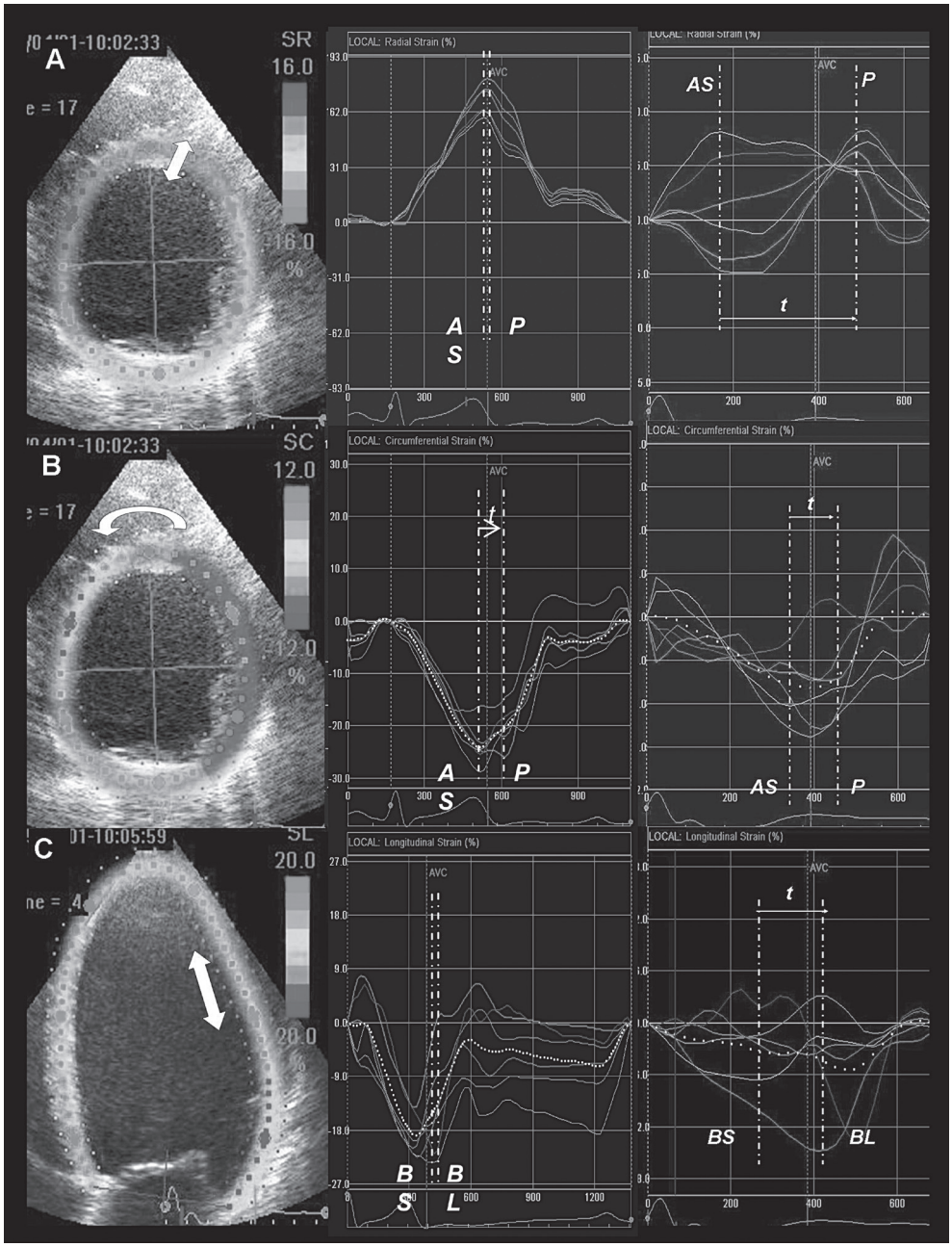


Figure 1. Two dimensional strain imaging: radial strain (A), circumferential strain (B) and longitudinal strain (C)

In the left corner the 2D strain images are represented. The light arrows depict the type of deformation assessed in each view: radial thickening (A), circumferential shortening (B) and longitudinal shortening (C). The middle and right panels demonstrate the segmental time-strain curves for a synchronous (middle) and dyssynchronous (right) LV for each view. Time differences in peak systolic strain (t) between anteroseptal (AS) and posterior (P) segments, in short-axis view, and between basal-septal (BS) and basal-lateral (BL) segments, in 4-chamber view, can be obtained from these curves.

region of interest was performed to ensure that all the myocardial regions were included. Next, acoustic markers, the so-called speckles, were distributed equally in the region of interest and can be followed throughout the entire cardiac cycle. The distance between the speckles was measured as a function of time and parameters of myocardial deformation could be calculated. Finally, the myocardium was divided into 6 segments that were color-coded as previously described (20) and displayed into 6 segmental time-strain curves for respectively RS, CS and LS (Figure 1).

For each type of strain analyzed, 2 different parameters for dyssynchrony were obtained; maximal time delay between peak systolic strain of 2 segments (most frequently observed between the (antero)septum and (postero)lateral wall) as well as an asynchrony index of the LV by calculating the standard deviation of time to peak systolic strain.

For RS and CS, difference between time to peak systolic strain of the (antero)septal and posterior segments (AS-P delay) and the standard deviation of time to peak systolic strain for all 6 segments (SDt_{6S}) were measured. For LS, the 2-and 4-chamber views were used to calculate the difference between time to peak systolic strain of the basal-septal and basal-lateral LV segment (BS-BL delay) as well as the standard deviation of time to peak systolic strain for 12 LV segments (SDt_{12S}).

Definition of response to CRT

Responders to CRT were defined as displaying a reduction of ≥15% in LVESV at 6-month follow-up (2). Patients who died within the 6-month follow-up period or underwent heart transplantation were classified as non-responders.

Statistical analysis

Continuous variables were presented as mean ± SD and compared with 2-tailed Student t test for paired and unpaired data. Categorical data were presented as number and percentage and compared with χ^2-test. Linear regression analysis was performed to assess the relation between the changes in LV end-systolic volume and baseline LV dyssynchrony. In addition, the extent of baseline LV dyssynchrony, as assessed with the different echocardiographic methods, needed to predict response to CRT was determined by receiver operator characteristic curve analysis. The optimal cut-off value was defined as the maximum value of the sum of sensitivity and specificity. Finally, 20 patients were randomly selected to test the intra- and interobserver variability for the LV dyssynchrony measurements. Subsequently, linear regression analysis and Bland-Altman analysis were performed. A P-value <0.05 was considered statistically significant.

RESULTS

Patient baseline characteristics

The baseline characteristics of the 161 patients (125 men, age 66±11 years) included in the present study are summarized in Table 1. According to the inclusion criteria, all patients had severe heart failure (mean functional class 3.0±0.5), with severe LV dysfunction (mean LVEF 23±7%) and wide QRS complex (mean 164±32 ms). Mean LV dyssynchrony as assessed

Table 1. Baseline characteristics of the study population

Variables	All patients (n = 161)	Responders (n = 88)	Non-responders (n = 73)	P-value
Age (yrs)	66±11	67±10	66±12	0.4
Gender (M/F)	125/36	64/24	61/12	0.1
Body surface area (m^2)	1.9±0.2	1.9±0.2	2.0±0.2	0.2
Ischemic etiology	92 (57%)	48 (55%)	44 (60%)	0.3
QRS duration (ms)	164±32	171±31	155±32	0.002
Sinus rhythm	123 (76%)	64 (73%)	59 (81%)	0.4
NYHA functional class	3.0±0.5	3.0±0.5	3.0±0.5	0.2
Quality-of-life score	41±16	39±16	44±16	0.1
6-minute walking distance (m)	279±132	294±122	263±142	0.2
LVEDD (mm)	70±11	71±11	69±11	0.2
LVEDV (ml)	245±89	260±90	226±86	0.01
LVEDV index (ml/m^2)	126±48	136±50	114±42	0.005
LVESV (ml)	191±82	208±85	171±75	0.004
LVESV index (ml/m^2)	99±44	108±47	86±37	0.001
LVEF (%)	23±7	21±6	25±8	0.001
Diastolic function				0.1
Normal filling pattern	11 (7%)	3 (11%)	8 (3%)	
Abnormal relaxation pattern	59 (37%)	37 (30%)	22 (42%)	
Pseudonormal filling pattern	36 (22%)	20 (22%)	16 (23%)	
Restrictive filling pattern	55 (34%)	28 (37%)	27 (32%)	
LV dyssynchrony by TDI (ms)	84±55	106±54	58±44	<0.001
AS-P delay by RS (ms)	180±135	251±138	94±65	<0.001
SDt_{6S} by RS (ms)	107±71	130±67	79±65	<0.001
AS-P delay by CS (ms)	162±128	204±143	162±128	0.1
SDt_{6S} by CS (ms)	128±69	145±59	128±69	0.1
BS-BL delay by LS (ms)	136±101	170±134	136±101	0.1
SDt_{12S} by LS (ms)	115±42	121±42	109±41	0.1
Medication				
Beta-blockers	100 (62%)	54 (61%)	46 (63%)	0.9
ACE-inhibitors/ARB	137 (85%)	74 (84%)	63 (86%)	0.8
Diuretics	137 (85%)	79 (90%)	58 (80%)	0.1
Spironolactone	64 (40%)	37 (42%)	27 (37%)	0.5

ACE: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; AS-P delay: difference between time to peak systolic strain of the anteroseptal and posterior LV segments; BS-BL delay: difference between time to peak systolic strain of the basal-septal and basal-lateral segments; CS: circumferential strain; EDD: end-diastolic diameter; EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; LV: left ventricular; LS: longitudinal strain; NYHA: New York Heart Association; RS: radial strain; SDt6S: standard deviation of the time to peak systolic strain of 6 segments; SDt12S: standard deviation of the time to peak systolic strain of 12 segments; TDI: tissue Doppler imaging.

with TDI was 84±55 ms. All patients had optimized medical therapy, including angiotensin-converting enzyme inhibitors or angiotensin-receptor antagonists, beta-blockers and diuretics, at maximum tolerated dosages. Device implantation was successful in all patients and no complications were observed.

Speckle tracking strain analysis and LV dyssynchrony

All patients were analyzed at baseline and at 6-month follow-up. In the mid-ventricular short-axis images, RS by speckle tracking was possible in 90% of 1896 attempted segments. Reliable CS-time curves were obtained in 85% of the same 1896 attempted segments. The feasibility for LS in 2- and 4-chambers views was 79%, and only 2990 segments from 3792 attempted segments could be reliably evaluated. The lesser feasibility for assessment of LS was due to non-valid tracking at the apical segments, where 30% of the segments had to be discarded. Furthermore, reproducibility for the different time delays was better when 2D RS was used (Table 2).

Table 2. Intra- and interobserver variability for the different LV dyssynchrony parameters

	Intraobserver		Interobserver	
	Difference	r	Difference	r
AS-P delay by RS (ms)	-3±23	0.98*	0.3±24	0.97*
SDt_{6S} by RS (ms)	-5±29	0.88*	3±28	0.88*
AS-P delay by CS (ms)	11±53	0.91*	-10±55	0.80*
SDt_{6S} by CS (ms)	6±36	0.66†	-6±27	0.70†
BS-BL delay by LS (ms)	-17±36	0.93*	4±22	0.92*
SDt_{12S} by LS (ms)	7±22	0.72*	-7±13	0.88*

Abbreviations as in Table 1.
*P < 0.001; †P <0.05.

In the overall population, substantial baseline dyssynchrony was present as indicated by long time-delays in peak systolic strain between the anteroseptal and posterior wall, as well as high standard deviations either by RS and CS (Table 1). Also, an important BS-BL delay was observed with longitudinal strain, as well as an important $SDt_{12S.}$

Response to CRT

Before the 6-month follow-up evaluation, 2 patients underwent heart transplantation and 4 died from worsening heart failure. In the entire patient group, a significant improvement in clinical status was noted, with a reduction in NYHA class (from 3.0±0.5 to 2.1±0.7, P<0.001), a reduction in quality-of-life score (from 41±16 to 27±19, P<0.001) and an increase in 6-minute walking distance (from 279±132 m to 377±139 m, P<0.001).

On echocardiography, LVEF improved significantly from 23±7% to 30±9% (P<0.001) and significant reductions in LVEDV (245±89 ml to 215±81 ml, P<0.001) and LVESV (191±82 ml to 155±71 ml, P<0.001) were observed.

In Table 3, the different parameters for LV dyssynchrony are reported at baseline and at 6-month follow-up. Both the AS-P delay and SDt_{6s} as assessed with RS showed a significant reduction in time delay at 6-month follow-up. In contrast, for the same parameters assessed with CS, only the SDt_{6s} demonstrates a significant reduction after CRT. In addition, BS-BL

Table 3. LV dyssynchrony measurements at baseline and after 6 months of CRT in overall population

	Baseline	6 months follow-up	P-value
AS-P delay by RS (ms)	180±135	112±101	<0.001
SDt_{6S} by RS (ms)	107±71	63±52	<0.001
AS-P delay by CS (ms)	162±128	165±117	0.2
SDt_{6S} by CS (ms)	128±69	109±63	0.04
BS-BL delay by LS (ms)	136±101	112±86	0.01
SDt_{12S} by LS (ms)	115±42	111±86	0.7

Abbreviations as in Table 1.

delay as assessed by LS also showed a significant reduction at 6-month follow-up, whereas the SDt_{12s} remained unchanged.

Responders versus non-responders to CRT

At 6-month follow-up, 88 patients (55%) were classified as responders to CRT, according to the pre-defined criterion of a reduction in LVESV by more than 15%. Conversely, 73 patients (45%) were non-responders including the 6 patients who died or underwent heart transplantation before 6-month follow-up.

Both patient groups showed significant improvements in clinical status (Figure 2). However, this improvement was more pronounced in the responder patients.

Responders showed (by definition) a reduction in LVESV (from 208±85 ml to 140±72 ml, P<0.001) and in LVEDV (from 260±90 ml to 203±82 ml, P<0.001, see Figure 2). Furthermore, an improvement in LVEF was noted (from 21±6% to 33±9%, P<0.001). In contrast, non-responders showed no improvement in LVEF (from 25±8% to 25±7%, NS) and showed a trend towards an increase in both LVESV (from 171±75 ml to 175±66 ml, P=0.05) and LVEDV at 6-month follow-up (from 226±86 ml to 230±77 ml, NS).

Baseline clinical and echocardiographic parameters between responders and non-responders were comparable; except for smaller LV volumes, higher LVEF and shorter QRS duration in non-responders. Furthermore, responders exhibited more baseline LV dyssynchrony as assessed with TDI as compared to non-responders (see Table 1).

Concerning the LV dyssynchrony parameters assessed with speckle tracking analysis at baseline, AS-P delay and SDt_{6S} as assessed by RS were significantly larger in responders as compared to non-responders (251±138 ms vs. 94±65 ms, P<0.001 and 130±67 ms vs. 79±65 ms, P<0.001, respectively). However, there were no differences between both groups in either AS-P delay and SDt_{6S} by CS or BS-BL delay and SDt_{12S} evaluated by LS (see Table 1). Linear regression analysis demonstrated a modest but significant relation between respectively baseline AS-P delay by RS and extent of LV reverse remodeling and baseline SDt_{6S} by RS and LV reverse remodeling (Figure 3); a higher value of baseline radial dyssynchrony corresponded with a larger reduction in LVESV.

Furthermore, after 6 months of CRT, responders showed a significant reduction in AS-P delay and SDt_{6S} as assessed by RS and in the BS-BL delay assessed by LS (see Figure 4). In non-responders, none of the dyssynchrony parameters showed a significant reduction.

Figure 2. Changes in clinical (A, B, C) and echocardiographic parameters (D,E,F) during follow-up according to CRT response

Dark bars represent baseline values whereas light bars represent 6 month follow-up values. LVEDV: LV end-diastolic volume; LVEF: LV ejection fraction; LVESV: LV end-systolic volume; NYHA: New York Heart Association; QoL: Quality-of-life.

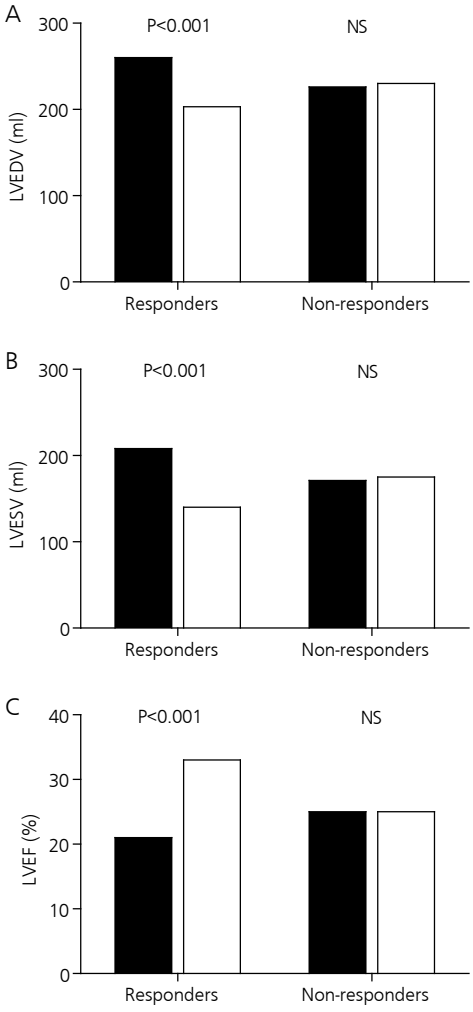
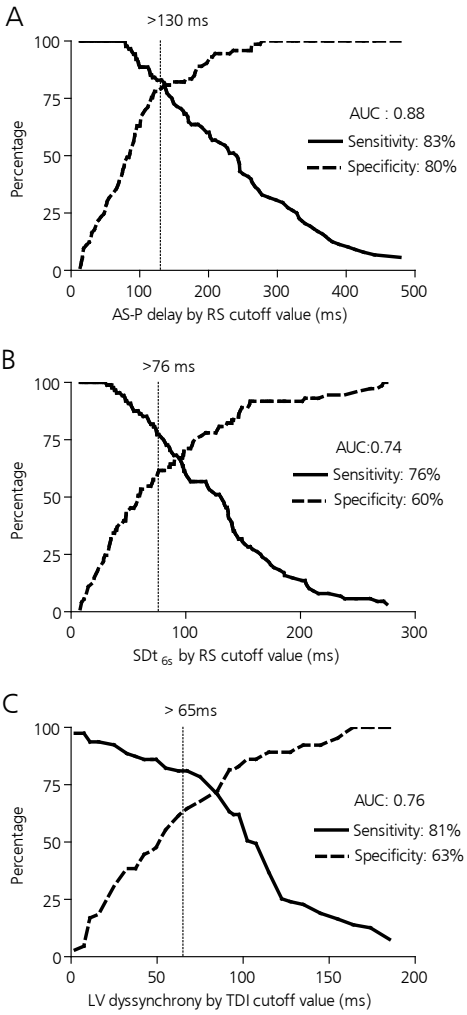


Figure 5. Receiver operating characteristics curves

Receiver operating characteristics curves for AS-P delay (A) and SDt_{6S} (B) as assessed by radial strain (RS) and LV dyssynchrony (C) as assessed by tissue Doppler imaging (TDI). Abbreviations as in Figure 3. AUC: area under the curve.



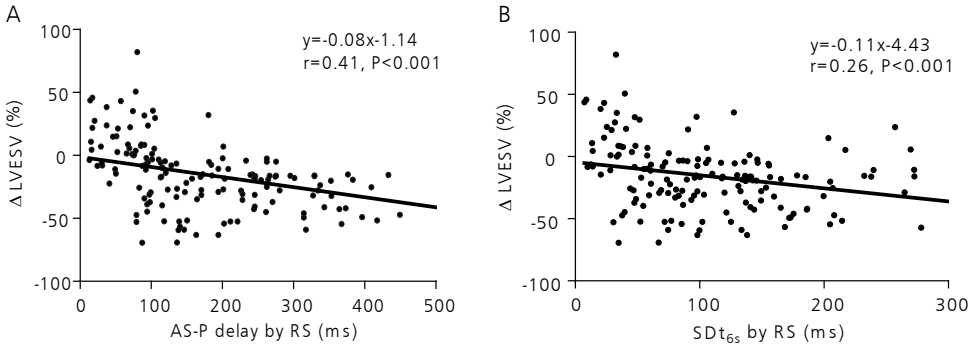
Prediction of response to CRT

Receiver operating characteristic curve analysis was performed to define the optimal cut-off value for both AS-P delay and SDt_{6s} as assessed with RS to predict response to CRT. In addition, the optimal cut-off value for LV dyssynchrony as assessed by TDI was calculated.

The area under the curve for AS-P delay was 0.88 and the optimal cut-off value to predict response to CRT was 130 ms, yielding a sensitivity and specificity of respectively 83% and 80% (Figure 5A). In addition, the area under the curve for SDt_{6S} was 0.74 and the optimal cut-off

Figure 3. AS-P delay (A) and SDt_{6S} (B) vs. LV reverse remodeling after CRT

Relationship between respectively baseline AS-P delay (A) and SDt_{6S} (B) as assessed by radial strain (RS) and the LV reverse remodeling (expressed as reduction in LV end-systolic volume [Δ LVESV]) after 6 months of CRT. AS-P delay: difference between time to peak systolic strain of the anteroseptal and posterior LV segments; SDt6S: standard deviation of the time to peak systolic strain of 6 LV segments.



value to predict response was 76 ms, yielding a sensitivity and specificity of respectively 77% and 60% (Figure 5B). The area under the curve for TDI-derived LV dyssynchrony was 0.76 and the accepted cut-off value of 65 ms to predict response to CRT yielded a sensitivity and specificity of 81% and 63% respectively (Figure 5C).

DISCUSSION

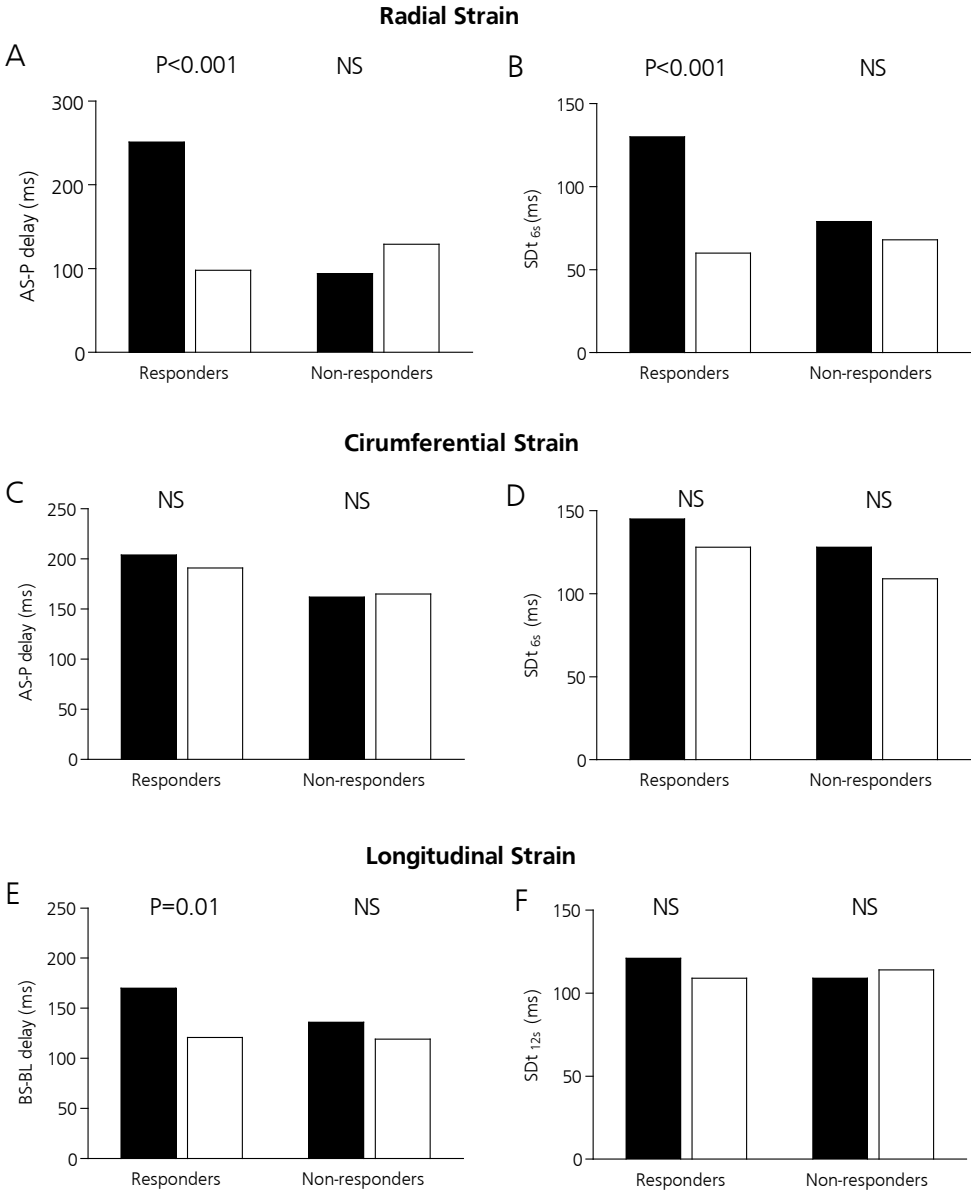
The present study demonstrates that evaluation of LV dyssynchrony using speckle tracking strain analysis is feasible and that substantial LV dyssynchrony is present in all three deformation types, radial, circumferential and longitudinal, in CRT candidates with depressed LV function and dilated cardiomyopathy. Furthermore, only baseline LV dyssynchrony parameters assessed with RS (both AS-P delay and SDt_{6S} delay) were able to identify potential responders to CRT, defined as a decrease of ≥15% in LVESV after 6 months of CRT. In addition, a decrease in extent of LV dyssynchrony during follow-up was only noted in responders to CRT for parameters assessed with RS (both AS-P delay and SDt_{6S} delay) and LS (BS-BL delay); no changes in LV dyssynchrony with CS were observed in responders to CRT. Non-responders to CRT did not show any significant change in extent of LV dyssynchrony using RS, LS or CS.

Changes in LV dyssynchrony after CRT

Three forms of strain were assessed before and 6 months after CRT to assess the effect biventricular pacing: radial, circumferential and longitudinal strain. Only few data are available on the changes in strain (assessed by 2D speckle tracking analysis) after CRT. Knebel et al evaluated 38 heart failure patients and demonstrated that responders to CRT revealed a significant decrease in time delays assessed with RS (from 168±104 ms at baseline to 98±44 ms at follow-up, P=0.04) and LS (from 168±104 ms at baseline to 112±81 ms at follow-up, P=0.02), whereas non-responders did not show reductions in dyssynchrony according to RS and LS analyses during follow-up (13). The results of the current study are in agreement with

Figure 4. Changes in LV dyssynchrony as assessed with radial strain (A, B), circumferential strain (C, D) and longitudinal strain (E, F) after CRT in responders and non-responders

Dark bars represent baseline values whereas light bars represent values at 6 month follow-up. Abbreviations as in Figure 3. BS-BL delay: difference between time to peak systolic strain of the basal-septal and basal-lateral LV segments.



these previous findings. In the present study, responders to CRT demonstrated a significant decrease in LV dyssynchrony as assessed with RS (using both the AS-P delay and the SDt_{6S}) and LS (only using the BS-BL delay). However, evaluation of dyssynchrony changes for CS did no reveal significant changes after CRT.

Initially, tagged magnetic resonance imaging (MRI) was used for assessment of myocardial strain in radial, circumferential and longitudinal orientation. Feasibility of this MRI technique for assessment of LV mechanical dyssynchrony has been demonstrated in previous studies (21, 22). Currently, no MRI studies evaluated assessment of dyssynchrony with RS. However, Leclercq et al used tagged magnetic resonance imaging with CS in an animal model on heart failure and demonstrated that biventricular pacing resulted in acute reduction LV dyssynchrony after biventricular pacing (23). In a subsequent animal study from the same group, both CS and LS analyses were used to evaluate LV dyssynchrony (12). Biventricular pacing improved synchronicity for both parameters, however this improvement was more pronounced using CS maps. In line with these results, although different parameters of LV dyssynchrony were used, CRT resulted in improvement of most dyssynchrony parameters. However, reductions in dyssynchrony parameters were largest using RS as compared to LS and CS.

Speckle tracking strain analysis and response to CRT

In the current study, 2D speckle tracking strain analysis was applied to 161 heart failure patients and 3 forms of strain were derived to assess LV dyssynchrony and predict response to CRT: radial, circumferential and longitudinal strain. Currently, data on 2D speckle tracking strain analysis in CRT candidates and prediction of response are scarce. Radial strain was first applied in 64 heart failure patients by Suffoletto and colleagues (14). Baseline AS-P delay was significantly higher in the patients that showed acute response, defined as an increase in stroke volume of ≥15%, as compared to patients who did not show an acute response (261±86 ms vs. 90±69 ms, P<0.001), and a pre-defined cut-off value of ≥130 ms predicted acute response after CRT with 91% sensitivity and 75% specificity. This same cut-off value predicted long-term response (≥15% in LVEF after 8±5 months) with 89% sensitivity and 83% specificity (14). In contrast, the aforementioned study by Knebel et al evaluated 38 heart failure patients undergoing CRT implantation, and reported that RS derived from 2D speckle tracking analysis could not predict response to CRT (13). The current findings are in line with the results presented by Suffoletto and coworkers (14); a cut-off value of ≥130 ms for AS-P delay assessed with RS was able to predict response with good sensitivity and specificity (Figure 4A). In addition, the results from the current study revealed that SDt_{6S} measured with RS is also a useful parameter to predict long-term response to CRT (Figure 4B), although the area under the curve was less than the area under the curve for the AS-P delay.

2D CS has been applied in only one previous study to assess LV dyssynchrony in patients undergoing CRT (11). Although that study was more focused on the effect of LV lead position in relation to outcome after CRT, the results also indicated that CS was not different between patients with and without response to CRT (161±32 ms vs. 159±35 ms, P=0.84) (11). Similarly, the current results also showed no differences in dyssynchrony assessed by CS between responders and non-responders; neither the baseline AS-P delay nor the SDt_{6S} delay could identify patients who responded to CRT.

Data on LS assessed by 2D speckle tracking analysis are also limited. Knebel et al reported more extensive LV dyssynchrony according to LS strain (217±125 ms vs. 168±91 ms), although prediction of response to CRT was not possible with LS strain (13). The present findings are in agreement with these results; regardless the parameters used (BS-BL delay or SDt_{12S}), LS was not able to predict response to CRT.

Finally, the value of the LV dyssynchrony parameters assessed by novel 2D RS in CRT candidates was comparable to the conventional TDI parameter of LV dyssynchrony (3, 24).

Value of speckle tracking strain analysis in CRT

The myofiber orientation in the human heart is complex with a characteristic helical distribution of the muscular fibers (25). In summary, the typical arrangement of the myocardial layers and its changes during the cardiac cycle has been related to the LV deformation in 3 directions: radial thickening, circumferential shortening and longitudinal shortening (10, 25). 2D speckle tracking imaging is a new echocardiographic technique which allows the study of all 3 types of deformation. Measurement of RS, CS and LS has recently been validated by cardiac magnetic resonance imaging (26). More importantly, 2D speckle tracking imaging is angle-independent and, as strain imaging technique, enables to differentiate those myocardial segments with active movement from those with passive movement (i.e. scarred tissue tethered by the non-scarred segments) (27, 28).

In the present study, both parameters measured with RS were able to predict response to CRT, whereas neither LS nor CS were able to predict response. However, focussing on the SDt_{6s} or SDt_{12s}, a decrease in their values at follow-up was observed in the overall population. A possible explanation may be that radial thickening mirrors the circumferential and longitudinal shortening (28, 29); the decrease in SDt_{6s}, assessed with RS could be accounted for a decrease in both SDt_{6s}, assessed with CS, and $SD\text{-}t_{12s}$, assessed with LS. As a consequence, the evaluation of LV dyssynchrony with RS with speckle tracking may provide more information in one single assessment than CS and LS could provide separately.

Of note, superior feasibility and reproducibility were noted for assessment of the RS parameters which may have influenced the current results. Larger studies are needed to further elucidate the relationship between electrical and mechanical activation of the LV and its impact on benefit from CRT.

CONCLUSIONS

2D speckle tracking RS enables the assessment of LV dyssynchrony and constitutes the best deformation study to identify potential responders to CRT. In addition, the predictive value of 2D RS was comparable to color-coded TDI. Furthermore, the long-term effect of CRT on LV dyssynchrony is better characterized with RS as compared to CS or LS. Reduction in LV dyssynchrony after CRT was only noted in responder patients, whereas in non-responders no changes were demonstrated.

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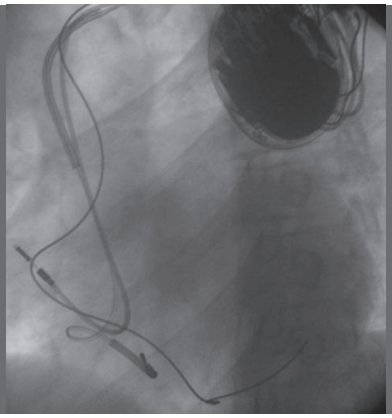
Chapter 3



Left ventricular resynchronization is mandatory for response to cardiac resynchronization therapy

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ABSTRACT

Background Recent studies have demonstrated that a positive response to cardiac resynchronization therapy (CRT) is related to the presence of pre-implantation left ventricular (LV) dyssynchrony. However, the time course and the extent of LV resynchronization following CRT implantation and their relationship to response are currently unknown.

Methods One hundred consecutive patients scheduled for the implantation of a CRT device were prospectively included, using the following criteria: NYHA class III-IV, LV ejection fraction ≤35%, QRS duration >120 ms and LV dyssynchrony (≥65 ms) on color-coded tissue Doppler imaging (TDI).

Results Immediately after CRT implantation, LV dyssynchrony was reduced from 114±36 ms to 40±33 ms (P<0.001) which persisted at 6 months follow-up (35±31 ms, P<0.001 vs baseline, NS vs. immediately post-implantation). At 6 months follow-up, 85% of patients were classified as responders to CRT (defined as >10% reduction in LV end-systolic volume). Immediately post-implantation, the responders to CRT demonstrated a significant reduction in LV dyssynchrony from 115±37 ms to 32±23 ms (P<0.001). The non-responders however, did not show a significant reduction in LV dyssynchrony (106±29 ms vs 79±44 ms, NS). If the extent of acute LV resynchronization was <20%, response to CRT at 6 months follow-up was never observed. Conversely, 93% of patients with LV resynchronization ≥20% responded to CRT.

Conclusion LV resynchronization following CRT is an acute phenomenon, and predicts response to CRT at 6 months follow-up.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is considered an important breakthrough in the treatment of selected patients with drug-refractory heart failure. Recent large randomized trials have clearly demonstrated the beneficial effects of CRT on heart failure symptoms and left ventricular (LV) systolic function. In addition, CRT resulted in a reduction in heart failure hospitalizations and an improvement in survival (1-4). Despite these impressive results, CRT was not successful in 20-30% of patients (1,5-7). Detailed analysis revealed that none of the established CRT selection criteria (NYHA class III-IV, LV ejection fraction [EF] ≤35% and QRS duration >120 ms) were able to predict a positive response to CRT (5,7). Recent studies have indicated that the benefit from CRT is related to the presence of LV dyssynchrony before implantation (5-10). It is currently unclear however, whether a reduction in LV dyssynchrony (LV resynchronization) after implantation of the CRT device is mandatory for a positive response. Moreover, whether LV resynchronization appears acutely after CRT implantation or occurs gradually over time is also unknown. Accordingly, a prospective analysis in patients with pre-implantation LV dyssynchrony on color-coded tissue Doppler imaging (TDI) was performed, aiming to answer the following questions: 1) What is the time course of LV resynchronization after CRT: does LV resynchronization occur acutely or develop gradually over time? 2) What extent of LV resynchronization is obtained following CRT? 3) Is LV resynchronization necessary for response to CRT?

METHODS

Study population and protocol

Consecutive heart failure patients, scheduled for implantation of a CRT device, were included in the study. The selection criteria for CRT included moderate-to-severe heart failure (NYHA class III or IV), LVEF ≤35% and QRS duration >120 ms. In addition, patients had to show substantial LV dyssynchrony (≥65 ms) on TDI. Patients with a recent myocardial infarction (<3 months) or decompensated heart failure were excluded. Before CRT implantation, clinical status was assessed and 2-dimensional echocardiography was performed to determine LV volumes and LV ejection fraction. Assessment of LV dyssynchrony using TDI was repeated immediately post-CRT implantation and at 6 months follow-up. The clinical status and changes in LV ejection fraction and LV volumes were re-assessed at 6 months follow-up.

Clinical evaluation

Evaluation of clinical status included assessment of NYHA functional class, quality-of-life score (using the Minnesota living with Heart Failure questionnaire) and evaluation of exercise capacity using the 6-minute hall-walk test. All parameters were re-assessed at 6 months follow-up.

Echocardiography

Patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed system Seven, General Electric-Vingmed, Milwaukee, Wisconsin, USA).

Images were obtained using a 3.5 MHz transducer, at a depth of 16 cm in the parasternal and apical views (standard long-axis, 2- and 4-chamber images). Standard 2-dimensional and color Doppler data, triggered to the QRS complex, were saved in cine-loop format. The LV volumes (end-systolic [ESV], end-diastolic [EDV]) and LVEF were calculated from the conventional apical 2- and 4-chamber images, using the biplane Simpson's technique (11).

Patients with a reduction of >10% in LVESV at 6 months follow-up were considered responders to CRT (12). In addition, patients who died from progressive heart failure before the 6 months follow-up assessment were classified as non-responders.

LV dyssynchrony assessment using color-coded TDI

In addition to the conventional echocardiographic examination, TDI was performed to assess LV dyssynchrony. For TDI, color Doppler frame rates were > 80 frames/s; pulse repetition frequencies were between 500 Hz and 1 KHz, resulting in aliasing velocities between 16 and 32 cm/s. TDI parameters were measured from color-coded images of 3 consecutive heart beats by offline analysis. To determine LV dyssynchrony, the sample volume (6 mm x 6 mm) was placed in the LV basal parts of the anterior, inferior, septal and lateral walls (using the 2-and 4-chamber apical views) and per region, the time interval between the onset of the QRS complex and the peak systolic velocity was derived (i.e. the electro-systolic delays). LV dyssynchrony was defined as the maximum delay between peak systolic velocities among the four walls within the left ventricle (most frequently observed between the inter-ventricular septum and the lateral wall) (7). The analysis of peak systolic velocities was limited to the LV ejection period and post-systolic peaks were excluded. To ensure highly interpretable and reproducible TDI curves (and minimize artefacts) high frame rates are crucial. The highest possible frame-rates were achieved by narrowing the 2- and 4-chamber apical TDI views down to the left ventricle (i.e. excluding the right ventricle and atria). Previously reported inter- and intra-observer agreement for assessment of LV dyssynchrony were 90% and 96%, respectively (13). Based on previous data, a cut-off value of 65 ms was used as a marker of LV dyssynchrony (7).

Data were analyzed using commercial software (Echopac version 5.0.1, General Electric – Vingmed). Echocardiographic data were analyzed by 2 independent observers, blinded to all other patient data.

Pacemaker implantation

The LV pacing lead was inserted transvenously via the subclavian route. A coronary sinus venogram was obtained using a balloon catheter. Next the LV pacing lead was inserted through the coronary sinus with the help of an 8Fr-guiding catheter, and positioned as far as possible in the venous system, preferably in a (postero-) lateral vein. The right atrial and right ventricular leads were positioned conventionally. CRT-device and lead implantation were successful in all patients without major complications (Contak TR or Contak Renewal TR2/1/2/4, Guidant, Minneapolis, Minnesota, USA and Insync (Marquis) III or Sentry, Medtronic Inc., Minneapolis, Minnesota, USA). Two types of LV leads were used (Easytrak, Guidant, or Attain, Medtronic Inc.). No adjustments were made to the V-V interval before the 6 months of follow-up assessment.

Statistical analysis

Continuous data were expressed as mean ± SD and compared with the 2-tailed Student's t test for paired and unpaired data when appropriate. Categorical variables were compared using the chi-square test with Yates' correction. Linear regression analysis was performed to determine the relationship immediate LV resynchronization and LV reverse remodeling at 6 months follow-up. For all tests, a P-value <0.05 was considered statistically significant.

RESULTS

A total of 100 consecutive patients were prospectively included, the study population comprised 86 men and 14 women, with a mean age of 67±11 years. By definition, all patients had pre-implantation LV dyssynchrony ≥65 ms (mean 114±36 ms). The baseline characteristics of the patients are summarized in Table 1.

Table 1. Baseline characteristics (n=100)

Age (yrs)	67±11
Gender (M/F)	86/14
Ischemic etiology	59 (59%)
QRS duration (ms)	168±27
Sinus rhythm	89 (89%)
NYHA functional class (III/IV)	95/5
Quality-of-life score	38±16
6-minute walking distance (m)	292±108
LV dyssynchrony (ms)	114±36
LVEF (%)	23±7
LVEDV (ml)	243±76
LVESV (ml)	188±71
Medication	
Diuretics	88 (88%)
ACE inhibitors	92 (92%)
Beta-blockers	77 (77%)

ACE: angiotensin-converting enzyme; EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; LV: left ventricular; NYHA: New York Heart Association.

Immediately after CRT implantation, QRS duration was reduced from 168±27 ms to 151±25 ms (P<0.001). One patient died at 3 months after CRT implantation as a result of worsening heart failure. Accordingly, this patient did not have the follow-up assessment at 6 months and was classified as a non-responder to CRT. In the remaining patients a significant improvement in NYHA class was observed (from 3.0±0.2 to 2.0±0.5, P<0.001) at 6 months follow-up. In addition, the quality-of-life score decreased from 38±16 to 19±15 (P<0.001) and the 6-minute walking distance increased from 292±108 m to 407±100 m (P<0.001). Echocardiography at 6 months follow-up revealed a significant improvement in LVEF from 23±7% to 33±10%

(P<0.001) and significant LV reverse remodeling with a decrease in LVEDV from 243±76 ml to 204±73 ml (P<0.001) and a decrease in LVESV from 188±71 ml to 136±63 ml (P<0.001). Eighty-five patients (85%) showed a reduction >10% in LVESV at 6 months follow-up and were therefore classified as responders to CRT.

LV resynchronization after CRT

Immediately after CRT implantation TDI demonstrated a reduction in LV dyssynchrony from 114±36 ms to 40±33 ms (P<0.001). At 6 months follow-up the reduction in LV dyssynchrony by CRT was sustained with a LV dyssynchrony of 35±31 ms (P<0.001 vs. baseline and NS vs. immediate post-implantation) (Figure 1).

Although the reduction in LV dyssynchrony following CRT was highly significant with an immediate reduction in LV dyssynchrony of 65% and a 69% reduction at 6 months follow-up, not all patients experienced a similar extent of LV resynchronization. The distribution of the extent of immediate LV resynchronization after CRT is displayed in Figure 2. In the majority

Figure 1. Time course of LV resynchronization following CRT implantation in all patients (n=100)

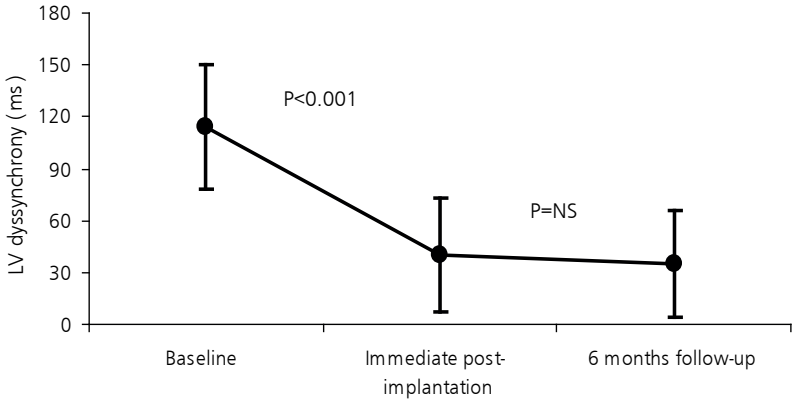
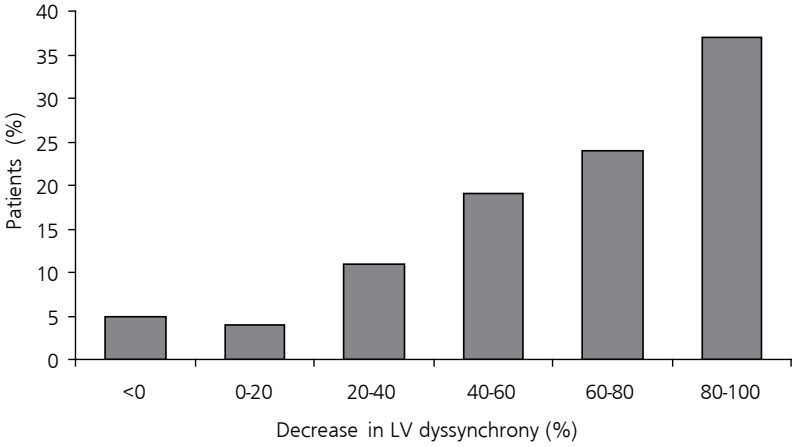


Figure 2. Extent of the decrease in LV dyssynchrony immediately following CRT implantation



of patients, CRT induced a ≥60% reduction in LV dyssynchrony both immediately post-implantation (n=61, 61%) and at 6 months follow-up (n=67, 67%). In other patients however, CRT resulted in only a minimal reduction or even an increase in LV dyssynchrony (Figure 2).

LV resynchronization versus response to CRT

As indicated above, 85 patients (85%) showed a reduction >10% in LV end-systolic volume at 6 months follow-up and were therefore classified as responders to CRT. Fourteen patients (14%) had a reduction ≤10% in LVESV and 1 patient died from progressive heart failure before 6 months follow-up; these patients were classified as non-responders to CRT (15%).

Table 2. Clinical and echocardiographic variables at baseline and at 6 months follow-up

Patients with LV reverse remodeling at 6 months follow-up (defined as a reduction in LV end-systolic volume >10%, n=85) versus patients without LV reverse remodeling (reduction of LV end-systolic volume ≤10%, n=15).

	LV reverse remodeling present	LV reverse remodeling absent #	P-value
Age (yrs)	67±10	66±15	NS
Gender (M/F)	73/12	13/2	NS
Ischemic etiology	47 (55%)	12 (80%)	NS
QRS duration (ms)	169±28	158±18	NS
NYHA class			
Baseline	3.0±0.2	3.1±0.3	NS
Follow-up	2.0±0.5*	2.6±0.5*	<0.05
Quality-of-life score			
Baseline	37±17	42±13	NS
Follow-up	18±14*	28±16*	<0.05
6-minute walking distance (m)			
Baseline	295±110	264±89	NS
Follow-up	419±85*	337±151*	<0.05
LV dyssynchrony (ms)			
Baseline	115±37	106±29	NS
Follow-up (acute)	2±23*	79±44	<0.05
LVEF (%)			
Baseline	23±7	24±7	NS
Follow-up	34±9*	25±7	<0.05
LVEDV (ml)			
Baseline	245±75	220±84	NS
Follow-up	200±72*	231±80	NS
LVESV (ml)			
Baseline	190±69	170±79	NS
Follow-up	130±59*	177±73	<0.05

Abbreviations as in Table 1. *: P<0.05 follow-up vs. baseline value, # 1 patient died before 6 months follow-up.

At baseline, no significant differences were observed between responders and non-responders (Table 2). In particular, baseline LV dyssynchrony was similar between responders and non-responders (115±37 ms versus 106±29 ms, NS). The prevalence of ischemic cardiomyopathy was higher in the non-responders, although this difference was not statistically significant (80% versus 55%, NS).

By definition, LVEDV did not decrease in the non-responders at 6 months follow-up (170±79 ml at baseline versus 177±73 ml at follow-up, NS). In contrast, the responders showed a significant reduction in LVESV from 190±69 ml to 130±59 ml (P<0.001). In addition, the non-responders showed no improvement in LVEF (from 24±7% to 25±7%, NS), whereas the responders improved from 23±7% to 34±9% (P<0.001) (Table 2).

Figure 3. Immediate decrease in LV dyssynchrony in the patients with response to CRT (n=85, 85%, defined as >10% reduction in LV end-systolic volume) versus the patients without response (n=15, 15%)

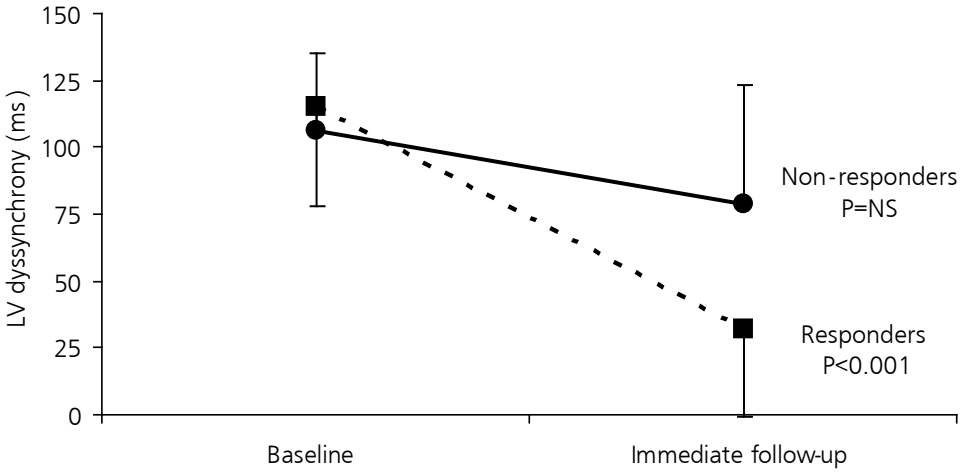
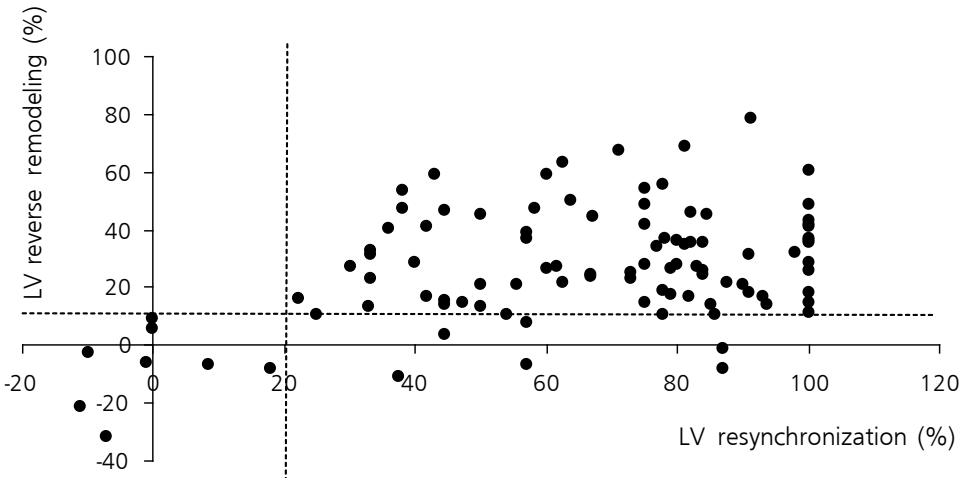


Figure 4. Relationship between immediate LV resynchronization and reduction in LV end-systolic volume at 6 months follow-up (y=0.29x+8, n=99, r=0.41, P<0.001)



An interesting observation was the difference in immediate LV resynchronization between the responders and the non-responders. The patients without response showed no significant reduction in LV dyssynchrony (from 106±29 ms to 79±44 ms, NS), whereas the responders demonstrated a significant reduction in LV dyssynchrony from 115±37 ms to 32±23 ms (P<0.001) (Figure 3).
Linear regression demonstrated a modest but significant relationship between the immediate reduction in LV dyssynchrony and the reduction in LV end-systolic volume at 6 months follow-up (y=0.29x+8, r=0.41, n=99, P<0.001) (Figure 4).
Of interest, when patients showed less than 20% LV resynchronization (n=9) immediately after CRT, response to CRT never occurred. Conversely, 85 of 91 patients with ≥20% LV resynchronization immediately after CRT implantation responded to CRT at 6 months follow-up. Applying this cut-off value of 20% immediate LV resynchronization, resulted in a positive and negative predictive value of 100% and 93% respectively, for prediction of response to CRT at 6 months follow-up. Importantly, no differences were observed in baseline characteristics between the patients with and without immediate LV resynchronization (Table 3).

Table 3. Baseline characteristics in patients with LV resynchronization (≥20% reduction in LV dyssynchrony, n=91) versus patients without LV resynchronization (n=9)

	Resynchronization present	Resynchronization absent #	P-value
Age (yrs)	67±10	65±17	NS
Gender (M/F)	79/12	7/2	NS
Ischemic etiology	53 (58%)	6 (67%)	NS
QRS duration (ms)	169±28	157±17	NS
NYHA class	3.0±0.2	3.1±0.3	NS
LV dyssynchrony (ms)	114±37	112±24	NS
LVEF (%)	23±7	23±7	NS
LVEDV (ml)	241±76	255±84	NS
LVESV (ml)	187±70	197±79	NS

Abbreviations as in Table 1. #1 patient died before 6 months follow-up

DISCUSSION

The main findings of the current study can be summarized as follows: 1) LV resynchronization following CRT occurs acutely and is sustained at 6 months follow-up, without further resynchronization over time however; 2) large inter-individual variation in the extent of LV resynchronization was observed, but the vast majority revealed more than 60% reduction in LV dyssynchrony acutely after CRT implantation; 3) less than 20% resynchronization never resulted in response to CRT, whereas 93% of patients with ≥20% resynchronization responded to CRT at 6 months follow-up.

Mechanism of response to CRT

Recent studies have clearly demonstrated that the presence of substantial LV dyssynchrony before implantation is an important predictor of a response to CRT (5-9), which may be superior over the traditional selection criteria (severe heart failure, depressed LV function and wide QRS complex). For example Dohi et al demonstrated that the extent of LV dyssynchrony was the only pre-implantation parameter that was different between responders and non-responders to CRT; responders had significantly larger septal to posterior peak wall strain as compared to non-responders (249±94 ms versus 137±136 ms, P<0.05) (14).

In the current study, all patients had echocardiographic evidence of LV dyssynchrony and the echocardiographic response rate (defined as a decrease >10% in LVESV at 6 months follow-up) was indeed much higher (85%) as compared to previous studies that included patients selected according to the traditional CRT selection criteria; these studies reported echocardiographic response rates in the range of 50-55% (5,6,15). The current findings strongly support the use of echocardiographic selection of potential candidates for CRT.

The parameter for LV dyssynchrony used in the current study was derived previously from 85 heart failure patients undergoing CRT, who were evaluated with color-coded TDI (7). ROC curve analysis revealed that LV dyssynchrony ≥65 ms (as determined from 4 basal LV segments) yielded a sensitivity and specificity of 92% to predict LV reverse remodeling after CRT implantation (7). Based on this pre-defined cut-off value, only patients with evidence of LV dyssynchrony ≥65 ms on TDI were included in the current study.

The definition of response used in the current study (reduction >10% in LVESV at 6 months follow-up was derived from a study by Yu et al who studied 141 patients undergoing CRT and observed that a reduction in LV end-systolic volume after 3-6 months of CRT was the most important predictor of all-cause and cardiovascular mortality, whereas clinical parameters were unable to predict response to CRT. ROC curve analysis revealed that a cut-off value of 10% reduction in LVESV was the optimal cut-off value for prediction of response to CRT (12).

Time course and extent of LV resynchronization following CRT

Various studies have reported on LV resynchronization after CRT (6,7,16,17). The majority of studies showed immediate resynchronization after CRT. For example Breithardt et al studied the acute effects of CRT on the extent of LV dyssynchrony in 34 patients using echocardiographic phase analysis (17). Immediately after implantation, a 37% decrease in LV dyssynchrony was observed (from 104±41° to 66±42°, P<0.001).

The time course however, of LV resynchronization during follow-up is currently unknown and the question whether initial LV resynchronization is followed by a further reduction in LV dyssynchrony is unanswered. The present findings clearly demonstrate that LV resynchronization is an acute phenomenon, which occurs immediately after CRT implantation. At mid-term follow-up, the extent of immediate LV resynchronization is sustained, but a further reduction in LV dyssynchrony could not be demonstrated (Figure 1). An interesting observation is the high inter-individual variation in the extent of immediate LV resynchronization following CRT implantation. Although the majority of patients demonstrated ≥60% reduction in LV dyssynchrony, some patients only demonstrated a minimal amount of LV resynchronization or even experienced an increase in LV dyssynchrony.

Lack of LV resynchronization

In search for optimal prediction of response to CRT, previous studies have shown that patients with LV dyssynchrony have a relatively high likelihood to respond to CRT whereas patients without LV dyssynchrony do not respond, although not all patients with LV dyssynchrony responded to CRT (7,14-16). In the current study, patients were selected based on the presence of LV dyssynchrony before CRT implantation, resulting in a high response rate (85%), but 15% of patients still did not respond. Comparison of responders and non-responders revealed no differences in baseline clinical and echocardiographic characteristics (Table 2). Interestingly, further analysis of the individual patient data revealed that the extent of immediate LV resynchronization can be used to optimize prediction of response. Patients with less than 20% reduction in LV dyssynchrony never responded to CRT. In contrast, patients with LV resynchronization ≥20% had an excellent response rate of 93%.

The explanation for absence of resynchronization may be related to LV lead positioning: a mismatch between the site of latest activation and position of the LV pacing may prohibit resynchronization. This issue needs further study.

CONCLUSION

LV resynchronization following CRT is an acute phenomenon, without further reduction in LV dyssynchrony during follow-up. Despite the presence of substantial LV dyssynchrony before implantation, patients with a <20% immediate reduction in LV dyssynchrony never showed response to CRT at 6 months follow-up, indicating that resynchronization is mandatory for response to CRT.

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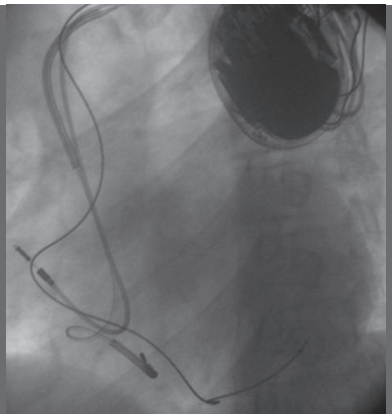
Chapter 4



Extent of viability to predict response to cardiac resynchronization therapy in ischemic heart failure patients

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ABSTRACT

Introduction The response to cardiac resynchronization therapy (CRT) varies significantly among individuals. Preliminary data suggest that the presence of myocardial viability may be important for response to CRT. The aim of the present study was to evaluate whether the extent of viability could predict response to CRT after 6 months.

Methods Sixty-one consecutive patients with advanced heart failure, left ventricular ejection fraction (LVEF) <35%, QRS duration >120 ms and chronic coronary artery disease were included. To determine the extent of viability all patients underwent nuclear imaging with F18-fluordeoxyglucose SPECT before implantation. Clinical and echocardiographic parameters were assessed at baseline and after 6 months of follow-up.

Results The presence of myocardial viability was directly related to an increase in LVEF after 6 months of CRT. Furthermore, the extent of viability in responders (n=38) was significantly larger compared to non-responders (n=23, 12±3 vs. 7±3 viable segments, P<0.01). Moreover, the optimal cut-off value to predict clinical response to CRT was identified at an extent of 11 viable segments or more (in a 17-segment model), yielding a sensitivity of 74% and a specificity of 87%.

Conclusion The presence of myocardial viability is directly related to response to CRT in patients with ischemic heart failure. Interestingly, using a cut-off level of 11 viable segments or more, the extent of viability could be used to predict response. Evaluation for myocardial viability may therefore be considered in the selection process for CRT.

INTRODUCTION

Despite significant advances in the treatment of congestive heart failure, the 5-year mortality exceeds 50% (1,2). Cardiac resynchronization therapy (CRT) has been introduced as a new treatment option for patients with severe heart failure, depressed left ventricular (LV) function, and wide QRS complex. Various randomized studies have demonstrated improvement in symptoms, exercise capacity, and LV systolic function (3-6). Furthermore, CRT reduces re-hospitalization for heart failure with a substantial survival benefit (7,8).

However, up to one-third of patients with New York Heart Association (NYHA) class III or IV, impaired LV ejection fraction (EF, <35%) and QRS >120 ms, do not clinically respond after CRT (3,4). The reasons for non-response to CRT are not well known, although presence of LV dyssynchrony is predictive for response to CRT (9,10). In addition, extensive scar tissue in the postero-lateral wall on contrast-enhanced MRI is associated with poor response to CRT and the extent of viable myocardium is associated with benefit from CRT (11,12). One could anticipate that a substantial amount of viable myocardium is needed for improvement in LV function after CRT, and the extent of viability may be useful for prediction of response to CRT.

Accordingly, the aim of the present study was to evaluate the value of viability for response to CRT and more specifically, to derive a cutoff value for the extent of viable myocardium that may be necessary for a good response to CRT.

MATERIALS AND METHODS

Patients

Consecutive patients with ischemic heart failure (NYHA class III or IV), depressed LVEF (<35%) and substantial LV dyssynchrony were prospectively included for implantation of a CRT device. Patients with a recent myocardial infarction (<3 months) or decompensated heart failure were excluded. Etiology was considered ischemic in the presence of significant coronary artery disease (≥50% stenosis in one or more of the major epicardial coronary arteries) and/or a history of myocardial infarction with ECG evidence, prior PCI or prior CABG.

Before CRT implantation, all patients underwent nuclear imaging with F18-fluorodeoxyglucose (FDG) to identify viable myocardium. Clinical status and echocardiographic parameters were evaluated before CRT implantation and repeated after 6 months of CRT.

F18-Fluordeoxyglucose Imaging

FDG imaging was performed after Acipimox administration (a nicotinic acid derivate, 500 mg, oral dose) (13). Acipimox enhances myocardial FDG uptake by reducing the plasma level of free fatty acids (14). A low-fat carbohydrate-rich meal was provided to further enhance myocardial FDG uptake by stimulating endogenous insulin release. One hour after acipimox administration, a blood sample was taken to assess plasma glucose levels. When plasma glucose was between 5 and 7 mmol/L, 185 MBq F18-FDG were injected at rest. Forty-five minutes thereafter, data acquisition was started (15). Metabolic imaging was performed at rest using a triple head SPECT camera system (GCA 9300/HG, Toshiba Corp., Tokyo) equipped with commercially

available 511 keV collimators. Data were acquired over 360 degrees and stored in a 64x64, 16-bit matrix.

Reconstructed FDG short-axis slides were displayed in polar map format (normalized to the maximum activity) and analyzed using a 17-segment model (16). Tracer uptake was analyzed quantitatively and categorized on a 4-point scale: 0= tracer activity >75% (normal, viable); 1= tracer activity 50-75% (minimal scar); 2= tracer activity 25-50% (moderate scar); 3= tracer activity <25% (extensive scar) (17). The number of viable (normal, score 0) segments per patient were noted. In addition, summation of the segmental scores yielded the total scar score, with the higher scores indicating more scar tissue (reflecting the extent of damage per patient).

Echocardiography

Transthoracic 2D echocardiography was performed the day before CRT implantation and after 6 months of CRT. Patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed Vivid Seven, General Electric-Vingmed, Milwaukee, Wisconsin, USA). Images were obtained using a 3.5 MHz transducer, at a depth of 16 cm in the parasternal and apical views (standard long-axis and two- and four-chamber images). Standard 2D and color Doppler data, triggered to the QRS complex were saved in cine-loop format. LV volumes (end-diastolic [EDV], end-systolic [ESV]) and LVEF were calculated from the conventional apical 2- and 4-chamber images, using the biplane Simpson's technique (18). Inter- and intra-observer agreement for assessment of LV function and volumes were 90% and 96% respectively.

Clinical Evaluation

Clinical evaluation was performed before implantation and after 6 months of CRT. NYHA class was used to evaluate heart failure symptoms and scored by an independent physician, who was blinded to all other patient data. NYHA class II was defined as shortness of breath during normal exercise, NYHA class III was defined as dyspnea during minimal exercise (e.g. not able to climb 1 flight of stairs), and NYHA class IV was defined as shortness of breath at rest. Quality-of-life score was assessed using the Minnesota Living with Heart Failure questionnaire (19). Exercise tolerance was evaluated with a 6-minute walk test and expressed in meters (20). In all patients, QRS duration was measured from the surface ECG using the widest QRS complex from the leads II, V1 and V6. The ECGs were recorded at a speed of 25 mm/sec and were evaluated by two independent observers without knowledge of the clinical status of the patient.

CRT Implantation

A coronary sinus venogram was obtained using balloon catheter, followed by the insertion of the LV pacing lead. An 8F guiding catheter was used to position the LV lead in the coronary sinus. The preferred position was a lateral or postero-lateral vein (21). The right atrial and ventricular leads were positioned conventionally. All leads were connected to a dual chamber biventricular ICD.

Statistical Analysis

Results are expressed as mean ± SD. Comparison of data was performed using the paired and unpaired Students t test for continuous variables and Fisher's exact test for proportions. Linear regression analysis was performed to evaluate the relation between the extent of viability and scar on FDG imaging and the change in LVEF after 6 months of CRT.

Uni- and multivariable logistic regression analysis were performed to determine the relation between potential risk factors at baseline and non-response to CRT. We considered the following variables to adjust for extent of viability and scar score separately: QRS duration, LV dyssynchrony, rhythm, LVEF, LV volumes. All variables entered the multivariable stage, irrespective of the results of the univariable analyses. We only report adjusted odds ratios (OR) with their corresponding 95% confidence intervals (CI).

The optimal extent of viability needed to predict response to CRT was determined by receiver operator characteristic (ROC) curve analysis. For all tests, a P-value <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

The baseline characteristics of the 61 patients (47 men, age 68±9 years) included in this study, are summarized in Table 1.

Table 1. Patient characteristics (n=61)

Age (yrs)	68±9
Gender (M/F)	47/14
NYHA class	3.0±0.5
QRS duration (ms)	165±36
LBBB	38 (78%)
Rhythm (SR/AF/paced)	49/8/4
LV dyssynchrony (ms)	88±41
LVEF (%)	23±6
LVEDV (ml)	245±81
LVESV (ml)	192±72
Medication	
Diuretics	57 (93%)
ACE-inhibitors	51 (84%)
Beta-blockers	37 (61%)
Spironolactone	19 (31%)
Digoxin	16 (26%)
Amiodarone	17 (28%)

ACE: angiotensin-converting enzyme; AF: atrial fibrillation; EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; LBBB: left bundle branch block; LV: left ventricular; NYHA: New York Heart Association; SR: sinus rhythm.

By definition, all patients had severe heart failure (mean NYHA class 3.0±0.5). Echocardiographic evaluation revealed LV dilatation (mean LVEDV 245±81 ml), severely depressed LV function (mean LVEF 23±6%) and substantial LV dyssynchrony (88±41 ms). All patients had optimized medical therapy that included ACE-inhibitors, beta-blockers, and diuretics, if tolerated.

All patients received a biventricular ICD (Contak CD or Renewal, Guidant Corporation, St. Paul, Minnesota, USA; or Insync III-CD or Marquis, Medtronic Inc., Minneapolis, Minnesota, USA). Two types of LV leads were used (Easytrak 4512-80, Guidant Corporation; or Attain-SD 4189, Medtronic Inc.). The procedure was successful in all patients and no procedure-related complications were observed. Five patients died before the 6-month follow-up evaluation due to worsening heart failure.

Clinical Response to CRT

After 6 months of CRT, mean NYHA class had decreased from 3.0±0.5 to 2.2±0.8 (P<0.01). The 6-minute walking distance improved significantly from 301±107 m to 386±136 m (P<0.01). Also, symptoms improved as evidenced by the significant decrease in quality-of-life score (from 37±16 at baseline to 22±18 at follow-up, P<0.01).

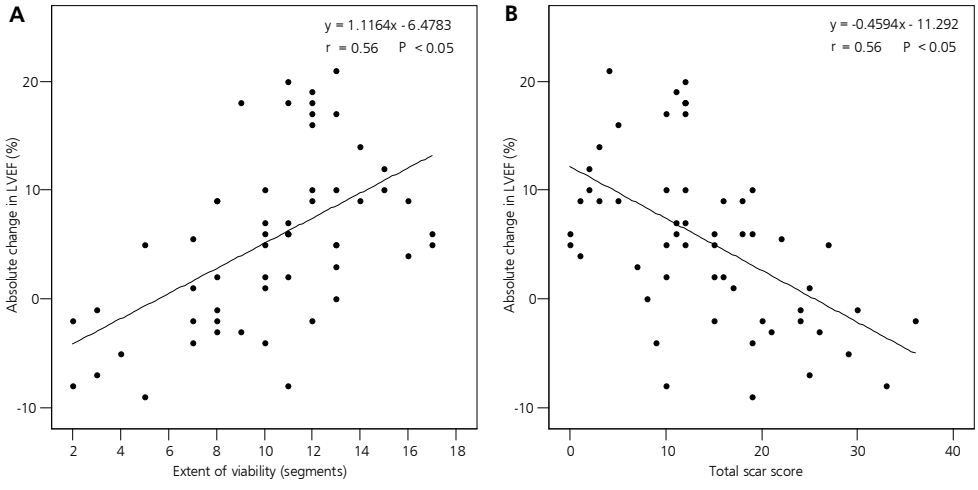
The LVEF increased significantly from 23±6% to 29±9% after 6 months of CRT (P<0.01). In addition, significant reverse remodeling was observed, as evidenced by a decrease in LVEDV from 245±81 ml at baseline to 217±77 ml (P<0.01) at follow-up and a decrease in LVESV from 192±72 ml to 156±70 ml (P<0.01).

Extent of Viability

On FDG imaging, 610 (59%) segments were classified as having normal tracer uptake. Of the 427 segments with reduced FDG uptake, 121 (12%) were classified as having minimal scar (score 1), and 306 (29%) as having extensive scar (scores 3 and 4). The number of normal,

Figure 1. Viability vs. improvement in LV function after CRT

Relationship between the extent of viability (number of viable segments) and the absolute change in LV ejection fraction (LVEF) after 6 months of CRT (A), and the relationship between total scar score and the absolute change in LVEF after 6 months (B).



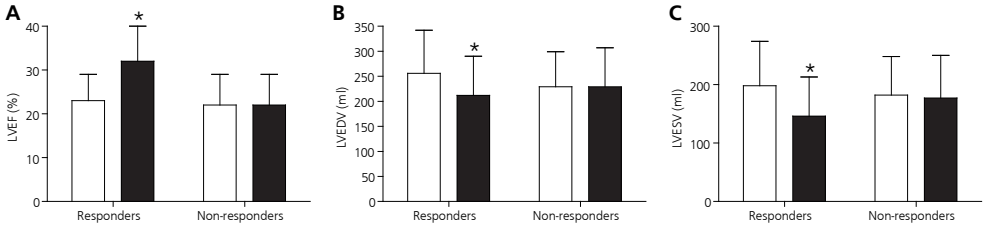
viable segments (extent of viability) ranged from 2 to 17 (mean 10±4). In addition, extensive regions of scar tissue were present as indicated by a total scar score of 15±9 per patient.
As shown in Figure 1A, there was a significant relation between the extent of viability on FDG imaging and the absolute change in LVEF after 6 months of CRT. Furthermore, the total scar score was inversely related to the change in LVEF (Figure 1B).

Responders and Non-responders

After 6 months of CRT, 38 patients (62%) were considered responders according to an improvement of ≥1 NYHA class after 6 months of CRT. There were 23 (38%) non-responders, of whom 5 died of progressive heart failure before 6 months follow-up.
At baseline, there were no significant differences in most of the clinical characteristics between responders and non-responders. However, QRS duration was less in the non-responders (147±34 ms vs. 175±33 ms, P<0.05) and non-responders tended to have smaller LV volumes, although the difference was not significant.
In the responders, there was a significant improvement in NYHA class (2.9±0.5 vs. 1.8±0.5, P<0.01), 6-minute walking distance (305±106 m vs. 438±114 m, P<0.01) and quality-of-life score (36±15 vs. 14±11, P<0.01) after 6 months of CRT. The non-responders however showed no improvement in the clinical parameters. In addition, an improvement in LVEF and a reduction in LV volumes were observed in the responders whereas these effects were not observed in the non-responders (Figure 2).
The extent of viability at baseline was significantly larger in responders as compared to non-responders (12±3 vs. 7±3 viable segments, P<0.01). Furthermore, the total scar score was lower

Figure 2. Echocardiographic changes after CRT

Mean LV ejection fraction (LVEF) (A), LV end-diastolic volume (LVEDV) (B) and LV end-systolic volume (LVESV) (C) at baseline (white columns) and after 6 months of CRT (black columns). *P<0.01 baseline vs. follow-up



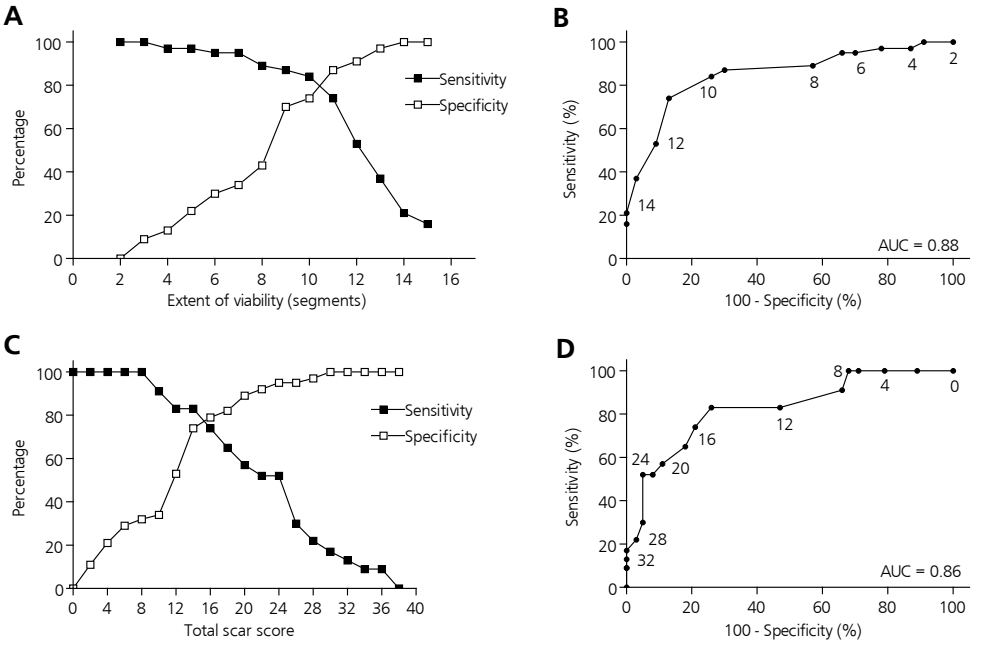
in the group of responders (responders: 11±7 vs. non-responders: 22±8, P<0.01). Multivariate analysis revealed that both extent of viability and total scar score were highly predictive for response to CRT (OR 1.632, 95% CI 1.235 – 2.156, P<0.001, and OR 0.836, 95% CI 0.754 – 0.927, P<0.001). Also, the presence of LV dyssynchrony was associated with response to CRT. Importantly, LV volumes at baseline had no influence on response, and QRS duration was only borderline predictive (P=0.05).

Extent of Viability to Predict Response to CRT

To define the optimal cut-off value to predict response to CRT, ROC curve analysis was performed. Figure 3 A and B show the ROC curves of the extent of viability to predict response

Figure 3. Viability to predict CRT response

ROC curve analysis on the extent of viability before CRT implantation and response after 6 months of CRT (A), with a good predictive value (area under curve [AUC] = 0.88) to predict response (B). The small numbers (2-16) next to the line indicate the extent of viability. ROC curve analysis on the total score before CRT implantation and response after 6 months of CRT (C), with also a good predictive value (AUC = 0.86) to predict non-response (D). The small numbers indicate the total scar score.



and showed a good predictive value in differentiating responders and non-responders (area under the curve [AUC] = 0.88). The optimal cut-off value, defined as the maximum value of (sensitivity + specificity)/2, was identified at an extent of 11 viable segments, yielding a sensitivity of 74% and specificity of 87% to predict response to CRT.

Furthermore, to predict non-response to CRT, a ROC curve of the total scar score was performed (Figure 3C en 3D). The scar score showed a good predictive value (AUC = 0.86), and optimal cut-off value to predict non-response was a scar score of 14 (sensitivity 83%, specificity 74%).

DISCUSSION

The findings in the current study demonstrate that response to CRT is directly related to the extent of viability. In addition, the presence of scar tissue is frequent and total scar score shows an inverse relation to response to CRT. In attempt to define a cut-off value to determine how many viable segments are needed to result in response to CRT, ROC curve analysis was used; this analysis demonstrated that in the presence of 11 or more viable segments, a sensitivity of

74% with a specificity of 87% were obtained to predict clinical response to CRT. Furthermore, having a total scar score of more than 14 appeared to predictive for non-response.
In large clinical trials, the beneficial effect of CRT has been demonstrated (3-8). On an individual basis, however, 20-30% of patients still do not respond to CRT (3,4). Current selection of patients is based on heart failure symptoms, LV function and QRS duration. Thus, additional criteria are needed to identify those patients, who are likely to benefit from CRT. Observational studies have demonstrated that the presence of LV dyssynchrony is an important factor determining response to CRT (9,10). Furthermore, ischemic etiology has been identified to be a predictor of non-response (22). Also, Woo et al described that the benefits of CRT with respect to EF and reverse remodeling were greater in patients with non-ischemic cardiomyopathy (23). These data suggest that a certain extent of viability is needed to permit response to CRT.

Myocardial viability vs. response to CRT

Thus far, data about myocardial viability in CRT patients are scarce. Only one small study addressed this issue. Hummel et al performed contrast echocardiography before CRT implantation in 21 patients with ischemic cardiomyopathy and demonstrated a significant relationship between the perfusion score index (based on contrast echocardiography), calculated by dividing the summed scores by the number of segments, and the change in LVEF as determined immediately after CRT implantation (12). Also, the change in LVEF after 6 months of CRT was significantly related to the perfusion score index. In line with these observations, a linear relation was demonstrated in the present study between the extent of viability (expressed as the number of viable segments on FDG imaging) and improvement in LVEF after 6 months of CRT (Figure 1A). Moreover, a relationship was noted between the extent of scar tissue (expressed as the total scar score) and improvement in LVEF after 6 months, reflecting that extensive scar tissue does not permit improvement of systolic LV function after CRT (Figure 1B).
Furthermore, in the study by Hummel et al patients with a higher perfusion score index, indicating more viable segments, tended to have greater improvement in NYHA class, 6-minute walking distance and quality-of-life score. In the current study, significantly more viable segments were noted in the group of responders as compared to the non-responders. These results imply that, in patients with ischemic cardiomyopathy, CRT may not result in clinical and echocardiographic improvement after 6 months when a substantial amount of viable myocardium is absent.
In the current study, nuclear imaging with FDG was used to assess myocardial viability. FDG imaging allows detection of cardiac glucose metabolism simultaneously and is considered an accurate technique for viability assessment. Of note, in the "classical viability studies" dysfunctional myocardium is evaluated for the potential to improve in function post-revascularization (24-27). In CRT however, one is interested not per se in dysfunctional but viable myocardium, but in all myocardium that is alive, which has the potential to improve in contraction after CRT. Therefore, it is of more interest to detect normal, viable myocardium rather than severely dysfunctional myocardium. In this respect, the definition of viable myocardium in the current study was rather conservative and only segments with FDG uptake ≥75% of maximum tracer uptake, since these segments most likely do not contain scar tissue. Two other small studies used nuclear imaging to assess viability in a similar patient group (CRT candidates), but only described the definition of non-viable myocardium. Sciagra et al used

resting gated perfusion SPECT with 99m-Tc tetrofosmin and quantified perfusion defects as percentage of LV wall, with the defect threshold set at 50% of peak uptake, to identify the likely nonviable myocardium (28). De Winter et al used resting gated SPECT with 99m-Tc sestamibi and considered a myocardial wall to contain substantial nonviable tissue if none of the segments had a mean myocardial uptake higher than 55% of the maximum uptake in the myocardium on the resting perfusion images (29). Optimal assessment of viability may include the integration of perfusion and metabolic imaging (as used in assessment of myocardial hibernation), but in the current study only metabolic imaging with FDG was used.

From a methodologic point of view, it is important to emphasize that attenuation correction and scatter correction was not used in this SPECT study. However, substantial experience has been gained with FDG SPECT to predict improvement after revascularization, and the lack of attenuation correction and scatter correction did not negatively affect accuracy (which is comparable to that of FDG PET) (30).

How much viable tissue is needed to benefit from CRT?

Ideally, a cut-off value should be identified indicating how much viable myocardium needs to be present to result in response to CRT. Accordingly, ROC curve analysis was performed to identify this cut-off value. As can be observed from Figure 3A, a small amount of viable myocardium was very sensitive for prediction of response to CRT, but at the cost of a low specificity. Conversely, when a larger number of viable segments is present, a substantial increase in specificity is noted, with a drop in sensitivity however. The optimal cut-off value was identified at 11 (65% in a 17-segment model) viable segments; this value yielded a sensitivity of 74% with a specificity of 87%. Moreover, having a total scar score of more than 14 appeared to predictive for non-response (sensitivity 83%, specificity 74%) (Figures 3C and D). These cut-off values need further testing in prospective, larger studies in patients undergoing CRT.

CONCLUSION

The presence of myocardial viability is directly related to response to CRT in patients with ischemic cardiomyopathy. A cut-off value of ≥11 viable segments on FDG imaging yielded a sensitivity and specificity of 74% and 87% respectively to predict response to CRT.

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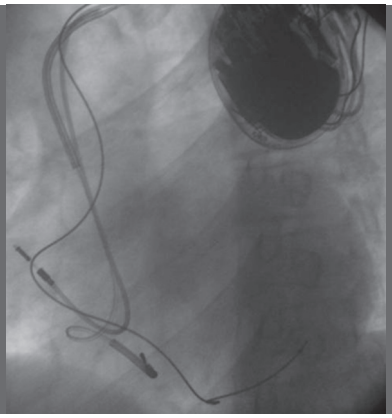
Chapter 5



Impact of viability and scar tissue on response to cardiac resynchronization therapy in ischemic heart failure patients

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ABSTRACT

Aims At present, 20-30% of patients do not respond to cardiac resynchronization therapy (CRT). In this study, the relation between the extent of viable myocardium and scar tissue versus response CRT was evaluated. In addition, the presence of scar tissue in the left ventricular (LV) lead position was specifically related to response to CRT.

Methods and Results Fifty-one consecutive patients with ischemic heart failure and substantial LV dyssynchrony undergoing CRT were included. All patients underwent gated SPECT before CRT implantation to determine the extent of scar tissue and viable myocardium. Clinical and echocardiographic parameters were assessed at baseline and after 6 months of CRT. The results demonstrated direct relations between the response to CRT and the extent of viable myocardium and scar tissue. In addition, the 15 patients (29%) with transmural scar tissue (< 50% tracer activity) in region of the LV pacing lead showed no improvement after 6 months of CRT.

Conclusion The extent of scar tissue and viable myocardium were directly related to the response to CRT. Furthermore, scar tissue in the LV pacing lead region may prohibit response to CRT. Evaluation for viability and scar tissue may be considered in the selection process for CRT.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is an accepted therapy for patients with advanced heart failure. The technique improves heart failure symptoms, exercise capacity, and left ventricular (LV) function with a reduction in morbidity and mortality (1-4). The response to CRT however varies significantly among individuals, and different predictors of response to CRT have been proposed. One of the most important predictors of response is the presence of LV dyssynchrony (5-7). In addition, some studies have suggested that etiology is related to response to CRT (8-10). Molhoek et al (11) have demonstrated that the percentage of responders was comparable between patients with ischemic and non-ischemic cardiomyopathy, but Woo and colleagues (12) showed that the magnitude of benefit was larger in patients with non-ischemic cardiomyopathy. In particular, the improvement in LV ejection fraction (EF) and the reduction in LV volumes after CRT was more outspoken in patients with non-ischemic cardiomyopathy. Moreover, ischemic etiology of heart failure has been identified as a potential predictor of non-response (13). The response to CRT may thus be related to the extent of viable myocardium and inversely related to the extent of scar tissue (14). In addition, not only the extent of scar tissue may be important for the response to CRT, but also the location of scar tissue. Initial data suggested that scar tissue in the postero-lateral wall (as assessed by contrast-enhanced MRI) resulted in non-response of CRT (15). To further evaluate these issues, 51 consecutive patients with substantial LV dyssynchrony underwent nuclear imaging with technetium-99m tetrofosmin to assess viability and scar tissue, prior to CRT implantation. The extent of viable myocardium and scar tissue were subsequently related to the response to CRT. Also, the influence of scar tissue in the region of the LV lead was evaluated.

METHODS

Patients

The study population consisted of 51 consecutive patients with ischemic cardiomyopathy who were scheduled for CRT implantation. Selection criteria for CRT were severe heart failure (New York Heart Association (NYHA) class III or IV), depressed LVEF (<35%), and prolonged QRS duration (>120 ms); patients had substantial LV dyssynchrony, averaging 86±42 ms, as assessed by tissue Doppler imaging (7). Ischemic etiology was based on the presence of significant coronary artery disease (>50% stenosis in one or more of the major epicardial coronary arteries) on coronary angiography and/or a history of myocardial infarction with ECG evidence, prior PCI or prior CABG.

The study protocol was as follows: before pacemaker implantation a resting single-photon emission computed tomography (SPECT) with technetium-99m tetrofosmin was performed to assess scar tissue and viable myocardium (16,17). Next, the clinical status was assessed and resting 2D transthoracic echocardiography was performed to measure LV volumes and LVEF. Clinical status and echocardiographic characteristics were re-assessed at 6 months follow-up.

Single-Photon Emission Computed Tomography (SPECT) with Technetium-99m Tetrosfosmin

SPECT imaging with technetium-99m tetrofosmin (500 MBq, injected at rest) was performed using a triple head SPECT camera system (GCA 9300/HG, Toshiba Corp.) equipped with low energy general-purpose collimators. Around the 140-KeV energy peak of technetium-99m tetrofosmin, a 20% window was used. A total of 90 projections (step and shoot mode, 35 seconds per projection, imaging time 23 minutes) were obtained over a 360-degree circular orbit. Data were stored in a 64 x 64, 16-bit matrix. Data were displayed in polar map format (normalized to the maximum tracer activity) and analyzed using a 17-segment model (18). Segmental tracer uptake was quantified and a segmental score was appointed with 0 = ≥75% of maximum tracer activity, 1 = 50-75% of maximum tracer activity, 2 = 25-50% of maximum tracer activity and, 3 = ≤25% of maximum tracer activity. Segments with tracer uptake ≥75% were considered normal (viable), segments with tracer uptake 50-75% were considered to contain some scar tissue (non-transmural infarction), and segments with tracer uptake <50% were considered to have extensive scar tissue (transmural infarction). Summation of the segmental scores yielded the total scar score, with the higher scores indicating more extensive scar tissue. In addition to a general score, the presence of regional scar tissue was also evaluated in the area where the LV pacing lead was positioned (see below). Regions with a tracer activity <50% (score 2 or 3) were considered as having transmural scar formation in the LV pacing lead area.

Echocardiography

Patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed Vivid Seven, General Electric-Vingmed, Milwaukee, Wisconsin, USA). Images were obtained using a 3.5 MHz transducer, at a depth of 16 cm in the parasternal and apical views (standard long-axis and two- and four-chamber images). Standard 2D and color Doppler data, triggered to the QRS complex were saved in cine loop format. LV end-diastolic volume (LVEDV), end-systolic volume (LVESV) and LVEF were calculated from the conventional apical 2- and 4-chamber images, using the biplane Simpson's technique (19).
The severity of mitral regurgitation was graded semi-quantitatively from color-flow Doppler images in the apical 4-chamber view. Mitral regurgitation was classified as: mild=1+ (jet area/left atrial area <10%), moderate=2+ (jet area/left atrial area 10-20%), moderately severe =3+ (jet area/left atrial area 20-45%), and severe=4+ (jet area/left atrial area >45%) (20).

Clinical evaluation

Clinical evaluation was performed at baseline and after 6 months of follow-up by an independent physician blinded to all other data. The clinical characteristics included NYHA class, quality-of-life score (using the Minnesota Living with Heart Failure questionnaire) and 6-minute walking distance (21,22). In all patients, QRS duration was measured from the surface ECG using the widest QRS complex from the leads II, V1 and V6.

CRT implantation and LV lead position

A coronary sinus venogram was obtained using a balloon catheter, followed by the insertion of the LV pacing lead. An 8F guiding catheter was used to position the LV lead (Easytrak 4512-80,

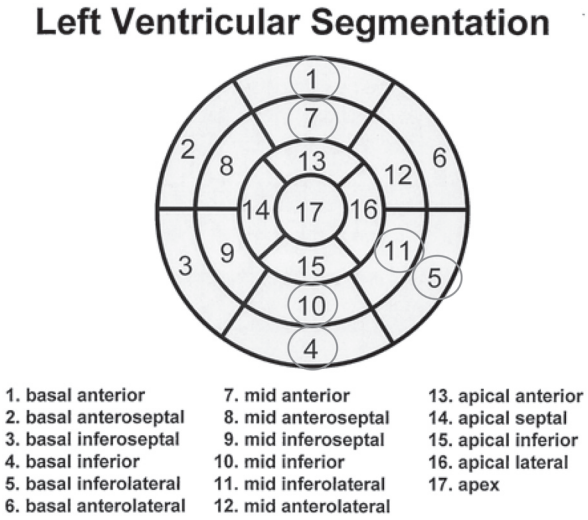
Guidant Corporation, St. Paul, Minnesota; or Attain-SD 4189, Medtronic Inc., Minneapolis, Minnesota) in the coronary sinus, preferably in the lateral or postero-lateral vein (23). The right atrial and ventricular leads were positioned conventionally. All leads were connected to a dual chamber biventricular ICD (Contak CD or Renewal, Guidant Corporation; or Insync III-CD or Marquis, Medtronic Inc.) After implant, the LV lead position was assessed from a chest-X-ray. Using the frontal views (scored base, mid or apex) and lateral views (scored anterior, lateral or posterior) the LV lead locations were determined (24). To determine whether the LV lead was positioned in a region with scar tissue (score 2 or 3), the LV lead position was related to the 17-segment SPECT model .The preferred locations mid-lateral and mid-posterior corresponded with segments 5 and 11 and 4 and 10 respectively (see Figure 1).

Statistical analysis

Most continuous variables had non-normal distribution (as evaluated by Kolmogorov-Smirnov tests). For reasons of uniformity, summary statistics for all continuous variables are therefore presented as medians together with the 25th and 75th percentiles. Categorical data are summarised as frequencies and percentages. Patients were classified as responders of CRT ('responders') if they improved at least 1 level in NYHA class and had an improvement of 25% in exercise distance after 6 months of CRT. The remaining patients, including those who died during the 6-month follow-up period, were classified as 'non-responders'. Differences in baseline characteristics between responders and non-responders, and between patients with and without scar tissue in the target pacing region, were analysed using Wilcoxon-Mann-Whitney tests, Chi-square tests or Fisher's exact tests, as appropriate.

Figure 1. 17-segment LV model

The LV pacing lead positions were positioned mid-lateral (n=22), mid-posterior (n=27) and mid-anterior (n=2). These lead positions corresponded with segments 5 and 11, 4 and 10, and 1 and 7 respectively in this 17-segment model. Segments with a tracer activity of <50% (score 2 or 3) were considered as having transmural scar formation. Accordingly, 15 patients (29%) had scar formation in the region of the LV pacing lead. Adapted from Cerqueira et al (18).



Changes that occurred over time in clinical (QRS duration), functional (NYHA class, 6 minutes exercise distance, quality of life) and echocardiographic (LVEF, LVEDV, LVESV) characteristics were studied by subtracting the baseline values from the values at 6 months follow-up for each individual patient. These changes were then summarised as median values (25^{th} and 75^{th} percentiles). Differences in changes between subgroups of patients were studied by applying the statistical tests that are mentioned above.

Linear regression analyses were performed to evaluate the relations between the overall scar score and the number of viable segments (results of SPECT imaging), and changes in LVEF, LVEDV and LVESV (indicating the magnitude of LV reverse remodeling) after 6 months of CRT. We also aimed to study to what extent SPECT imaging results are associated with response to CRT. For this purpose, two multivariable logistic regression models were constructed, with overall scar score (first model) and the number of viable segments (second model) as main exposure, and age, QRS duration, the presence of LV dyssynchrony, LVEF, LVEDV and LVESV as confounding factors. Adjusted odds ratios (OR) with their corresponding 95% confidence intervals (CI) are reported. Note that it was not our intention to formally build an outcome prediction model. Still, all the continuous variables were assessed for linearity by entering a transformed variable in addition to the variable of interest. The natural logarithm and square transformations were used. A significant change in the -2 log-likelihood was considered as a sign of non-linearity, otherwise the linearity assumption was accepted. All variables met the linearity assumption. All statistical tests were 2-sided. For all tests, a P-value <0.05 was considered statistically significant.

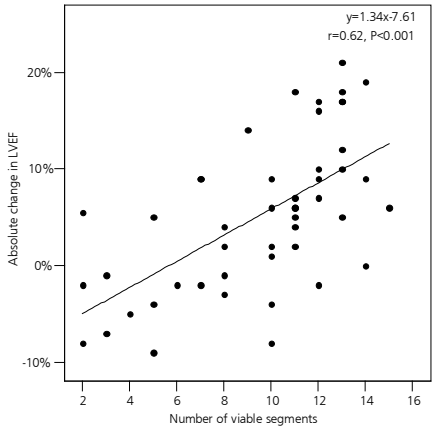
Table 1 . Baseline characteristics of the study population (n=51)

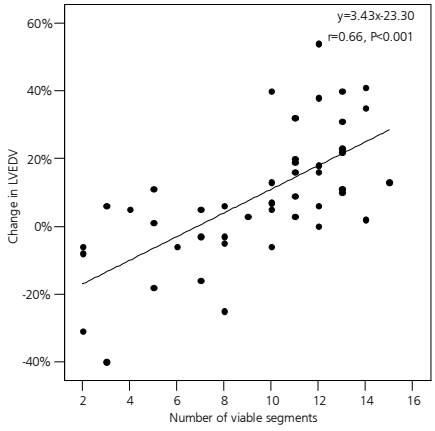
Age (yrs)	68 (62, 76)
Gender (M/F)	40/11
NYHA class (I/II/III/IV)	1/1/43/6
QRS duration (ms)	166 (140, 188)
LBBB	39 (76%)
Rhythm (SR/AF/paced)	44/6/1
LV dyssynchrony (ms)	80 (70, 110)
LVEF (%)	22 (17, 28)
LVEDV (ml)	223 (184, 280)
LVESV (ml)	176 (139, 238)
Mitral regurgitation grade 3-4+	10 (20%)
Medication	
Diuretics	48 (94%)
ACE-inhibitors	43 (84%)
Beta-blockers	29 (57%)
Spironolactone	15 (29%)
Amiodarone	12 (24%)

ACE: angiotensin-converting enzyme; AF: atrial fibrillation; EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; LBBB: left bundle branch block; LV: left ventricular; NYHA: New York Heart Association; SR: sinus rhythm.

Figure 2. Viability vs. echocardiographic changes after CRT

Relationship between the number of viable segments and the absolute change in LV ejection fraction (LVEF) (A), the relative change in LV end-diastolic volume (LVEDV) (B) and the relative change in LV end-systolic volume (LVESV) (C) after 6 months of CRT.





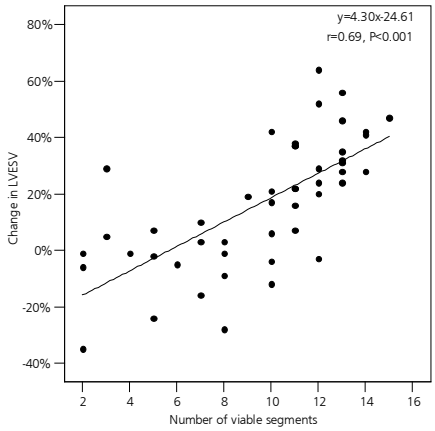
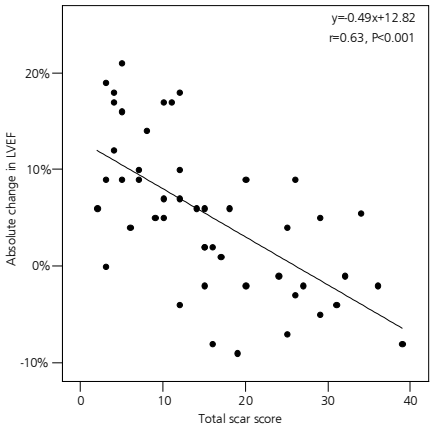
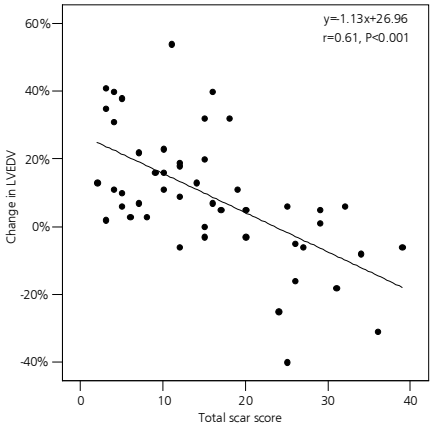


Figure 3. Total scar score vs. echocardiographic changes after CRT

Relationship between the total scar score and the absolute change in LV fraction (LVEF) (A), the relative change in LV end-diastolic volume (LVEDV) (B) and the relative change in LV end-systolic volume (LVESV) (C) after 6 months of CRT.





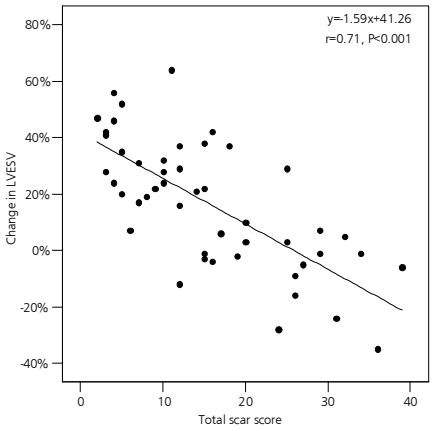


Table 2. Comparison of patients with (n=15) and without transmural scar (n=36) in the LV pacing lead region

	Transmural scar	No transmural scar	P-value
Baseline clinical characteristics			
Age (years)	68 (61, 71)	68 (62, 77)	0.5
Gender (M/F)	13/2	27/9	0.5
QRS duration (ms)	132 (116, 166)	176 (148, 190)	0.002
LBBB	7 (47%)	32 (89%)	0.003
LV dyssynchrony (ms)	70 (20, 100)	90 (73, 120)	0.030
Rhythm (SR/AF/paced)	14/1/0	30/5/1	0.8
Mitral regurgitation grade 3-4+	3 (20%)	7 (19%)	1.0
No. of viable segments	7 (3, 10)	11 (8, 13)	0.001
Total scar score	26 (15, 32)	11 (5, 19)	<0.001
Functional characteristics			
NYHA class			
Baseline (I/II/III/IV)	0/0/13/2	1/1/30/4	1.0
Follow-up (I/II/III/IV)	0/3/9/2	4/25/5/0	
Δ (-2/-1/0/1) *	0/3/10/1	4/24/6/0	<0.001
6-MWD (m)			
Baseline	340 (190, 410)	287 (230, 380)	0.5
Follow-up	360 (240, 420)	393 (340, 500)	
Δ *	5 (-40, 90)	120 (50, 159)	0.026
Quality-of-life score			
Baseline	37 (25, 48)	38 (25, 49)	0.8
Follow-up	31 (21, 40)	15 (8, 24)	
Δ *	-7 (-13, 3)	-17 (-6, -25)	0.015
Echocardiographic characteristics			
LVEF (%)			
Baseline	22 (17, 30)	22 (17, 28)	0.7
Follow-up	22 (19, 28)	30 (26, 36)	
Δ *	-2 (-4, 2)	7 (4, 14)	0.002
LVEDV (ml)			
Baseline	212 (173, 270)	227 (187, 299)	0.4
Follow-up	225 (200, 263)	186 (156, 230)	
Δ *	13 (-9, 39)	-25 (-11, -65)	<0.001
LVESV (ml)			
Baseline	176 (135, 215)	174 (139, 251)	0.5
Follow-up	170 (134, 219)	133 (102, 159)	
Δ *	8 (1, 36)	-50 (-24, -71)	<0.001

Abbreviations as in Table 1. 6-MWD: 6-minute walking distance.* Follow-up minus baseline value

RESULTS

Patient characteristics

Baseline characteristics of the 51 consecutive patients (40 men, median age 68 years) included in this study are summarized in Table 1. A total of 43 (84%) patients were in NYHA class III before CRT implantation. The median QRS duration was 166 and the median LVEF was 22%. All patients received optimized medical therapy, if tolerated.

Device implantation was successful in all patients and no procedure-related complications were observed. The LV pacing lead was positioned in the mid-lateral region in 22 (43%) patients, in the mid-posterior region in 27 (53%) and in the mid-anterior region in 2 (4%) patients. Three patients died of worsening heart failure before the 6-month follow-up evaluation.

Clinical and echocardiographic improvement after CRT

After 6 months of CRT, 27 patients improved one NYHA functional class and 3 patients improved two NYHA functional classes (McNemar test $P<0.001$). The quality-of-life score decreased from 37 (25, 48) to 18 (10, 32) ($P<0.001$). In addition, a significant increase in 6-minute walking distance was seen (from 300 (220, 400) m to 368 (328, 455) m, $P<0.001$). The LVEF showed a modest improvement from 22 (17, 28) % to 28 (22, 34) % ($P<0.001$). Significant reverse remodeling was observed at 6-months follow-up, as evidenced by a decrease in LVEDV from 223 (184, 280) ml at baseline to 199 (164, 245) ml ($P<0.001$) after 6 months of CRT. Similarly, LVESV decreased from 176 (139, 238) ml to 138 (107, 185) ml ($P<0.001$).

Viability and scar score

A total of 867 segments were evaluated, with 476 (55%) classified as normal or viable (score 0), 128 (15%) having non-transmural scar (score 1), and 263 (30%) having transmural scar (95 with score 2 and 168 with score 3). The median number of normal viable segments was 10 (7, 12). A median scar score of 15 (7, 25) per patient was determined.

Changes in LVEF, LVEDV and LVESV after 6 months of CRT were significantly correlated with the number of viable segments at baseline (Figure 2). Changes in LV function and LV dimensions were also associated with the total scar score (Figure 3).

Transmural scar tissue in the LV pacing target region

Fifteen patients (29%) had transmural scar tissue (score 2 or 3) in the region where the LV pacing lead was positioned (see Figure 1). We observed significant differences between patients with and without scar tissue in the target region in QRS duration, the frequency of left bundle branch block, LV dyssynchrony, the number of viable segments and total scar score (see Table 2). No differences were observed in LV function and LV volumes.

Immediately after implantation of the CRT device, the QRS duration was reduced from 176 (148, 190) ms to 155 (141, 165) ms in patients without scar tissue in the target region. In the patients with scar tissue, QRS duration increased from 132 (116, 166) ms to 168 (133, 176) ms. The difference in median change between the two groups was statistically significant (-21 [-41, 1] ms vs. 7 [-4, 48] ms, $P=0.001$)

In patients without scar tissue in the target region NYHA class, 6-minute walking distance, quality-of-life score, LV function and LV dimensions had improved at 6-months follow-up compared

to the baseline value. No improvement was seen in patients without scar tissue (Table 2). The differences in median change between the two groups were statistically significant for all these variables.

Of note, the overall scar score was significantly higher in patients with than in those without scar tissue in the LV pacing lead region (median 26 vs. 11, P<0.001, Table 2). A difference was also observed in the number of viable segments (median 7 vs. 11, P=0.001). The relations between viability and improvement in LVEF and LV volumes after CRT were maintained when patients with scar tissue in the target region of the LV pacing lead were excluded (Figures 4 A-C).

Responders and non-responders

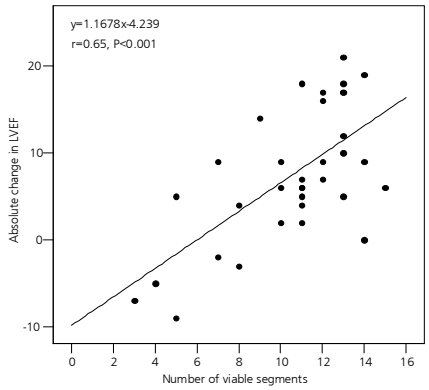
At 6-month follow-up, 27 (53%) patients were classified as responders to CRT (the remaining 21 patients were classified as non-responders). We observed statistically significant differences between responders and non-responders in QRS duration, LV dyssynchrony, number of viable segments, total scar score, presence of scar tissue in the LV pacing target region, and LVEDV at baseline (Table 3).

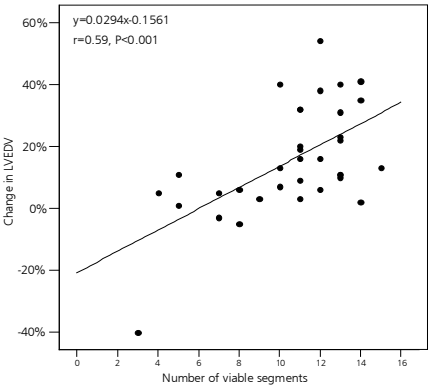
After implantation of the CRT device, QRS duration in responders decreased from 176 (150, 190) ms to 154 (140, 166) ms. QRS duration in non-responders, however, increased from 145 (131, 176) ms to 159 (131, 176) ms. The difference in median QRS duration change between responders and non-responders was statistically significant (-23 [-40, -2] ms vs. 5 [-15, 40] ms, P=0.007). Six months after implantation, quality-of-life score, LV function and LV dimensions had improved in responders of CRT compared to their baseline values, whereas no improvement was found in non-responders. The differences in median change between responders and non-responders were statistically significant for all these variables.

The overall scar score on SPECT was significantly lower in responders as compared

Figure 4. Viability without scar tissue in the LV pacing lead position vs. echocardiographic changes after CRT

Relationship in patients without scar tissue in the LV pacing region between the number of viable segments and the absolute change in LV ejection fraction (LVEF) (A), the relative change in LV end-diastolic volume (LVEDV) (B) and the relative change in LV end-systolic volume (LVESV) (C) after 6 months of CRT.





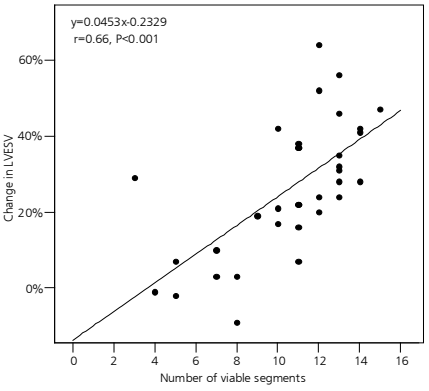


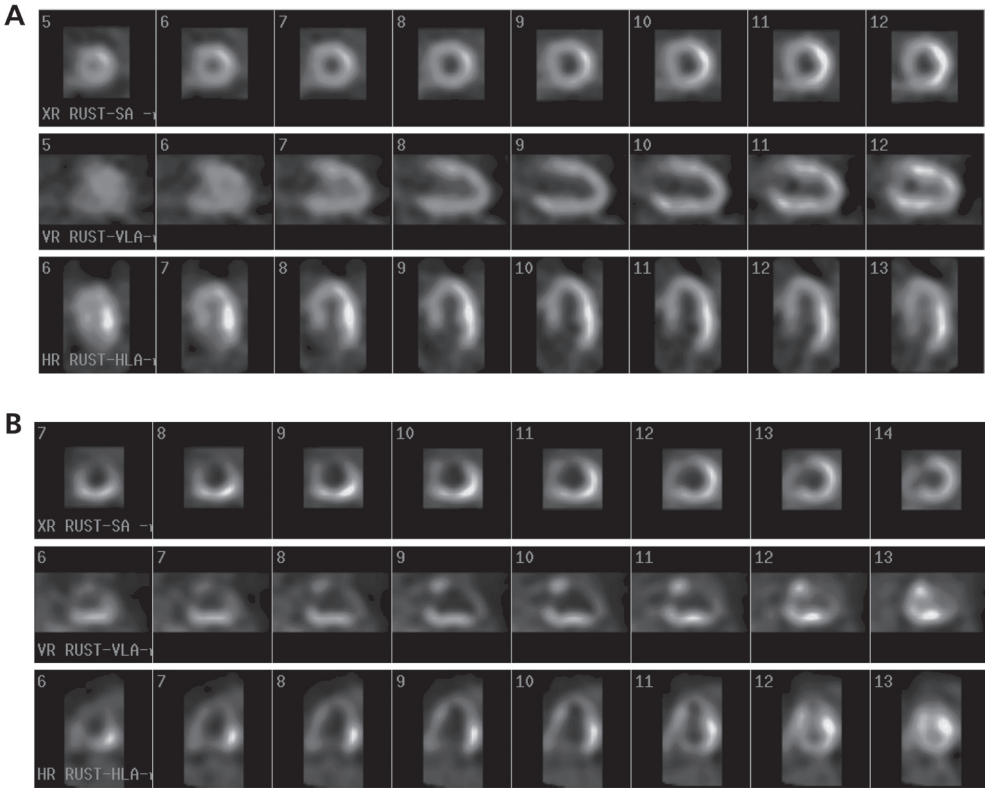
Table 3. Comparison of characteristics of responders (n=27) and non-responders (n=24) at baseline and after 6 months of CRT

	Responders	Non-responders	P-value
Baseline clinical characteristics			
Age (years)	68 (62, 77)	69 (62, 76)	0.7
Gender (M/F)	21/6	19/5i	1.0
QRS duration (ms)	176 (150, 190)	145 (119, 180)	0.011
LBBB	23 (85%)	16 (67%)	0.2
LV dyssynchrony (ms)	90 (80, 120)	70 (20, 100)	0.003
Rhythm (SR/AF/paced)	24/2/1	20/4/0	0.4
Mitral regurgitation grade 3-4+	4 (15%)	6 (25%)	0.5
No. of viable segments	12 (11, 13)	8 (5, 10)	<0.001
Total scar score	10 (5, 15)	25 (15, 28)	<0.001
Scar in LV pacing region	3 (11%)	12 (50%)	0.005
Functional characteristics			
NYHA class			
Baseline (I/II/III/IV)	0/1/25/1	1/0/18/5	0.07
Follow-up (I/II/III/IV)	3/24/0/0	1/4/14/2	
Δ (-2/-1/0/1) *	3/24/0/0	1/3/16/1	<0.001
6-MWD (m)			
Baseline	280 (220, 340)	343 (230, 405)	0.2
Follow-up	420 (350, 500)	340 (240, 380)	
Δ *	140 (120, 170)	-30 (-50, 30)	<0.001
Quality-of-life score			
Baseline	37 (24, 50)	38 (27, 47)	1.0
Follow-up	12 (5, 18)	32 (24, 44)	
Δ *	-21 (-15, -40)	2 (-7, 5)	<0.001
Echo characteristics			
LVEF (%)			
Baseline	22 (17, 28)	22 (17, 31)	1.0
Follow-up	31 (26, 36)	23 (19, 29)	
Δ *	9 (5, 16)	-2 (-4, 4)	<0.001
LVEDV (ml)			
Baseline	249 (188, 326)	204 (178, 248)	0.048
Follow-up	198 (164, 233)	204 (164, 251)	
Δ *	-45 (-74, -12)	0 (-13, 23)	<0.001
LVESV (ml)			
Baseline	190 (153, 259)	157 (133, 219)	0.1
Follow-up	137 (103, 164)	138 (113, 195)	
Δ *	-56 (-74, -27)	3 (-12, 17)	<0.001

Abbreviations as in Table 1 and 2. * Follow-up minus baseline value

Figure 5. Patient examples

SPECT imaging in a responder (A) and non-responder patient (B). As demonstrated in the short axis, vertical long axis and horizontal long axis of the LV the extent of viable myocardium is larger in the responder (total scar score 5, number of viable segments 13) compared to the non-responder patient (total scar score 29, number of viable segments 4).



to non-responders (Table 3, Figure 5). Responders also had higher numbers of viable segments, compared to non-responders. Vice-versa, the overall scar score and the number of viable segments were strongly related to the probability of being a responder of CRT. Among the patients with an overall scar score below the median (15) only 33% were classified as a responder compared to 88% in those with a value above the median. Similarly, in patients with less than 10 viable segments (median value) only 29% were responders versus 80% in patient with 10 or more viable segments. After adjustment for multiple confounders, a higher scar score remained associated with a lower probability of response (adjusted OR 0.89 per point and 95% CI 0.81 to 0.98, P=0.017); a higher number of viable segments remained associated with a higher probability of response (adjusted OR 1.36 per segment and 95% CI 1.04 to 1.77, P=0.013).

DISCUSSION

The current findings illustrate that extensive scar tissue is frequently present in patients with ischemic cardiomyopathy and substantial LV dyssynchrony. In these patients, response to CRT is directly related to the extent of viable myocardium and inversely related to the extent of scar tissue. In addition, the location of the scar tissue is important; patients with extensive scar tissue in the region where the LV lead is positioned do not respond to CRT. Consequently, the group of non-responders thus consisted mainly of patients with scar tissue in the region of the LV lead or with viable tissue in region of the LV lead but with extensive scar tissue.

Viability and scar tissue versus response to CRT

The observation that 20-30% of patients do not respond to CRT has resulted in a search for factors that may predict response. Various studies have recently demonstrated the value of LV dyssynchrony for prediction of response to CRT (5,7,25). It has also been suggested that the extent of scar tissue on the one hand, and the extent of viable myocardium on the other hand, are important for response to CRT. At present only 1 study has systematically evaluated the relation between viability and the response to CRT (14). In 21 patients with ischemic cardiomyopathy (mean LVEF 21±5%) contrast echocardiography was performed before pacemaker implantation. With the use of contrast echocardiography, segmental perfusion was evaluated and a perfusion score index was derived, reflecting the extent of viable myocardium. The perfusion score index was directly related to the change in LVEF as assessed immediately after CRT. Similarly, the perfusion score index was also related to LV reverse remodeling (indicated by LV end-diastolic dimension) at 6 months after CRT. The current observations are in line with these findings; the extent of viability (expressed as the number of viable segments) was linearly related to the increase in LVEF, and the decrease in LVESV and LVEDV assessed at 6-months follow-up (Figures 2A-C). These findings are not surprising since one could anticipate that a substantial amount of viable myocardium is needed for improvement in systolic LV function after CRT.

In the present study, nuclear imaging with technetium-99m tetrofosmin SPECT was used to assess viability. SPECT imaging with technetium-99m labelled tracers has extensively been used for assessment of viability, and tracer uptake is dependent on a combination of intact perfusion, cell membrane and mitochondrial integrity (26). However, viability assessment in patients with LBBB, may be affected by partial volume effects in particular in the septum with asynchronous regional wall thickening. Still, SPECT imaging may be an ideal technique for assessment in these patients, since a resting SPECT is sufficient and the technique is widely available.

In addition to viability, the extent of scar tissue is also important for response to CRT, as reflected in the inverse relation between the extent of scar tissue and the change in LVEF and LV volumes (Figures 3A-C). Substantial improvement in LVEF was rare in patients with extensive scar tissue (Figure 3A), reflecting that too much scar tissue does not permit recovery of systolic LV function after CRT. In particular, when the scar score exceeded 15 (median value), the response rate to CRT was only 12%. Future studies are needed to specifically elucidate how much scar tissue and/or viable myocardium is needed to result in improvement of LVEF after CRT.

Scar tissue in the region of the LV pacing lead versus response to CRT

Besides the extent of scar tissue, the location of scar tissue is also important. In a recent case report (27) it was demonstrated that acute infarction in the region where the LV lead was positioned resulted in acute loss of response to CRT. Moreover, it was demonstrated with contrast-enhanced MRI that transmural scar tissue in the region of the LV pacing lead prohibited response to CRT (28). The findings in the current study are in line with these observations. The patients with a transmural scar on technetium-99m tetrofosmin SPECT, did not improve in LV function, did not show reverse remodeling and did not improve in clinical characteristics. These observations suggest that extensive scar tissue in the region of the LV pacing lead results in inadequate pacing with no response to CRT.

In the current study (in patients with severe ischemic LV dysfunction) 15 (29%) patients had transmural scar tissue in the region of the LV pacing lead. Of interest, another recent observational study (with 91 patients with ischemic cardiomyopathy and QRS >120 ms) reported a similar percentage of patients with scar tissue in the infero-lateral wall, which is the target region for LV lead positioning (29). Accordingly, evaluation for the extent and location of scar tissue may be considered in the selection process for CRT to avoid non-response. Larger studies are needed to confirm our findings and to fully elucidate the clinical relevance of viability and scar tissue for response to CRT.

Of note, adjustments in V-V intervals were not evaluated in the present study. V-V optimization may be of particular importance in patients with ischemic cardiomyopathy and scar tissue. This issue needs further study in future trials.

Responders versus non-responders

Multivariable analysis revealed that a higher scar score was associated with a lower probability of response, and vice versa, a higher number of viable segments was associated with a higher probability of response. Importantly, both LV dyssynchrony (as assessed with TDI) and the extent of scar tissue (as assessed with SPECT imaging) are of value in the prediction of response to CRT.

Of note, the non-responder rate in our study was quite high as compared to several clinical trials. We feel that this may be due to fact that we only included patients with previous myocardial infarction, who appeared to have a worse outcome after CRT than patients with a non-ischemic cardiomyopathy (12,13).

CONCLUSION

Transmural scar formation is frequently observed in patients with ischemic cardiomyopathy. A higher number of viable segments at baseline was associated with a higher probability of response; vice versa, a higher total scar score was associated with a lower probability of response. In addition, transmural scar tissue in the region of the LV pacing lead may prohibit response. Evaluation for viability and scar tissue may be considered in the selection process for CRT.

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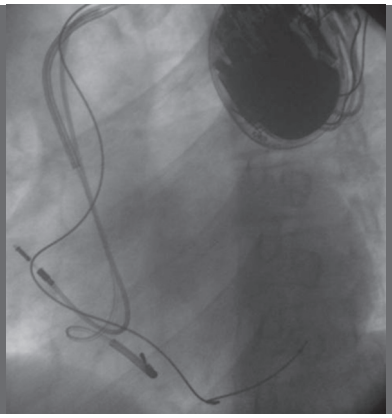
Chapter 6



Effect of total scar burden on contrast-enhanced magnetic resonance imaging on response to cardiac resynchronization therapy

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ABSTRACT

It has been demonstrated that improvement in left ventricular (LV) function and reverse remodeling after cardiac resynchronization therapy (CRT) were greater in patients with non-ischemic cardiomyopathy than in patients with ischemic cardiomyopathy. The aim of this study was therefore to evaluate the influence of scar burden on response to CRT. We included 34 patients with ischemic cardiomyopathy (New York Heart Association class 3.1±0.4, LV ejection fraction 23±7%). Contrast-enhanced magnetic resonance imaging (MRI) was used to determine the total scar burden, using a 17-segment model with a 5-point hyperenhancement scale (from score 0= no hyperenhancement indicating no scar, to score 4= hyperenhancement >76%, transmural scar). Linear regression analysis showed a significant correlation ($r=-0.91$, $P<0.05$) between the total scar burden at baseline and the change in LV end-systolic volume after 6 months of CRT. Also, patients not responding to CRT had significantly more scar tissue than responders. In fact, a scar burden of >1.20 resulted in complete functional non-response. In conclusion, total scar burden, as assessed with contrast-enhanced MRI is an important factor influencing response to CRT and may be included in the selection process for CRT candidates.

INTRODUCTION

Recently, Bleeker et al suggested that, besides the presence of left ventricular (LV) dyssynchrony, transmural scar tissue in the region of the LV pacing lead may prohibit functional and clinical response to cardiac resynchronization therapy (CRT) (1). Furthermore, Woo et al demonstrated that reverse remodeling and improvement in LV ejection fraction (EF) after CRT were larger in non-ischemic patients than in ischemic patients (2). This may imply that not only the location but also the size of infarcted myocardium (total scar burden) is important for response to CRT. One could anticipate that in patients with a large extent of scar tissue, improvement in LV function after CRT will be limited, even if the region of the LV pacing lead is viable. The current study evaluates the importance of the total scar burden for functional response to CRT. Contrast-enhanced magnetic resonance imaging (MRI) was used to determine the extent and transmurality of the scar tissue.

METHODS

Patients, study protocol

A total of 34 consecutive patients with ischemic cardiomyopathy who were scheduled for CRT implantation were prospectively enrolled in this study. Fifteen patients were included in a previous study (1). The traditional selection criteria for CRT were used: New York Heart Association (NYHA) class III or IV, LVEF <35% and QRS duration >120 ms. Ischemic etiology was based on the presence of significant coronary artery disease (>50% stenosis in one or more of the major epicardial coronary arteries) on coronary angiography and/or a history of myocardial infarction, prior percutaneous coronary intervention or coronary artery bypass graft surgery. None of the patients had a recent myocardial infarction (<3 months) or presented with decompensated heart failure. Patients with pacemakers or intracranial clips were excluded.
The study protocol included contrast-enhanced MRI to determine the extent and transmurality of infarcted myocardial tissue (total scar burden) before CRT implantation. Furthermore, clinical status was assessed and resting 2-dimensional transthoracic echocardiography was performed to measure LV volumes and LVEF before implantation. Clinical status and echocardiographic parameters were re-assessed after 6 months of CRT to determine response to CRT.

Magnetic resonance imaging, data acquisition and analysis

A 1.5-Tesla Gyroscan ACS-NT MRI scanner (Philips Medical Systems, Best, the Netherlands) equipped with powertrack 6000 gradients was used. Patients were positioned in a supine position and images were acquired during breathholds of approximately 15 seconds. The heart was imaged from apex to base (3), with 10 to 12 imaging levels (dependant on the heart size) in the short axis view using a sensitivity encoding, balanced fast-field echo sequence.
Contrast-enhanced images were acquired 17 to 19 minutes after bolus injection of gadolinium diethylenetriamine penta-acetetic acid (Magnevist, Shering/Berlex, Berlin, Germany; 0.15 mmol/kg) with an inversion-recovery gradient echocardiographic sequence; the inversion time was determined with a real-time scan plan. Depending on the patient's heart rate and heart

size, 20 to 24 slices were obtained in 2 breathhold acquisitions of approximately 15 seconds. The following parameters were applied: 400 x 400 mm² field of view, 256 x 256 matrix size, a 5 mm slice thickness, slice gap of -5 mm, 15º flip angle, echo time of 1.36 ms, and 4.53 ms repetition time (4).

The contrast-enhancement images were scored visually by two experienced observers (blinded to all other data) according to a previously described 17-segment model (5). Segmental scar score was appointed with 0=absence of hyperenhancement, 1=hyperenhancement of 1% to 25% of LV wall thickness, 2=hyperenhancement extending 26% to 50%, 3=hyperenhancement extending 51% to 76%, and 4=hyperenhancement extending 76% to 100% (4). The number of affected segments was considered to reflect the spatial extent of scar tissue. The number of segments with a segmental scar score of 3 and 4 was considered to reflect the transmurality of scar tissue in the infarct zone. Patients' segmental scores were summed and divided by 17 to yield the total total scar burden (which reflected the damage per patient). Reproducibility for visual analysis was reported in a previous study; the inter- and intraobserver variability were 4.2±6.6% and 3.0±5.1% respectively (6).

Echocardiography, data Acquisition and analysis

Baseline and follow-up examinations were performed in the left lateral decubitus position using a commercially available system (Vingmed Vivid Seven, General Electric-Vingmed, Milwaukee, Wisconsin, USA). Images were obtained using a 3.5 MHz transducer, at a depth of 16 cm in the parasternal and apical views (standard long-axis and 2- and 4-chamber images). Standard 2-dimensional and color Doppler data, triggered to the QRS complex were saved in cine-loop format. LV end-diastolic (EDV) and end-systolic volumes (ESV) were derived and LVEF was calculated from the conventional apical 2- and 4-chamber images, using the biplane Simpson's technique (7). Inter- and intra-observer variability for the assessment of LVEF and LV volumes was 90% and 96% respectively.

The severity of mitral regurgitation was graded semi-quantitatively from color-flow Doppler images using the apical 4-chamber views. Mitral regurgitation was graded on a 4-point scale: mild=1+ (jet area/left atrial area <10%), moderate=2+ (jet area/left atrial area 10-20%), moderately severe =3+ (jet area/left atrial area 20-45%), and severe=4+ (jet area/left atrial area >45%) (8).

Clinical evaluation

Evaluation of clinical status was performed at baseline and after 6 months of follow-up by an independent physician blinded to all other data. The clinical parameters included NYHA class, quality-of-life score (using the Minnesota Living with Heart Failure questionnaire) and 6-minute walking distance (9,10). In all patients, QRS duration was measured from the surface electrocardiogram using the widest QRS complex from the leads II, V1 and V6.

Device implantation

First, a coronary sinus venogram was obtained using balloon catheter, followed by the insertion of the LV pacing lead. An 8F guiding catheter was used to guide the LV lead (Easytrak 4512-80, Guidant Corporation, St. Paul, Minnesota; or Attain-SD 4189, Medtronic Inc., Minneapolis, Minnesota) into the coronary sinus. The preferred position was a lateral or postero-lateral vein (11). The right atrial and ventricular leads were positioned conventionally. All leads were

connected to a dual chamber biventricular ICD (Contak CD or TR, Guidant Corporation; or Insync III or CD, Medtronic Inc.)

Statistical analysis

Results are expressed as mean ± SD. Comparison of data was performed using the paired and unpaired Students t test for continuous variables and Fisher's exact test for proportions. Linear regression analysis was performed to evaluate the relation between the magnitude of LV reverse remodeling (reduction in LVESV) after 6 months of CRT and total scar burden, spatial extent, and transmurality respectively. For all tests, a P-value <0.05 was considered statistically significant.

RESULTS

Study population

Baseline characteristics are listed in Table 1. Device implantation was successful in all patients and no procedure-related complications were observed. Two patients died of worsening heart failure before the 6-month follow-up evaluation.

Total scar burden

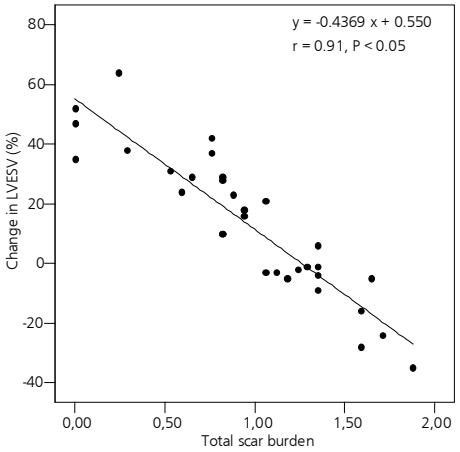
Of the 578 segments evaluated, 329 (57%) showed no hyperenhancement (score 0), 68 (12%) showed minimal hyperenhancement (score 1), and 63 (11%) had hyperenhancement

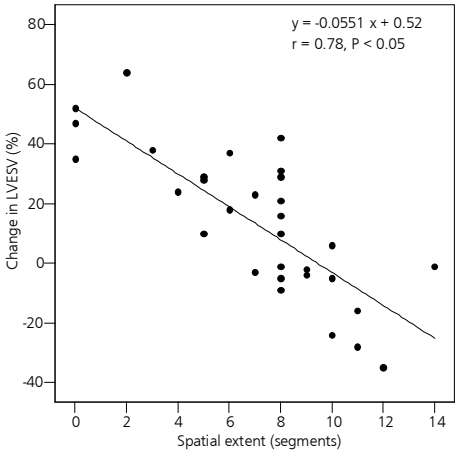
Table 1. Patient characteristics (n=34)

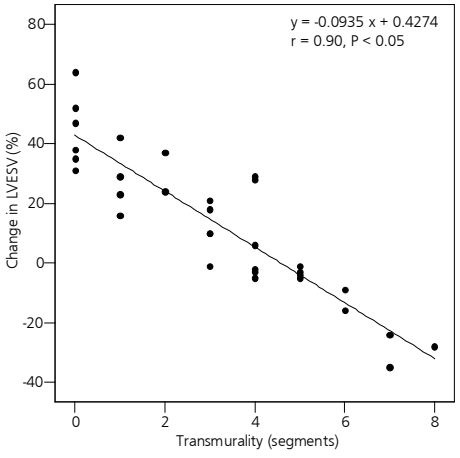
Age (yrs)	68±10
Gender (M/F)	29/5
NYHA class	3.1±0.4
QRS duration (ms)	152±36
LBBB	21 (62%)
Sinus rhythm	29 (85%)
LV dyssynchrony (ms)	85±37
LVEF (%)	23±7
LVEDV (ml)	228±77
LVESV (ml)	180±72
Grade 3-4+ mitral regurgitation	6 (18%)
Medication	
Diuretics	33 (97%)
ACE-inhibitors	28 (82%)
Beta-blockers	22 (65%)
Spironolactone	14 (41%)
Digoxin	8 (24%)

ACE: angiotensin-converting enzyme; EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; LBBB: left bundle branch block; LV: left ventricular; NYHA: New York Heart Association.

Figure 1. Relationship between the percentage change in LV end-systolic volume (LVESV) after 6 months of CRT and the total scar burden (A), spatial extent (B), and transmurality (C) at baseline







score 2, 64 (11%) had score 3, and 54 (9%) score 4. Accordingly, 118 segments showed transmural scar tissue (score 3 and 4) and mean transmurality (number of segments with score 3 or 4) per patient was 3.4±2.5. The number of segments with any hyperenhancement (spatial extent) ranged from 0 to 14 per patient (mean 7.3±3.5). Extensive regions of scar tissue were present as indicated by a total scar burden of 1.0±0.6 (ranging from 0 to 2.12).

Response to CRT

After 6 months of CRT, mean NYHA class had decreased from 3.1±0.4 to 2.4±0.8 (P<0.01). In addition, the 6-minute walking distance improved from 299±97 m to 350±132 m (P<0.01). Also, symptoms improved as evidenced by the significant decrease in quality-of-life score of 32% on average (from 41±14 to 28±19, P<0.01). Echocardiographic evaluation after 6 months of CRT showed significant reverse remodeling; LVESV decreased from 180±72 ml to 150±57 ml (P<0.01). Also, the LVEDV decreased from 227±77 ml at baseline to 208±63 ml after 6 months of CRT (P<0.01). LVEF was 23±7% at baseline and improved significantly at 6 months follow-up to 28±9% (P<0.01).

On the basis of an improvement of ≥10% in LVESV (12), 18 patients (53%) were classified as responders and 16 (47%) as non-responders. The patients who died before 6 months follow-up were classified as non-responders. Baseline characteristics were comparable between responders and non-responders, except that QRS duration was less in the non-responders (167±34 ms vs. 135±31 ms, P<0.05) and non-responders had significantly smaller LV volumes (Table 2).

After 6 months of CRT, responders showed a significant improvement in clinical parameters after CRT, whereas none of the clinical parameters improved in the non-responders (Table 3). In addition, an

Table 2. Echocardiographic and MRI findings at baseline in responders (n=18) and non-responders (n=16)

	Responders	Non-responders	P-value
LVEF (%)	22±6	24±7	NS
LVEDV (ml)	253±92	198±44	<0.05
LVESV (ml)	205±84	152±43	<0.05
Spatial extent (No. of segments with any hyperenhancement)	5.1±3.0	9.8±2.2	<0.05
Transmurality (No. of segments with hyperenhancement score 3 or 4)	1.6±1.5	5.6±1.6	<0.05
Total scar burden (Summation of individual segmental hyperenhancement scores)	0.6±0.4	1.5±0.3	<0.05

Abbreviations as in Table 1.

Table 3. Clinical and functional improvement (Δ) in CRT responders and non-responders

	Responders	Non-responders	P-value
Δ NYHA class	1.1±0.7	0.1±0.5	<0.05
Δ Quality-of-life score	21±19	4±10	<0.05
Δ 6-minute walking distance (m)	100±100	7±102	<0.05
Δ LVEF (%)	9±7	-1±5	<0.05
Δ LVEDV (%)	-16±19	8±12	<0.05
Δ LVESV (%)	-31±14	9±12	<0.05

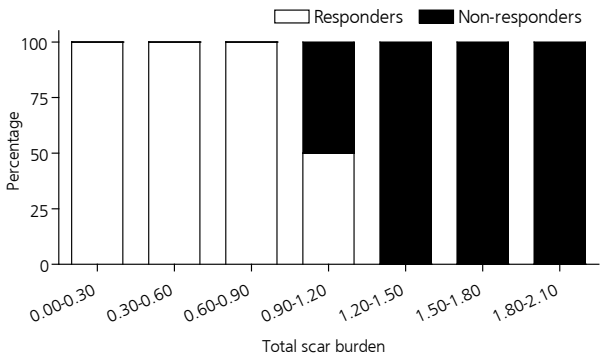
Abbreviations as in Table 1.

improvement in LVEF with reverse remodeling was noted in the responders after CRT; these effects were not observed in the non-responders.

Total scar burden and response to CRT

Linear regression analysis showed a significant inverse relation between the total scar burden and reverse remodeling, defined as the relative change of LVESV after 6 months of CRT (Figure 1A, r=-0.91, P<0.05); the more scar burden the less reverse remodeling. Also, the spatial extent and transmurality were correlated with a change in LVESV (Figures 1B and C).
Furthermore, patients not responding to CRT had significantly more scar tissue than responders, as demonstrated by significantly higher spatial extent, transmurality and total scar burden

Figure 2. Relation between total scar burden (categorized) and response to CRT. A score >1.20 will result in functional non-response



(Table 2). In fact, none of the patients with a total scar burden >1.20 had responded to CRT (Figure 2).

DISCUSSION

The results of the current study in ischemic heart failure patients demonstrate that the total scar burden, as assessed with contrast-enhanced MRI, is an important factor influencing response to CRT; the more extensive the scar burden, the lower the likelihood of LV reverse remodeling after CRT.

Currently, data about infarct size and response to CRT are scarce. Only one study by Hummel et al evaluated the relation between viability and response to CRT using contrast echocardiography (13). A perfusion score index, reflecting the extent of viable myocardium, was related to LV reverse remodeling (defined as a reduction LV end-diastolic dimension) after 6 months ($P=0.003$, $r=-0.68$), indicating that the more viable myocardium present, the larger the reverse remodeling. This observation is in line with the findings in the current study; the total scar burden was linearly related to the relative change in LVESV after 6 months of CRT (Figure 1A). Also, the spatial extent and transmurality of scar tissue showed strong relations ($r=-0.78$ and $r=-0.90$ respectively, both $P<0.05$) with echocardiographic improvement during follow-up (Figures 1B and C).

Furthermore, the present study demonstrated that echocardiographic responders to CRT (reduction in LVESV ≥10%) had a significantly smaller total scar burden as compared to non-responders (0.6 ± 0.4 vs. 1.5 ± 0.3, $P<0.05$). Figure 2 indicates that a total scar burden >1.20 will result in non-response to CRT in terms of LV reverse remodeling. Also, Hummel et al demonstrated that the patients with lower perfusion score index (less viable segments) tended to have less clinical improvement (13). Still, future larger studies are needed to identify the precise cut-off value for the total scar burden beyond which response of CRT will not occur.

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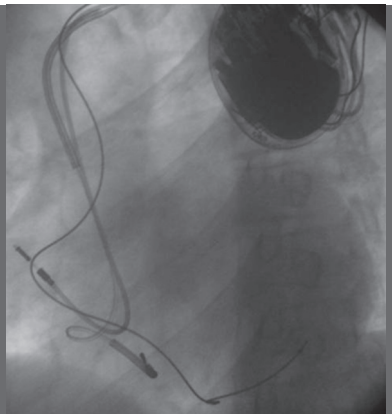
Chapter 7



Myocardial contractile reserve predicts improvement in left ventricular function after cardiac resynchronization therapy

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ABSTRACT

Background Myocardial contractile reserve has been shown to provide important prognostic information in heart failure patients. We hypothesized that myocardial contractile reserve would predict left ventricular (LV) reverse remodeling after cardiac resynchronization therapy (CRT).

Methods Thirty-one consecutive heart failure patients (LV ejection fraction [EF] 26±7%, 35% non-ischemic cardiomyopathy) underwent echocardiography during low-dose dobutamine infusion before CRT implantation to assess global contractile reserve (improvement in LVEF) and local contractile reserve in the region of the LV pacing lead (assessed by radial strain using speckle tracking analysis). Responders were defined by a decrease in LV end-systolic volume ≥15% after 6 months of CRT.

Results During low-dose dobutamine infusion, responders showed a greater increase in LVEF as compared to non-responders (Δ 13±8% vs. 3±4%, p<0.001). Furthermore, contractile reserve was directly related to improvement in LVEF after 6 months of CRT (r=0.80, P<0.001). Moreover, a cut-off value of >7.5 % increase in dobutamine-induced LVEF exhibited a sensitivity of 76% and specificity of 86% to predict response after 6 months of CRT (AUC 0.87). Lastly, contractile reserve in the region in the LV pacing lead was present only in responders (Δ strain during low-dose dobutamine 6±5% in responders vs. -1±4% in non-responders, P=0.002).

Conclusions The current study demonstrates that myocardial contractile reserve (>7.5% increase in LVEF during low-dose dobutamine infusion) predicts LV reverse remodeling after CRT.

INTRODUCTION

Previous studies have demonstrated that cardiac resynchronization therapy (CRT) not only improves clinical status (New York Heart Association (NYHA) class, quality of life and exercise capacity) (1-3), but also reverses left ventricular (LV) remodeling and improves systolic function (4,5). Furthermore, Yu and colleagues reported that a reduction in LV end-systolic volume (ESV) after 6 months of CRT was predictive for long-term survival after CRT (6). However, approximately one third of patients in clinical studies do not show LV reverse remodeling after CRT, and do thus not respond to CRT.

Myocardial contractile reserve has been shown to provide important prognostic information in both ischemic (7-9) and non-ischemic cardiomyopathy (10,11). We hypothesized that myocardial contractile reserve, as determined with echocardiography during low-dose dobutamine infusion, would predict LV reverse remodeling and improvement in LV function by CRT in both ischemic and non-ischemic patients. Furthermore, lack of contractile reserve in the region of the LV pacing lead, i.e. scar tissue (12) or fibrosis, may also denote a low likelihood of response.

METHODS

Patients

Thirty-one consecutive patients with advanced heart failure (NYHA class III or IV), depressed LV function (LV ejection fraction (EF) <35%), wide QRS complex (>120 ms) were prospectively included for implantation of a CRT device. Patients with a recent myocardial infarction (<3 months), or decompensated heart failure were excluded. All patients underwent coronary angiograms prior to implantation to exclude treatable ischemic heart disease. Etiology was considered ischemic in the presence of significant coronary artery disease (≥50% stenosis in one or more of the major epicardial coronary arteries) and/or a history of myocardial infarction or prior revascularization.

The study protocol included evaluation of global contractile reserve during low-dose dobutamine (up to 10 μg/kg/min) infusion. The increment in LVEF was considered a marker of global contractile reserve. In addition, the presence of regional contractile reserve in the region where the LV pacing lead was positioned (the postero-lateral wall in all patients, see below) was also evaluated. Resting echocardiography was repeated after 6 months of CRT to evaluate changes in LVEF and LV volumes. Clinical status was assessed at baseline and after 6 months of CRT.

Clinical evaluation

Clinical evaluation was performed before implantation and after 6 months of CRT. NYHA functional class was used to evaluate heart failure symptoms and scored by an independent physician, who was blinded to all other patient data. Quality-of-life score was assessed using the Minnesota Living with Heart Failure questionnaire (13). Exercise tolerance was assessed using the 6-minute walk test (14). In all patients, QRS duration was measured from the

surface ECG using the widest QRS complex from the leads II, V1 and V6, at baseline and after implantation.

Echocardiography

Echocardiographic images were obtained with a 3.5-MHz transducer in the left lateral decubitus position using a commercially available system (Vivid Seven, General Electric-Vingmed, Milwaukee, Wisconsin). Standard 2-dimensional and color Doppler data, triggered to the QRS complex were saved in cine-loop format for off-line analysis (EchoPac 6.06, GE Medical systems, Horten, Norway). LVEDV and LVESV were derived and LVEF was calculated from the conventional apical 2- and 4-chamber images, using the biplane Simpson's technique (15). Wall motion score analysis was applied to a 16-segment model of the LV using a semi-quantitative scoring system (1=normal, 2=hypokinesia, 3=akinesia, 4=dyskinesia) (15). The number of akinetic segments was noted for each patient. LV dyssynchrony was assessed with Tissue Doppler imaging obtained in the apical 4- and 2-chamber views and calculated as the maximum time delay between the peak systolic velocities of 4 opposing basal walls (16). Based on previous observations maximum time delay of ≥65 ms was considered to represent substantial LV dyssynchrony (16). The severity of mitral regurgitation was graded semi-quantitatively from color-flow Doppler images using the apical 4-chamber views. Mitral regurgitation was graded on a 3-point scale: mild (jet area/left atrial area <20%), moderate (jet area/left atrial area 20-45%), and severe (jet area/left atrial area >45%) (17).

Assessment of global contractile reserve

After acquisition of baseline echocardiographic data, stepwise infusion of dobutamine was started. The initial infusion rate was 5 µg/kg/min and was increased after 5 minutes to 10 µg/kg/min. Standard echocardiographic images (parasternal long- and short-axis, apical 2- and 4-chamber views, apical long-axis) were obtained and cine-loops were saved in digital format at rest, and during 5 and 10 µg/kg/min dobutamine infusion. LV volumes and LVEF fraction were assessed off-line at rest and at maximal low-dose dobutamine level (10 µg/kg/min) to determine global ventricular contractile reserve (expressed as the change in LVEF from baseline to 10 µg/kg/min dobutamine infusion).

Assessment of regional contractile reserve

Myocardial strain was measured using speckle tracking analysis from LV short-axis images at the papillary muscle level (18,19,20). After tracing the endocardial borders in the end-systolic frame, an automated tracking algorithm outlined the myocardial deformation in 6 separate LV segments (septal, antero-septal, anterior, posterior, lateral and inferior). Peak systolic radial strain was measured in the lateral and posterior regions, where the LV lead was positioned (see below); peak strain was measured at baseline and at 6 months follow-up to determine improvement in regional strain (regional contractile reserve) after CRT.

Definition of response to CRT

Patients were classified as responders to CRT ('responders') if they showed a decrease of ≥15% in LVESV after 6 months of CRT (16,21).The remaining patients, including those who died during the 6-month follow-up period, were classified as 'non-responders'.

CRT implantation and LV lead position

A coronary sinus venogram was obtained using balloon catheter, followed by the insertion of the LV pacing lead. An 8F guiding catheter was used to position the LV lead (Easytrak 4512-80, Guidant Corporation, St. Paul, Minnesota; or Attain-SD 4189, Medtronic Inc., Minneapolis, Minnesota) in the coronary sinus. The preferred position was a lateral or postero-lateral vein (22). The right atrial and ventricular leads were positioned conventionally. All leads were connected to a dual chamber biventricular ICD (Contak Renewal II or H195, Guidant Corporation; or Insync III or Insync Sentry, Medtronic Inc.).
One day after implantation, the LV lead position was assessed from a chest-X-ray. Using the frontal views (scored base, mid or apex) and lateral views (scored anterior, lateral or posterior) the LV lead locations were determined (23,24).

Statistical analysis

Continuous variables are expressed as mean ± SD. Categorical data are summarized as frequencies and percentages. Differences in baseline characteristics between responders and non-responders were analyzed using unpaired Students t tests (continuous variables) and chi-square or Fisher's exact tests (dichotomous variables) as appropriate. The paired Students t test was used to compare continuous data within the subgroups during follow-up.
Linear regression analysis was performed to evaluate the relation between the improvement in LVEF during 10 µg/kg/min dobutamine infusion and after 6 months of CRT. The optimal improvement in LVEF during dobutamine infusion to predict response to CRT was determined by receiver operator characteristic (ROC) curve analysis.
Uni- and multivariable logistic regression analyses were performed to determine the relation between potential risk factors at baseline and response to CRT. We considered the following variables: dobutamine-induced increase in LVEF, QRS duration, gender, age, etiology, LV dyssynchrony, rhythm, LVEF, LV volumes. Only significant univariate variables entered the multivariable stage, because of the small study population. We report only adjusted odds ratios (OR) with their corresponding 95% confidence intervals (CI). For all tests, a P-value <0.05 was considered statistically significant.

RESULTS

Patients

Baseline characteristics of the 31 consecutive patients (27 men, mean age 64±10 years) included in this study are summarized in Table 1. The number of akinetic segments in each patient ranged from 0 to 13 segments (mean 5.5±3.1). All patients received optimized medical therapy, if tolerated. Device implantation was successful in all patients and no procedure-related complications were observed. The LV pacing lead was positioned in the mid-lateral region in 18 (58%) patients, in the mid-posterior region in 13 (42%) patients. LV pacing threshold after implant was 1.2±0.7 Volt. Two patients were admitted for LV lead repositioning during follow-up, one due to phrenic nerve stimulation and one due to LV dislocation resulting in non-capture.

Table 1. Patient characteristics (n=31)	
Age (yrs)	64±10
Gender (M/F)	27/4
NYHA class (II/III/IV)	2/28/1
Ischemic etiology	20 (65%)
QRS duration (ms)	154±30
LBBB/RBBB/IVD/Normal	22/3/3/3
Sinus rhythm/Atrial fibrillation/Paced	27/2/2
LV dyssynchrony (ms)	64±42
LVEF (%)	26±7
LVEDV (ml)	216±76
LVESV (ml)	163±66
No. of akinetic segments	5.5±3.1
Mitral regurgitation (moderate-to-severe)	5 (16%)
Medication	
Diuretics	29 (94%)
ACE-inhibitors	30 (97%)
Beta-blockers	24 (77%)
Spironolactone	16 (51%)

ACE: angiotensin-converting enzyme; EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; IVD: interventricular delay; LBBB: left bundle branch block; LV: left ventricular; NYHA: New York Heart Association; RBBB: right bundle branch block.

Responders versus non-responders

After 6 months of CRT, 17 patients (55%) were considered responders according to the predefined criterium of reduction in LVESV ≥15%. The remaining 14 patients were classified as non-responders, including one patient who died of worsening heart failure before re-evaluation after 6 months of CRT.

Baseline characteristics between responders and non-responders were comparable; except for more baseline LV dyssynchrony in responders (82±43 ms vs. 42±27 ms, P=0.005). Furthermore, responders tended to have smaller LV volumes and less akinetic segments (4.8±2.9 vs. 6.4±3.1, P=0.2). Responders showed significant improvement in clinical parameters after 6 months of CRT; all patients showed improvement of at least 1 NYHA functional class (P<0.001), quality-of-life score improved from 36±17 to 19±21 (P=0.05), and 6-minute walking distance improved from 355±113 m to 431±71 m (P<0.001). The non-responders showed no significant improvement in clinical parameters. By definition, responders showed significant reverse remodeling and an increase in LV function (LVEF from 27±7% to 39±7%, P<0.001). Non-responders did not show reverse remodeling or improvement in LV function (LVEF 23±5% versus 25±7%, P=0.1) during follow-up.

Contractile reserve to predict response

All patients completed the echocardiographic protocol without complications. During low-dose dobutamine infusion, responders showed a greater increase in LVEF as compared to non-responders (Δ LVEF 13±8% vs. 3±4%, P<0.001, Table 2). Furthermore, improvement in

LVEF during dobutamine infusion was directly related to the improvement in LVEF after CRT (r=0.80, Figure 1A). Also, a relation was noted between contractile reserve at baseline and LV reverse remodeling after 6 months (r=0.60, Figure 1B).

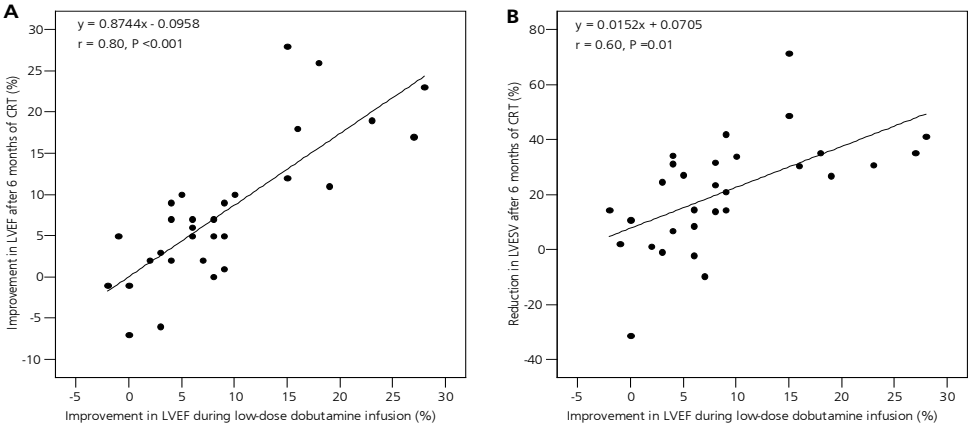
Table 2. Changes during low-dose dobutamine infusion according to response to CRT

	All (n=31)	Responders (n=17)	Non-responders (n=14)	P-value
LVEDV				
- Baseline (ml)	216±76	208±57	233±94	0.4
- Low-dose dobutamine (ml)	211±73	203±58	227±91	0.4
- Δ (ml)	5±14	5±12	7±16	0.7
LVESV				
- Baseline (ml)	163±66	153±45	184±83	0.2
- Low-dose dobutamine (ml)	141±65	123±44	171±78	0.04
- Δ (ml)	21±19	30±17	13±16	0.01
LVEF				
- Baseline (%)	26±7	27±7	23±5	0.1
- Low-dose dobutamine (%)	35±10	40±8	27±6	<0.001
- Δ (%)	9±8	13±8	3±4	<0.001
Strain target LV lead wall				
- Baseline (%)	21±9	20±9	21±10	0.8
- Low-dose dobutamine (%)	24±10	27±9	20±9	0.05
- Δ (%)	3±6	6±5	-1±4	0.002

Abbreviations as in Table 1. Δ: difference between baseline and low-dose dobutamine infusion.

Figure 1. Contractile reserve vs. response after CRT

Relationship between contractile reserve (improvement in LV ejection fraction [LVEF] during dobutamine infusion) at baseline and improvement in LVEF (A) and LV reverse remodeling (B), respectively, after 6 months of CRT.

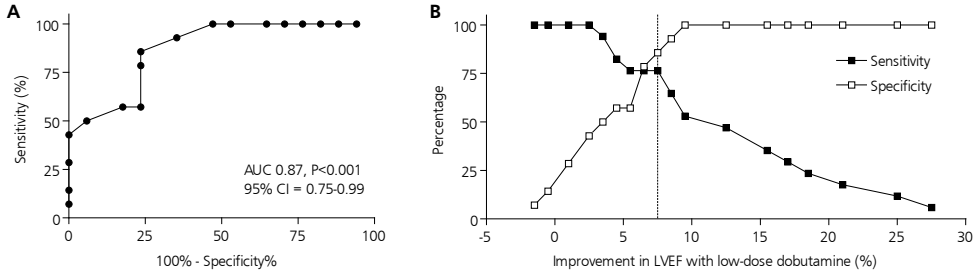


ROC curve analysis revealed that dobutamine-induced increase in LVEF is a good predictor for response to CRT (AUC 0.87, Figure 2). Using a cut-off value of 7.5% increase in LVEF, a sensitivity of 76% and a specificity of 86% were obtained to predict response to CRT (defined as a decrease in LVESV ≥15%) at 6 months follow-up.

Moreover, contractile reserve in the region where the LV lead was positioned was present in responders, as indicated by an improvement in regional strain of 6±5% during low-dose dobutamine infusion as compared to absence of contractile reserve in non-responders (change in regional strain -1±4%, P=0.002). Also, despite similar strain values at baseline, responders showed an increase in strain values of the target LV lead wall (from 20±9% to 28±13%, P=0.003) after 6 months of CRT; whereas non-responders showed a small decrease in strain values (from 21±10% to 19±11%, P=0.4). Of note, LV pacing thresholds were comparable between responders and non-responders (1.1±0.8 Volt vs. 1.4±0.7 Volt, P=0.2) and remained stable during follow-up (responders 1.2±0.9 vs. baseline, P=0.1; non-responders 1.3±0.7 vs. baseline, P=0.4).

Figure 2. Contractile reserve to predict response after CRT

Receiver operating characteristics curve analysis on contractile reserve (improvement in LV ejection fraction [EF] during low-dose dobutamine infusion) to predict response after CRT.



Contractile reserve vs. LV dyssynchrony

Responders showed, despite more improvement in LVEF during low-dose dobutamine infusion at baseline, also significantly more LV dyssynchrony at baseline (82 ± 43 ms vs. 42 ± 27 ms, p=0.005), implying that both parameters may be important for response.

Response rate in the patients with presence of baseline dyssynchrony (cut-off 65 ms) was 88% (=15 responders of the 17 patients with dyssynchrony). Similarly, response rate in the patients with contractile reserve (cut-off 7.5%) was 87% (=13 responders in the 15 patients with contractile reserve). Moreover, multivariate analysis revealed that both LV dyssynchrony and contractile reserve are independent predictors of response (LV dyssynchrony ≥65 ms, OR 15.002, 95% CI 1.789 – 125.979, P=0.013; Dobutamine-induced LVEF ≥7.5%, OR 9.306, 95% CI 1.070 – 80.956, P=0.043).

DISCUSSION

The findings in the present study demonstrate a direct relation between myocardial contractile reserve as assessed during low-dose dobutamine infusion and degree of ventricular function improvement after CRT. Furthermore, besides the presence of LV dyssynchrony, a cutoff value of 7.5% for dobutamine-induced increase in LVEF can be used to predict LV reverse remodeling after 6 months of CRT. Lastly, lack of contractile response in the region of the LV pacing lead may lead to non-response to CRT.

Role of global contractile reserve

The presence of myocardial contractile reserve as assessed during low-dose dobutamine infusion has been shown to provide important prognostic information in both ischemic and non-ischemic cardiomyopathy (7-11). For example, Ramahi et al demonstrated in 62 non-ischemic patients that an improvement in LVEF of ≥8% during low-dose dobutamine infusion exhibited a survival rate of 97% after 3 years of follow-up, compared to the 56% survival rate in patients showing an improvement in LVEF of <8% (P<0.001) (10).

Similarly, the presence of LV contractile reserve may predict functional response to CRT. At present, data on myocardial contractile reserve in CRT candidates is limited. Da Costa et al evaluated 67 CRT patients (34% ischemic) and observed that the presence of contractile myocardial reserve was an independent predictor of event-free survival after CRT (25). In the patients without events (n=20) 60% showed contractile reserve at baseline, as compared to 30% in the patients with events (P=0.008). Furthermore, a cut-off value of 25% increase in dobutamine-induced LVEF yielded a sensitivity of 70% and a specificity of 62% for predicting major clinical events 12±8 months after CRT. Another study in 28 patients revealed that patients with contractile reserve (n=21) had a higher response rate to CRT as compared to patients without myocardial contractile reserve (n=7) (29% vs. 81%, P<0.01) (26).

In the current study we related myocardial contractile reserve to improvement in LV function after CRT in both ischemic and non-ischemic patients. Responders showed greater contractile reserve at baseline than non-responders (improvement in LVEF 13±8% vs. 3±4%, P<0.001, Table 2). Furthermore, an increase of 7.5% in LVEF during low-dose dobutamine infusion was predictive for significant LV reverse remodeling and improvement in LV function 6 months after CRT. These findings confirm our hypothesis that a substantial amount of 'alive' myocardium is needed to obtain improvement in LV function after CRT. One can imagine that in myocardium with advanced remodeling, fibrosis and loss of contractile material may have severely altered contractile properties which impairs efficient biventricular pacing. Furthermore, our findings may raise the potential interest to perform CRT in less advanced stages of heart failure when reverse remodeling is still possible.

Role of regional contractile reserve in the area of the LV pacing lead

It was hypothesized that myocardial viability of the stimulated LV area is necessary in order to obtain efficient LV pacing, resulting in successful CRT. This was recently supported by Bleeker at al who demonstrated that patients with transmural scar in the postero-lateral region did not respond to CRT, whereas 81% of the patients without posterolateral scar responded well to CRT(12). In addition, Hummel et al, using contrast echocardiography to identify myocardial viability, reported similar findings in 21 patients with ischemic cardiomyopathy; viability in

the lateral and posterior regions correlated with improvement in LVEF after 6 months of CRT (r=0.52 and r=0.54 respectively, both P<0.05) (27).
In line with these results, the current data demonstrate that responders to CRT showed an increase in strain in the region of the LV pacing lead during low-dose dobutamine infusion; non-responders to CRT on the contrary, had no contractile reserve as evidenced by absence of increase in strain during low-dose dobutamine infusion.

Still, the number of patients evaluated in the current study is small and future larger studies are needed to further elucidate the role of global and regional myocardial contractile reserve for prediction of response to CRT.

CONCLUSIONS

The current findings demonstrate that, besides the presence of LV dyssynchrony, myocardial contractile reserve (resulting in ≥7.5% increase in LVEF during low-dose dobutamine infusion) predicts LV reverse remodeling and improvement in LV function after 6 months of CRT. These data provide further support for the need of myocardial contractile reserve/viability assessment in the selection of CRT candidates. Moreover, not only global contractile reserve is important but also regional contractile reserve in the region where the LV pacing lead is positioned, to allow response to CRT.

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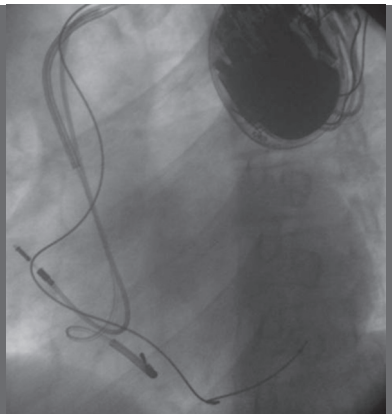
Chapter 8



Optimal left ventricular lead position predicts reverse remodeling and survival after cardiac resynchronization therapy

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ABSTRACT

Objectives Aim of the current study was to evaluate echocardiographic parameters after 6 months of cardiac resynchronization therapy (CRT) as well as long-term outcome in patients with the left ventricular (LV) lead positioned at the site of latest activation (concordant LV lead position) as compared to patients with a discordant LV lead position.

Background A non-optimal LV pacing lead position may be a potential cause for non-response to CRT.

Methods Site of latest mechanical activation was determined by speckle tracking radial strain analysis and related to the LV lead position on chest X-ray in 244 CRT candidates. Echocardiographic evaluation was performed after 6 months. Long-term follow-up included all-cause mortality and hospitalizations for heart failure.

Results Significant LV reverse remodeling (reduction in LV end-systolic volume from 189±83 ml to 134±71 ml, P<0.001) was noted in the group of patients with a concordant LV lead position (n=153, 63%), whereas patients with a discordant lead position showed no significant improvements. In addition, during long-term follow-up (32±16 months), less events (combined for heart failure hospitalizations and death) were reported in patients with concordant LV lead position. Moreover, a concordant LV lead position appeared to be an independent predictor of hospitalization-free survival after long-term CRT (hazard ratio 0.22, P=0.004).

Conclusions Pacing at the site of latest mechanical activation, as determined by speckle tracking radial strain analysis, resulted in superior echocardiographic response after 6 months of CRT and better prognosis during long-term follow-up.

INTRODUCTION

The rationale for cardiac resynchronization therapy (CRT) for the treatment of severe congestive heart failure is to coordinate the contraction of the dyssynchronous dilated heart, thereby improving left ventricular (LV) systolic function. Several large randomized studies demonstrated that CRT not only improved clinical status but also reverses LV remodeling (1-5). However, a significant percentage of patients do not show benefit from CRT (2,6). Different factors may influence the likelihood of response to CRT, such as lack of baseline mechanical dyssynchrony, insufficient device programming and suboptimal LV lead position (7,8).

Currently, the LV pacing lead is positioned preferably in a lateral or posterolateral branch of the coronary sinus. This approach is based on initial studies which demonstrated that a (postero) lateral position of the LV pacing lead yielded greater acute hemodynamic benefit as compared with an anterior LV lead position (9). However, a few studies show no difference in long-term follow-up between patients with a lead in the anterior versus a posterolateral position (10-12). In addition, it has been shown that the region of maximal mechanical delay varies significantly between patients and may involve other sites remote of these branches (13). It has been suggested that positioning of the LV lead at the site of latest mechanical activation may result in maximum benefit of CRT (13-17).

Aim of the current study was to evaluate clinical and echocardiographic 6 months outcome as well as long-term prognosis in a large cohort of patients by comparing patients with the LV lead positioned in the region of latest mechanical activation with patients with the LV positioned outside the site of latest mechanical activation. Two-dimensional (2D) speckle tracking radial strain analysis was used to determine the presence of LV dyssynchrony and the region of latest mechanical activation.

METHODS

Patients and study protocol

Two-hundred fifty-seven consecutive patients with advanced heart failure (New York Heart Association (NYHA) class III or IV), depressed LV ejection fraction (EF, <35%), wide QRS complex (>120 ms) were prospectively included for implantation of a CRT device (18). Patients with a recent myocardial infarction (<3 months), or decompensated heart failure were excluded. Etiology was considered ischemic in the presence of significant coronary artery disease (≥50% stenosis in one or more of the major epicardial coronary arteries) and/or a history of myocardial infarction or prior revascularization.

The study protocol was as follows: before implantation, resting transthoracic echocardiography was performed to measure LVEF and LV volumes. Next, 2D speckle tracking radial strain analysis was performed to determine the extent of LV dyssynchrony as well as the site of latest mechanical activation. Clinical status was assessed at baseline and after 6 months of CRT, including assessment of NYHA class, quality-of-life score (using the Minnesota Living with Heart Failure questionnaire) (19) and evaluation of exercise capacity using the 6-minute walking test (20). At 6 months follow-up, LV volumes and LVEF were re-assessed. Hospitalization for

decompensated heart failure and survival and cardiac transplantation were assessed during follow-up after CRT device implantation.

Echocardiography and data acquisition/analysis

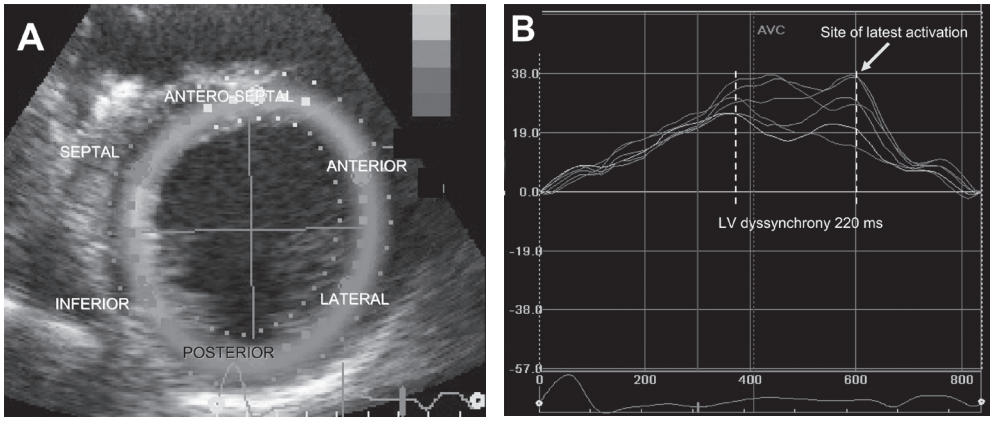
Echocardiographic images were obtained with a 3.5-MHz transducer in the left lateral decubitus position using a commercially available system (Vivid Seven, General Electric-Vingmed, Milwaukee, Wisconsin). Standard 2D and color Doppler data, triggered to the QRS complex were saved in cine-loop format for off-line analysis (EchoPac 6.06, GE Medical systems, Horten, Norway).

LV end-diastolic volume (EDV) and LV end-systolic volume (ESV) were derived and LVEF was calculated from the conventional apical 2- and 4-chamber images, using the biplane Simpson's technique (21). The severity of mitral regurgitation was graded semi-quantitatively from color-flow Doppler images using the apical 4-chamber views. Mitral regurgitation was graded on a 3-point scale: mild (jet area/left atrial area <20%), moderate (jet area/left atrial area 20-45%), and severe (jet area/left atrial area >45%) (22).

LV dyssynchrony was assessed using 2D speckle tracking radial strain analysis on baseline mid-ventricular short-axis images (23,24). All the images were recorded with a frame rate of at least 30 frames/s to allow for reliable operation of the software (EchoPac 6.1, GE Medical Systems, Horten, Norway). Time-strain curves for the 6 segments (septal, anteroseptal, anterior, posterior, lateral and inferior) were constructed (see Figure 1). Times from QRS onset to peak radial strain were obtained for all 6 segments and reliable curves were obtained in 92% of 1542 attempted segments. Consequently, the location of the earliest and latest activated segments and the heterogeneity in time-to-peak radial strain for the 6 segments were determined (25). LV dyssynchrony was defined as the maximal time difference between the earliest and latest activated segments. The site of latest mechanical activation was also

Figure 1. Speckle tracking radial strain analysis

A Short-axis of the left ventricle at the level of the papillary muscles, with reconstruction of the 6 LV segments. B demonstrates the separate strain-time curves for each individual segment. In this patient example severe baseline LV dyssynchrony was present; a maximum delay of 220 ms was calculated between the septum and the posterior wall. Site of latest activation was the posterior LV segment.



noted. Inter- and intra-observer variability for the assessment of the site of latest activation showed a good agreement, with respectively 80% and 83% of the segments scored identically (κ=0.71 and κ=0.76).

Response to CRT and long-term follow-up

Echocardiographic and clinical improvement were assessed after 6 months of CRT.
Patients were classified as responders to CRT ('responders') if they showed a decrease of >15% in LVESV (26,27).The remaining patients, including those who died during the 6-month follow-up period, were classified as 'non-responders'.
Long-term follow-up was performed by chart review, device interrogation and telephone contact. Events were defined as follows: death from any cause or cardiac transplantation and heart failure requiring hospitalization. The primary endpoint was the composite of death, cardiac transplantation and hospitalization for decompensated heart failure.

CRT implantation and LV lead position

A coronary sinus venogram was obtained using balloon catheter, followed by the insertion of the LV pacing lead. An 8F guiding catheter was used to position the LV lead (Easytrak 4512-80, Guidant Corporation, St. Paul, Minnesota; or Attain-SD 4189, Medtronic Inc., Minneapolis, Minnesota) in the coronary sinus. The preferred position was a lateral or postero-lateral vein (28). Of note, the electrophysiologist was blinded for all echocardiographic data, so LV lead positioning was not guided by the echocardiographic information on latest mechanical activation.
The right atrial and ventricular leads were positioned conventionally. All leads were connected to a dual chamber biventricular ICD (Contak Renewal II or H195, Guidant Corporation; or Insync III or Insync Sentry, Medtronic Inc.).
One day after implantation, the LV lead position was assessed from a chest-X-ray (29). LV lead positions were scored anterior, lateral, posterior or inferior using the lateral views. Only LV lead positions that were located in the basal and mid region of the LV (frontal views) were related to the site of latest mechanical activation model (mid-ventricular short-axis view); LV lead positions that were located in the apical regions were excluded from further analysis. LV lead positions were classified as 'concordant' when the lead was positioned at the latest activated segment; in case of differences between the LV lead position and site of latest mechanical activation, these positions were classified as 'discordant'. Inter- and intra-observer agreement for the assessment of LV lead position were excellent with both 91% LV lead positions scored identically (κ=0.88).

Statistical analysis

Continuous variables are expressed as mean ± SD. Categorical data are summarized as frequencies and percentages. Differences in baseline characteristics between patients with concordant and discordant LV lead positions were analyzed using unpaired Students t tests (continuous variables) and chi-square or Fisher's exact tests (dichotomous variables) as appropriate. The paired Students t test was used to compare continuous data within the subgroups during follow-up. Inter- and intra-observer agreement for assessment of site of latest activation and LV lead position were calculated and κ values were determined (<0.40 poor agreement, 0.40–0.75 fair to good, and >0.75 excellent).

Event and survival curves were determined according to the Kaplan-Meier method, with comparisons of cumulative event rates by the log-rank test. To adjust for (potential) confounding factors for LV lead position such as age, gender, etiology, NYHA class, QRS duration, left bundle branch block configuration (LBBB), cardiac rhythm, LV volumes and LV dyssynchrony, uni- and multivariable Cox proportional hazards (PH) analysis was performed. All variables entered the multivariable stage, irrespective of the results of the univariable analyses. Multivariable regression was then performed according to the principle of backward deletion. All variables with a p-value of <0.15 remained in the final model. Adjusted hazard ratios (HR) with their 95% confidence intervals (CI) are reported. For all tests, a P-value <0.05 was considered statistically significant.

To check the PH assumption, log(–log[survival probability]) was plotted against time for patients with concordant versus discordant LV lead position. Similar plots were created for (different categories of) potential confounders. The curves were reasonably parallel for all variables studied, indicating that the proportionality assumptions were not violated. However, there were two exceptions: there was evidence that the PH assumption was violated for the relation between LV lead position and the single endpoint hospitalization for heart failure, and the composite endpoint of all-cause death, cardiac transplant or hospitalization for heart failure. Since the event curves representing the latter endpoint diverged at 24 months follow-up (see Results), we decided to report separate HR for the first 24 months and the subsequent period.

RESULTS

Patients

Baseline characteristics of the 257 consecutive patients (211 men, mean age 66±10 years) included in this study are summarized in Table 1. Patients had severely depressed LV function, with a mean LVEF of 24±7%. Mean LVEDV was 232±86 ml and mean LVESV was 180±76 ml. Severe LV dyssynchrony was present, as indicated by a maximal delay of 177±117 ms. The site

Figure 2. Distribution of site of latest activation

Ant-sept: antero-septal LV segment; Ant: anterior LV segment; Lat: lateral LV segment; Post: posterior LV segment; Inf: inferior LV segment; Sept: septal LV segment.

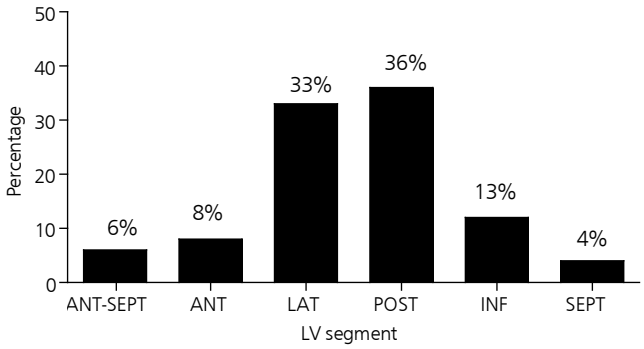


Table 1. Patient characteristics (n=257)	
Age (yrs)	66±10
Gender (M/F)	211/46
NYHA class (III/IV)	232/25
Ischemic etiology	148 (58%)
QRS duration (ms)	161±33
LBBB	181 (70%)
Sinus rhythm/Atrial fibrillation/Paced	208/29/30
LVEF (%)	24±7
LVEDV (ml)	235±86
LVESV (ml)	182±76
Mitral regurgitation (moderate-to-severe)	46 (18%)
LV dyssynchrony (ms)	177±117
Medication	
Diuretics	219 (85%)
ACE-inhibitors	232 (90%)
Beta-blockers	176 (68%)
Spironolactone	114 (44%)

ACE: angiotensin-converting enzyme; EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; LBBB: left bundle branch block; LV: left ventricular; NYHA: New York Heart Association.

of latest mechanical activation was most frequently located in the lateral (84 patients, 33%) and posterior segments (93 patients, 36%) (Figure 2).

Device implantation was successful in all patients and no procedure-related complications were reported. Most LV pacing leads were positioned in the basal-mid-ventricular region, including the lateral region in 111 patients (45%), the posterior region in 119 patients (49%) and the anterior region in 14 patients (5%); no patients received an LV lead in the inferior region. Thirteen patients had an apical LV lead position and were excluded for further analysis.

Concordant vs. discordant LV lead position

One-hundred fifty-three patients (63%) had an LV lead position located in the latest activated region, whereas 91 patients (37%) had a discordant LV lead position. Baseline characteristics were comparable between the two groups, except for a significantly shorter QRS duration and more often ischemic etiology in patients with discordant LV lead positions (Table 2).

6-months clinical follow-up after CRT

After 6 months of CRT, 152 patients (62%) showed an improvement of at least 1 NYHA functional class (106 patients showed an improvement of 1 NYHA class, 46 patients showed an improvement of 2 NYHA classes, P<0.001 vs. baseline). The quality-of-life score improved from 39±18 to 23±18 and exercise capacity improved as indicated by an increase in 6-minute walking distance from 292±120 m to 388±131 m (both P<0.001). In addition, LVEF improved from 23±7% to 31±9%, with a reduction in LVEDV (236±85 ml to 204±80 ml) and LVESV (183±75 ml to 144±70 ml, all P<0.001).

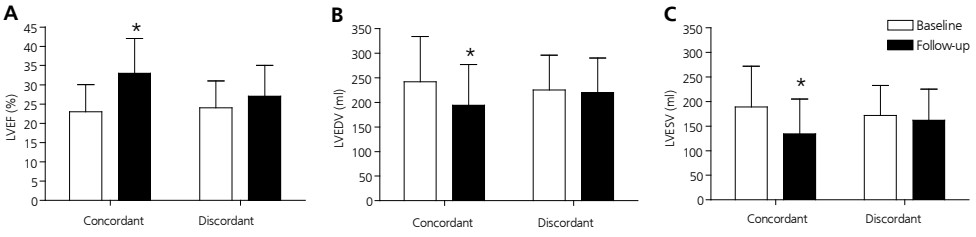
Table 2. Baseline characteristics between patients with concordant LV lead positions (n=153) and patients with discordant LV lead position (n=91)

	Concordant LV lead position	Discordant LV lead position	P-value
Age (yrs)	67±10	65±10	0.3
Gender (M/F)	120/33	79/12	0.1
NYHA class (III/IV)	140/13	81/10	0.5
Ischemic etiology	75 (49%)	67 (74%)	<0.001
QRS duration (ms)	164±31	154±34	0.02
LBBB	114 (75%)	66 (73%)	0.4
Sinus rhythm/Atrial fibrillation/Paced	121/10/22	80/13 /8	0.6
LVEF (%)	23±7	24±7	0.3
LVEDV (ml)	242±92	225±71	0.1
LVESV (ml)	189±83	172±61	0.1
Mitral regurgitation (moderate-to-severe)	24 (16%)	17 (19%)	0.6
LV dyssynchrony (ms)	189±118	160±119	0.1

Abbreviations as in Table 1.

Figure 3. Echocardiographic response after CRT in patients with concordant LV lead positions (n=153) and patients with discordant LV lead positions (n=91)

White bars: baseline, black bars: follow-up, * p<0.001.



6-months CRT response vs. LV lead position

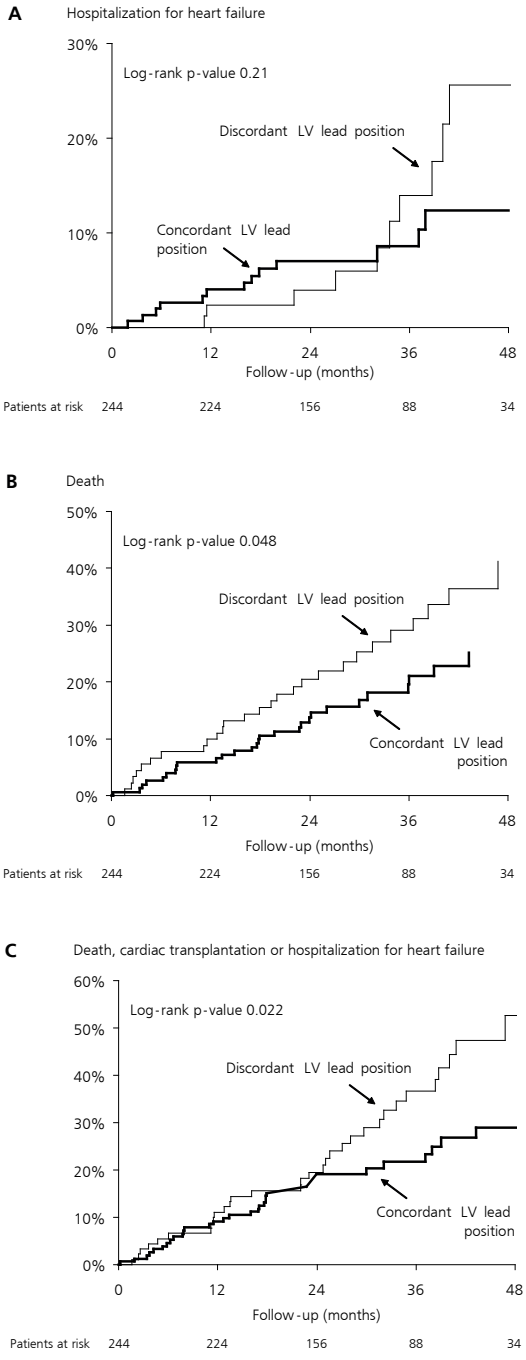
After 6 months of CRT, patients with a concordant LV lead position demonstrated significant improvements in echocardiographic parameters; LVEDV decreased from 242±92 ml to 194±83 ml, LVESV from 189±83 ml to 134±71 ml and consequently LVEF increased from 23±7% to 33±9% (all P<0.001). However, patients with a discordant LV lead position showed no significant reduction in LV volumes (LVEDV from 225±71 ml to 220±70 ml and LVESV from 172±61 ml to 162±63 ml, both NS) and no improvement in LVEF (from 24±7% to 27±8%, NS) (Figure 3).

Long-term prognosis versus LV lead position

Mean duration of follow-up was 32±16 months (range 3 to 92 months). There were 55 hospitalizations for decompensated heart failure in 25 patients (10%). Patients were hospitalized 24±15 months (range 1 to 55 months) after CRT implantation. Furthermore, 56 patients died

Figure 4. Survival and event-curves after CRT according to LV lead position

A hospitalizations for heart failure, B survival and C event-free survival including death, heart transplantation and hospitalization for hear failure.



(23%) after a mean follow-up of 20±14 months (range 2 to 55 months) and one patient underwent heart transplantation.

Hospitalization rates for decompensated heart failure in the 2 groups are shown in Figure 4A. During follow-up, patients with a discordant LV lead position experienced more hospitalizations for decompensated heart failure as compared to patients with a concordant LV lead position (20 vs. 35 hospitalizations, P=0.04). However, the number of patients who were hospitalized was not significantly different among both groups as demonstrated by Figure 4A. At 24 months of follow-up hospitalization rates were respectively 4% and 7%. However, during long-term follow-up a trend for more hospital admissions in the discordant group was noted (at 48 months respectively 12% vs. 26%, Figure 4A).

Mortality rates for the 2 groups are shown in Figure 4B. Importantly, 13 patients (14%) in the discordant patient group already died before the 6 months follow-up evaluation as compared to 1 patient (1%) in the concordant group (P<0.001). Furthermore, 12- and 24-months survival rates for patients with concordant LV lead positions were 94% and 85%, respectively; in patients with discordant LV lead positions the 12- and 24-months survival rates were 90% and 79%, respectively (Figure 4B).

The cumulative event-rates of the primary end-point (combined for death, hospitalization for heart failure and heart transplantation) in both groups are shown in Figure 4C. The 12- and 24-month event-free survival rates were quite similar in patients with a concordant LV lead position as

compared to the discordant group; respectively 9% vs. 11% at 12 months and both 19% at 24 months of follow-up. However, longer follow-up revealed worse outcome in patients with a discordant LV lead position; 3-year event-free survival is 57% in the discordant patient group vs. 78% in the concordant group.

Univariate analysis revealed that a concordant lead position was no predictor of primary outcome within the first 24 months of follow-up (HR 0.96, 95% CI 0.527-1.758, P=0.9). After 24 months however, both uni- and multivariate analysis revealed that concordant lead position was an independent predictor of hospitalization-free survival (HR 0.22, 95% CI 0.078-0.623, P=0.004).

DISCUSSION

The findings of the present study can be summarized as follows: 1) patients who are candidates for CRT exhibit varying sites of latest mechanical activation; 2) in one-third of patients undergoing CRT, the position of the LV lead did not match the site of latest mechanical activation on echocardiography; 3) a match between LV lead position and site of latest mechanical activation resulted in a better echocardiographic response after 6 months of CRT, with a superior long-term outcome after CRT.

Importance of LV lead position in CRT

It has been suggested that 20-30% of patients do not respond to CRT when a clinical end-point is used (e.g. improvement in NYHA class, quality-of-life score etc); however, when reverse LV remodeling is considered as an end-point the non-response rate may be as high as 40-50% (2,6,7). Several studies have demonstrated that the key mechanism of benefit from CRT is the presence of baseline mechanical LV dyssynchrony as assessed with echocardiography and its subsequent reduction following CRT implantation (5,27,30). In this perspective, the position of the LV pacing lead is important. A recent animal study using magnetic resonance imaging highlighted that regions with maximal resynchronization after CRT, also exhibited maximum gain in systolic LV function; these regions were referred to as the "sweet spot" and may be the optimal regions for the LV lead (31).

With the more advanced echocardiographic techniques adequate identification of the region of latest mechanical activation is possible and recent data emphasized that the site of latest activation may vary significantly with 67% having the (postero-)lateral wall as site of latest activation, but 33% having different regions of latest activation (32). Similarly in the current study, 2D speckle tracking radial strain analysis was used to asses the site of latest mechanical activation. In the majority of patients (n=177), the posterolateral region was the site of latest mechanical activation, whereas one third of the patients (n=80) revealed another region of latest mechanical activation.

Recent studies in small patient groups have indeed shown that patients with a concordance between the LV lead position and the site of late mechanical activation responded significantly better to CRT, as compared to patients with discordance between LV lead position and the site of latest activation. Ansalone and colleagues evaluated 31 patients undergoing CRT and demonstrated that patients (42%) who were paced at the site of latest activation (according to tissue Doppler echocardiography) showed significant improvements in LVESV, LVEF and

exercise tolerance after one week of CRT, whereas patients paced at any other site (58%) showed no improvement (13). Longer follow-up was obtained in two studies, both using 2D strain analysis to determine the site of latest mechanical activation. Suffoletto et al demonstrated that patients with a concordance between the LV lead position and the site of latest activation had a larger increase in LVEF at mid-term follow-up as compared to patients with a discordance (10±5% vs. 6±5%, P<0.05) (25). Becker at al confirmed these findings and reported that the distance between site of latest mechanical activation and the actual pacing site was predictive for reverse LV remodeling at 10 months follow-up (16). Murphy and coworkers used a more sophisticated approach with 3D tissue synchronization imaging; the patients were divided into 3 groups according to the relation between the LV lead position and the area of latest mechanical activation (15). The greatest hemodynamic and clinical benefit from CRT was observed patients who were paced at the site of latest mechanical activation, whereas response was less in patients with the LV lead adjacent to the site of latest mechanical activation and absent in patients with the LV lead placed remote from the site of latest mechanical activation.

The current study evaluated a large cohort of patients undergoing CRT (n=257) and confirmed the aforementioned findings; a greater echocardiographic improvement (reverse LV remodeling and increase in LVEF) was noted in patients with a concordant LV lead position as compared to patients with a discordant LV lead position. Clinically more important however, is whether concordance or discordance between LV lead position and site of latest mechanical activation has prognostic value. Regarding hospitalizations for heart failure, a trend for more admissions in the discordant group was noted. Importantly, mortality was significantly lower in the patients with concordant LV lead position (15% vs. 21% at 24 months, log- rank P=0.048). Moreover, a concordant LV lead position appeared to be an independent predictor for the combined end-point of hospitalization and mortality after long-term CRT.

Clinical implications

The current study further supports the importance of the LV lead position in CRT. With sophisticated echocardiographic techniques, including tissue Doppler imaging and speckle tracking 2D radial strain imaging, it is possible to locate (before device implantation) the site of latest activation, which may even be further optimized by 3D echo techniques. Ideally, positioning of the LV pacing lead could thus be guided by echocardiography during the CRT implantation. However, it is important to realize that LV lead positioning may be limited by anatomical and technical factors including presence, accessibility and lead stability within the appropriate region of the appropriate vein. Venous anatomy can be obtained during the procedure with retrograde venography but is also possible with non-invasive imaging using multi-slice computed tomography before CRT implantation (33). The precise incidence of suitable veins for CRT is not known and may differ between patients with ischemic and non-ischemic cardiomyopathy (34). When the site of latest activation is not in the region of suitable veins, surgical LV lead positioning may be considered, using limited left-lateral thoracotomy with direct epicardial LV lead placement (35). Ideally, one could thus integrate the information from echocardiography (latest mechanical activation) and multi-slice computed tomography (venous anatomy) to determine the approach. In addition, the presence of postero-lateral scar tissue appeared to be an important factor for non-response after CRT (36). However, assessment of scar tissue was not routinely performed in the current study population. Still,

prospective large studies are needed comparing empiric and guided LV lead implantation (targeted at the site of latest activation).

Conclusions

Positioning of the LV pacing lead at the site of latest mechanical activation resulted in significant reverse LV remodeling and increase in LVEF after 6 months of CRT, whereas as discordant LV lead position did not result in echocardiographic improvement. Moreover, long-term prognosis was significantly better in patients with a concordant LV lead position; a concordant LV lead position appeared to be an independent predictor of outcome (combined end-point of hospitalization and death) after long-term CRT.

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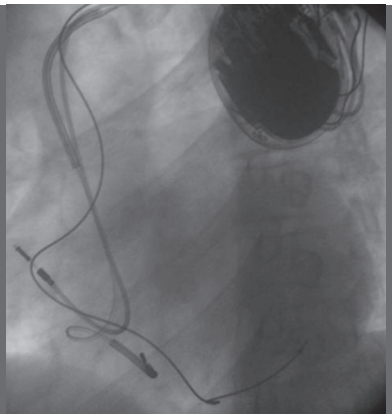
Chapter 9



Non-invasive imaging in cardiac resynchronization therapy – part 1: selection of patients

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ABSTRACT

Cardiac resynchronization therapy (CRT) is an established therapy for patients with advanced heart failure, depressed left ventricular function and wide QRS complex. However, individual response varies, and a substantial amount of patients do not respond to CRT. Recent studies observed that assessment of inter- and particularly intraventricular dyssynchrony may allow identification of potential responders to CRT. In addition, presence of scar tissue and venous anatomy may play a role in the selection of candidates. In this review, an extensive overview of the available dyssynchrony measurements is provided using echocardiography as well as magnetic resonance imaging (MRI) and nuclear imaging. Furthermore, other information derived from MRI, nuclear imaging and computed tomography useful for the selection of potential candidates for CRT will be discussed.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is an effective treatment for patients with end-stage drug-refractory heart failure (HF), depressed left ventricular (LV) function and wide QRS complex as demonstrated in various large multi-center trials. CRT has a beneficial effect on HF symptoms, exercise capacity, LV function, HF hospitalization and mortality rates (1-6). Based on the available evidence, the American College of Cardiology/American Heart Association/ Heart Rhythm Society guidelines consider end-stage HF as a class I indication for CRT according to the following selection criteria (7):

- New York Heart Association (NYHA) class III or IV despite maximal therapy
- LV ejection fraction (EF) <35%
- QRS duration >120 ms

Despite the impressive results of CRT in the large clinical trials, a consistent percentage of patients failed to benefit when the above criteria were used, the so-called "non-responders". The prevalence of responders is around 70% when clinical end-points are used (e.g. improvement in NYHA class, Table 1A), but can be much lower when echocardiographic end-points are used. Most studies used a cut-off value for substantial reverse remodeling of 10% or 15%. Using these cut-off values the response rate after CRT in terms of reverse remodeling lies between 44% and 62% (Table 1B).

Response to CRT has been related to the presence of cardiac dyssynchrony prior to implantation. Patients with HF can exhibit dyssynchrony at different levels, which can be (partially) corrected by CRT (8):

- Interatrial dyssynchrony, reflecting dyssynchronous contraction between the right and left atrium (9)
- Atrioventricular (AV) dyssynchrony, resulting in reduced LV filling time,
- Interventricular dyssynchrony, resulting in dyssynchronous contraction between the left and right ventricle (RV),
- LV (or intraventricular) dyssynchrony, reflecting contraction delay within the LV
- Intramural dyssynchrony, reflecting heterogenous LV activation patterns with differing location and extents of specific ventricular delays (10)

A variety of techniques have been proposed to quantify cardiac dyssynchrony in HF patients, ranging from QRS duration to more sophisticated echocardiographic techniques such as 3-dimensional (3D) echocardiography and strain (rate) imaging. Non-echocardiographic imaging techniques have also been advocated to assess LV dyssynchrony such as magnetic resonance imaging (MRI) and nuclear imaging. Currently, echocardiography is considered the optimal method and it has been demonstrated that the presence of LV dyssynchrony is the dyssynchrony parameter that is most predictive for CRT response.

Besides lack of dyssynchrony, other factors may prohibit CRT response. Several imaging techniques may provide additional information on suboptimal lead positioning, scarred and viable myocardium, and venous anatomy.

In this review (part 1), the value of echocardiography and other non-invasive imaging techniques for selection of CRT candidates will be discussed. In part 2, the role of imaging techniques for follow-up of CRT patients and optimization of pacemaker settings after device implantation will be addressed.

Table 1A. Clinical response rates (expressed as improvement in NYHA class) in 15 currently largest observational and randomized CRT studies

Authors	No. of patients	Follow-up (mo)	Ischemic etiology (%)	NYHA class	QRS duration (ms)	LVEF (%)	Response rate (%)
Abraham et al. (3)	228	6	50	3.1±0.3	167±21	22±6	68
Gasparini et al. (100)	104	±9	55	3.0±0.7	165±37	27±7	69
Higgins et al. (101)	245	6	67	2.9±0.7	160±27	21±6	74
Young et al. (4)	187	6	64	3.1±0.3	165±22	24±7	±70
Bristow et al. (5)	1212	6	54	3.1±0.3	160	21	59
Molhoek et al. (102)	125	6	54	3.1±0.3	176±25	23±8	79
Bleeker et al. (103)	170	6	55	3.2±0.4	173±27	21±8	78
Leon et al. (104)	359	6	46	3.1±0.3	164±22	22±7	±70
Bleeker et al. (105)	173	6	56	3.1±0.3	173±27	21±7	80
Boriani et al. (106)	121	6	63	3.1±0.3	175±22	24±6	69
Bleeker et al.(107)	144	/6	53	3.1±0.4	157±26	21±8	70
Ypenburg et al. (108)	191	6	56	2.9±0.5	163±30	21±7	76
Pires et al. (109)	537	6	62	3.1±0.3	168±19*	22±7*	62
Yeim et al. (110)	100	6	46	3.1±0.2	158±28	27±6	71
Lellouche et al. (111)	164	6	47	3.2±0.4	158±37	22±7	65

LVEF: left ventricular ejection fraction; NYHA: New York Heart Association
* approximation (patients were divided into 4 groups)

Table 1B. Echocardiographic response rates (expressed as reduction in LVESV) in 15 currently largest observational CRT studies

Authors	No. of patients	Follow-up (mo)	Ischemic etiology (%)	NYHA class	QRS duration (ms)	LVEF (%)	Response rate (%)
Yu et al. (35)	54	3	41	3.2±0.4	147±25/155±33*	25±10	57 A
Yu et al. (112)	141	3/6	48	3.1±0.5	NA	27±7/24±11*	62 B
Notabartolo et al. (37)	49	3	69	3.1±0.5	158±31	24±9	59 A
Yu et al. (113)	56	3	50	3.2±0.4	NA	26±9	54 A
Murphy et al. (114)	54	6	54	3.0±0.3	157±34	27±8	44 A
Bleeker et al. (107)	144	3/6	53	3.1±0.4	157±26	21±8	56 A
Yu et al. (34)	55	3	51	3.2±0.4	NA	26±9	53 A
Jansen et al. (115)	69	3	55	3.1±0.3	172±30	21±7	55 A
Yu et al. (116)	76	3	49	3.0±0.2	NA	28±10	55 A
Zhang et al. (53)	50	3	48	3.2±0.4	151±27	27±9	60 B
Jansen et al. (117)	57	3	53	3.1±0.2	169±28	22±7	65 B
Fung et al. (118)	60	3	47	3.2±0.3	150±27/155±24*	23±8/23±7*	52 B
Yu et al. (119)	107	3	NA	3.2±0.5	NA	27±8	58 B
Fung et al. (120)	85	3	47	3.2±0.7	NA	27±9	52 B
Yu et al. (36)	265	3/10	56	3.1±0.4	NA	24±8	55 A

Abreviations as in Table 1A; ESV: end-systolic volume. * responders / non-responders
A reduction >15% in LVESV, B reduction >10% in LVESV

THE VALUE OF QRS FOR RESPONSE TO CRT

Initially, interventricular dyssynchrony (as reflected by QRS duration) was considered the most important mechanism underlying response to CRT. However, careful analysis of the individual CRT patients showed, that despite prolonged QRS duration, 30% of the patients showed no response to CRT (1,3). Accordingly, the value of the wide QRS complex has become questionable as a selection criterium. Kashani et al evaluated the value of baseline QRS duration by analyzing 34 CRT studies including 2063 patients (11). The authors demonstrated that despite a significant reduction in QRS after CRT initiation in 32 studies, a difference in baseline QRS duration between clinical responders and non-responders to CRT was only reported in 1 study (190±30 ms vs. 171±21 ms, p<0.01) (12). Mollema et al recently specifically addressed the value of baseline QRS duration for prediction of long-term clinical (improvement in NYHA class) and echocardiographic (reduction >10% in LV end-systolic volume, LVESV) CRT response in 242 patients (13). No differences in baseline QRS duration were noted between clinical responders and non-responders (165±21 ms vs. 164±25 ms, NS) as well as echocardiographic responders and non-responders (167±22 ms vs. 162±22 ms, NS). Importantly, baseline QRS duration showed no predictive value for both clinical and echocardiographic response (see Figure 1).

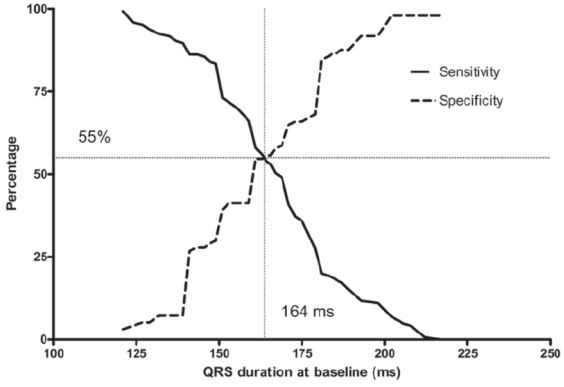


Figure 1. Value of QRS duration to predict response to CRT

Receiver-operating characteristic curve analysis for prediction of echocardiographic response. A cut-off value of 164 ms for QRS duration yielded a sensitivity and specificity of 55% to predict echocardiographic response. Adapted from Mollema et al (13).

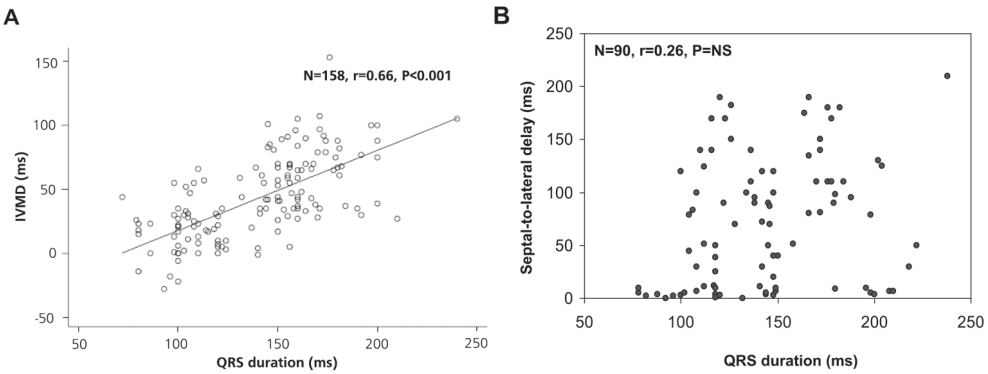
Of note, pure LV pacing or sequential pacing with LV pre-excitation are associated with significant QRS prolongation, in stead of QRS shortening as demonstrated by CRT, and show nonetheless significant clinical benefit (14).

This failure of QRS duration to predict response may be explained by the fact that QRS duration mainly reflects interventricular dyssynchrony, whereas data suggest that LV dyssynchrony is more important for prediction of CRT response. Indeed, various studies demonstrated that QRS duration is mainly related to interventricular dyssynchrony, and does not reflect LV dyssynchrony (Figure 2) (15,16). Still, up to 70% of patients with wide QRS complex also have evidence of LV dyssynchrony on echocardiography, indicating that the likelihood of LV dyssynchrony is high in patients with wide QRS complex. Alternatively, the majority of patients with a QRS duration <120 ms does not have LV dyssynchrony on echocardiography (15-18).

To further explore the relative merits of interventricular and LV dyssynchrony for response to CRT, 24 echocardiographic studies on prediction of CRT response were evaluated. The results showed that only 2 studies provided some value of interventricular dyssynchrony for prediction

Figure 2. Relation between electrical and mechanical dyssynchrony

A. QRS duration correlates well with dyssynchrony between the left and right ventricle or interventricular dyssynchrony (IVMD, measured as the time difference between aortic and pulmonary pre-ejection intervals as determined with pulsed-wave TDI) Adapted from Ghio et al who evaluated 158 HF patients with LV ejection fraction <35% (13). B. There is no relationship present between LV dyssynchrony (measured as septal-to-lateral delay using color-coded TDI) and QRS duration. Adapted from Bleeker et al who evaluated 90 HF patients with LVEF <35% (15).



of CRT response, whereas all 24 studies demonstrated the value of LV dyssynchrony as a predictor of response (19).

Table 2. Echocardiographic studies on prediction of response to CRT

Author	Nr pts	F-up (mo)	Measurement	Description
Pitzalis et al. (21)	20	1	SPWMD	Septal-to-posterior wall motion delay
Pitzalis et al. (121)	60	6	SPWMD	Septal-to-posterior wall motion delay
Marcus et al. (22)	79	6	SPWMD	Septal-to-posterior wall motion delay
Bleeker et al. (23)	98	6	SPWMD	Septal-to-posterior wall motion delay
			Septal-to-lateral delay	Delay in Ts between basal septal and lateral wall
Diaz-Infante et al. (122)	67	6	SPWMD	Septal-to-posterior wall motion delay
Achilli et al. (26)	133	6	IVMD	Interventricular mechanical delay
Penicka et al. (12)	49	6	Sum asynchrony	Delay in Ts of 3 basal LV (septal, lateral, posterior) and basal RV segment
Yu et al. (33)	30	3	Ts-SD	SD of Ts of 12 LV segments
Bax et al. (30)	25	Acute	Septal-to-lateral delay	Delay in Ts between the basal septal and lateral wall
Bax et al. (31)	85	12	Septal-to-lateral delay	Delay in Ts between the basal septal, lateral, inferior and anterior wall
Notabartolo et al. (37)	49	3	PVD	Peak velocity difference; Max delay in Ts of 6 basal LV segments
Yu et al. (35)	54	3	Ts-SD	SD of Ts of 12 LV segments
Yu et al. (34)	55	3	SD-12	SD of Ts of 12 LV segments
			Diff-12	Max delay in Ts of 12 LV segments

ECHOCARDIOGRAPHY TO ASSESS CARDIAC DYSSYNCHRONY

Echocardiographic techniques provide the most practical approach to evaluate LV dyssynchrony and predict CRT response. These techniques include M-mode and Doppler echocardiography as well as tissue Doppler imaging (TDI) with post-processing imaging techniques such as strain, strain rate, tissue tracking, 2-dimensional (2D)-derived strain analysis, velocity vector imaging (VVI) and 3D echocardiography. Table 2 summarizes the echocardiographic studies on prediction of CRT response including the predictive values of the various parameters and techniques. Table 3 includes the advantages and limitations of each of the echocardiographic modalities. The results from the PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) trial demonstrated that most echocardiographic techniques have limited interobserver reproducibility, and significant training is required (20).

A. M-mode echocardiography

M-mode echocardiography is a relatively simple technique to assess LV dyssynchrony. Using the parasternal short-axis view of the LV at the level of the papillary muscles, the time interval between peak systolic contraction of the septum and the peak inward contraction of the posterior wall can be obtained, the so-called septal-to-posterior wall motion delay (SPWMD, Figure 3A). Pitzalis et al evaluated 20 HF patients with non-ischemic etiology, LVEF ≤35% and QRS ≥140 ms (21). A SPWMD of ≥130 ms appeared to be predictive for a reduction of ≥15% in LVESV after 1 month of CRT (21). Retrospective analysis of 79 patients from the CONTAK-CD

Technique	Definition of response	Cut-off value	Sens (%)	Spec (%)
M-mode	↓ ≥15% LVESV	≥130 ms	100	63
M-mode	↑ ≥5% LVEF	≥130 ms	92	78
M-mode	↓ ≥15% LVESV	≥130 ms	24	66
M-mode	↓ >10% LVESV	≥130 ms	65	48
		≥148ms	55	55
Color-coded TDI		≥65 ms	90	82
M-mode	↓ ≥15% LVESV	≥130 ms	50	38
Doppler	↑ ≥5% LVEF	>44 ms	66	55
Pulsed-wave TDI	↑ ≥25% LVEF	>102 ms	96	77
Color-coded TDI	↓ >15% LVESV	≥32.6 ms	100	100
Color-coded TDI	↑ ≥5% LVEF	≥60 ms	76	78
Color-coded TDI	↓ ≥15% LVESV	≥65 ms	92	92
Color-coded TDI	↓ ≥15% LVESV	≥110 ms	97	55
Color-coded TDI	↓ >15% LVESV	≥31.4 ms	96	78
Color-coded TDI	↓ >15% LVESV	≥31.4 ms	96	78
		≥98.5 ms	90	76

Table 2. Echocardiographic studies on prediction of response to CRT (continued)

Author	Nr pts	F-up (mo)	Measurement	Description
Knebel et al. (38)	38	6	Max delay	Max delay in Ts of 6 basal opposing walls
Yu et al. (36)	256	6 ± 3	Ts-SD	SD of Ts of 12 LV segments
			Ts-diff	Max delay in Ts of 12 LV segments
			TS-OW	Max delay in Ts of opposing walls of 12 LV segments
				Delay in Ts between basal septal and lateral wall
			Ts-sept-lat	
Van de Veire et al. (123)	49	Acute	Ts-SD-6	SD of Ts of 6 basal segments
			Ts-SD-12	SD of Ts of 12 LV segments
			Max delay-6	Max delay in Ts of 6 basal segments
			Max delay-12	Max delay in Ts of 12 LV segments
			Septal-to-lateral delay	Delay in Ts between basal septal and lateral wall
Van de Veire et al. (39)	60	6	Ts-SD-12	SD of Ts of 12 LV segments
Gorcsan et al. (124)	29	Acute	(Antero)septal-to-posterior delay	Max delay in Ts between (antero)septal and posterior wall
Yu et al. (113)	56	3	Ts-SD	SD of Ts for 12 LV segments in ejection phase
Van de Veire et al. (40)	60	6	LV dyssynchrony	Delay in Ts between basal septal and lateral wall
Tada et al. (56)	22	27±9	IVCDmax	Max LV intraventricular conduction delay = Delay in Ts between basal septum and lateral wall
Dohi et al. (43)	38	Acute	Radial dyssynchrony	Delay in Tε between basal septum and posterior wall
Porciani et al. (57)	59	6	o-ExCT	Sum of time exceeding aortic closure of 12 LV segments
				SD of Ts in 12 LV segments
			Ts-SD-12	
Suffoletto et al.(47)	64	8	Radial dyssynchrony	Delay in Tε between anteroseptal and posterior wall
				Max delay in Ts of 12 LV segments
			Ts-diff	SD of Ts of 12 LV segments
			Ts-SD	
Gorcsan et al. (49)	190	6 ± 3	Combined longitudinal	Delay in Ts between basal septal and lateral wall
			and radial dyssynchrony	Delay in Tε between anteroseptal and posterior wall
Delgado et al. (50)	161	6	AS-P delay	Delay in Tε between anteroseptal and posterior wall

Technique	Definition of response	Cut-off value	Sens (%)	Spec (%)
Color-coded TDI	↓ ≥15% LVESV + ↑ ≥5% LVEF	≥105 ms	64	80
Color-coded TDI	↓ >15% LVESV	≥33ms	93	78
		≥100 ms	92	68
		≥90 ms	81	80
		≥60 ms	70	76
Tri-plane TDI	↓ ≥15% LVESV	≥36.5 ms	91	81
		≥35.8 ms	91	85
		≥95 ms	74	81
		≥95 ms	74	81
Color-coded TDI		≥65 ms	87	81
Tri-plane TDI	↓ ≥15% LVESV	>33 ms	90	83
TSI	↑ ≥15% stroke volume	≥65 ms	87	100
TSI	↓ ≥15% LVESV	>34 ms	87	81
TSI	↓ ≥15% LVESV	≥65 ms	81	89
TSI	↓ ≥15% LVESV	>150 ms	100	90
TDI-derived strain (radial)	↑ ≥15% stroke volume	>130 ms	95	88
TDI-derived strain (longitudinal)	↓ ≥15% LVESV	≥760 ms	94	83
Color-coded TDI				
		≥32 ms	82	39
2D-Strain (radial)	↑ ≥15% LVEF	≥130 ms	89	83
Color-coded TDI		≥65 ms	89	75
		≥34 ms	89	75
Color-coded TDI	↑ ≥15% LVEF	≥60 ms		
2D-strain (radial)		≥130 ms	88	80
2D-strain (radial)	↓ ≥15% LVESV	≥130 ms	83	80

Table 2. Echocardiographic studies on prediction of response to CRT (continued)

Author	Nr pts	F-up (mo)	Measurement	Description
Yu et al.(34)	55	3	SD-12	SD of Td of 12 LV segments
			Diff-12	Max delay in Td of 12 LV segments
Cannesson et al. (51)	23	8	Dyssynchrony	Max delay in Ts of opposing walls of 6 LV segments
Ajmone Marsan et al. (54)	60	Acute	SDI	Systolic dyssynchrony index = SD of Tv for 16 LV segments

EF: ejection fraction; ESV: end-systolic volume; LV: left ventricular; RT3DE: real-time 3-dimensional echocardiography; SD: standard deviation; Td: time from onset of QRS to peak displacement; Tε: time from onset of QRS to peak systolic strain; Ts: time from onset of QRS to peak systolic velocity; Tv: Time from onset of QRS to minimum systolic volume; TDI: tissue Doppler imaging; TSI: tissue synchronization imaging; TT: tissue tracking; VVI: velocity vector imaging.

trial revealed less favorable results (22). SPWMD measurement yielded only limited predictive value for CRT response (sensitivity 24%, specificity 66%, Table 2). More importantly, in 45% of the study population the SPWMD measurement could not be obtained (Figure 3B, Table 3). Recent data in 98 patients also reported poor feasibility of M-mode imaging to assess LV dyssynchrony, due to the absence of a clear systolic deflection on M-mode echocardiography (53% akinesia of the septum, 12% akinesia of the posterior wall, or 3% both) or a poor acoustic window in the parasternal view (32%) (23). Therefore, M-mode has limited value in patients with scar formation in the antero-septal and posterior walls.

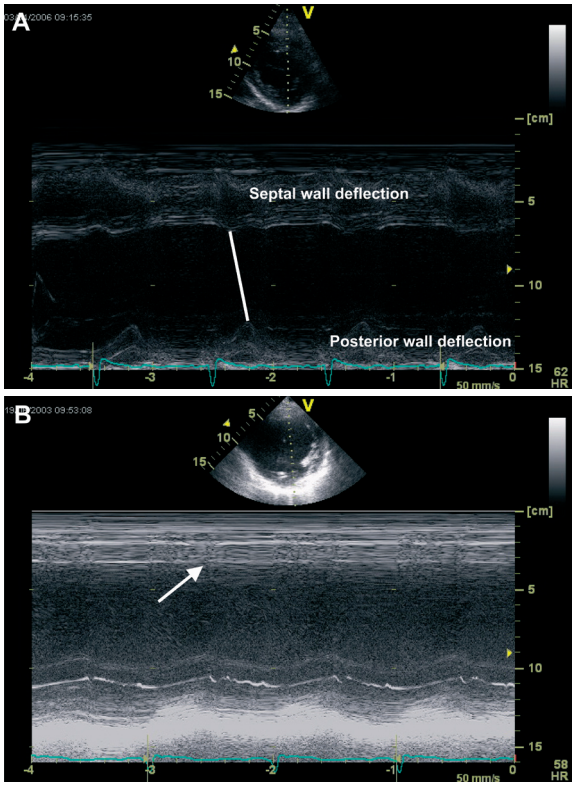


Figure 3. M-mode echocardiography

A. Parasternal M-mode recording of the LV in a HF patient. A clear delay between peak systolic septal and posterior wall inward motion can be seen (white line). B. Parasternal M-mode recording of the LV in a HF patient. Assessment of septal-to-posterior wall motion delay (SPWMD) is not possible due to the presence of an akinetic septum (arrow).

Technique	Definition of response	Cut-off value	Sens (%)	Spec (%)
TT	↓ ≥15% LVESV	≥75 ms	66	73
		≥205 ms	62	62
VVI	↑ ≥15% LVEF	≥75 ms	85	80
RT3DE	↓ ≥15% LVESV	≥5.6%	88	86

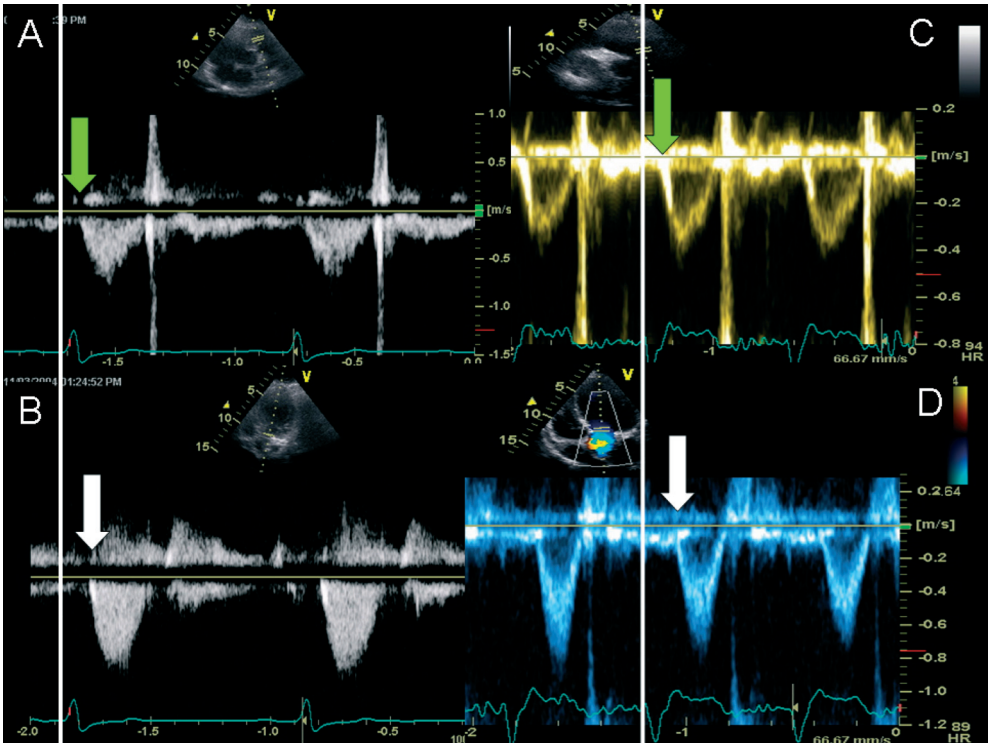
B. Doppler echocardiography

Doppler echocardiography can document dyssynchrony at various levels. AV dyssynchrony can be assessed by determining the LV filling time (LVFT) corrected for variations in heart rate (R-R interval). A LVFT/RR of <40% indicates AV dyssynchrony (24).

The LV-pre-ejection interval (LPEI) is defined as the time between the beginning of ventricular activation (QRS complex) and the beginning of LV ejection (onset aortic flow by Doppler echocardiography). A delay of ≥140 ms represents interventricular delay. Interventricular mechanical delay (IVMD) can also be assessed by measuring the pre-ejection intervals from the onset of QRS to the onset of aortic valve closure and pulmonic valve closure, respectively.

Figure 4. Doppler Interventricular mechanical delay (IVMD)

To measure IVMD, time to onset of flow is measured in the RVOT (A) and LVOT (B). Normal flow delays do not exceed 40 ms (A and B). C and D illustrate a dyssynchronous heart with a delay of 100 ms between RVOT flow (C) and LVOT flow (D).



The IVMD is calculated as the difference between these 2 measurements and should be <40 ms (Figure 4) (6,24).

Delayed activation of the lateral wall (LLWC) is calculated as the percentage of overlap between the end of lateral wall contraction on M-mode echocardiography and the onset of LV filling (onset of the E-wave on pulsed-wave Doppler of transmitral flow). Any overlap represents intraventricular dyssynchrony (24).

The protocol of the CARE-HF (Cardiac Resynchronization in Heart Failure) trial included LPEI, IVMD and LLWC measurements for cardiac dyssynchrony. At least 2 of the above criteria were required to confirm the presence of cardiac dyssynchrony in patients with QRS duration between 120 and 149 ms.

However, available evidence on the predictive value of these dyssynchrony parameters is still limited. Bordachar et al evaluated 41 HF patients and despite the significant reduction of IVMD after CRT initiation (from 58±28 ms to 31±18 ms, p<0.001), no relation was found between IVMD and hemodynamic improvement acutely after CRT (25). Longer follow-up was obtained in the SCART (Selection of Candidates for CRT) trial which reported significantly longer IVMD's in responders as compared to non-responders (52±26 ms vs. 36±44 ms, p=0.029) (26). Furthermore, a IVMD >44 ms was able to predict combined clinical and echocardiographic response after 6 months of CRT with a sensitivity of 66% and a specificity of 55% (Table 2), whereas LLWC and pulsed-wave TDI parameters showed no predictive value. In addition, recent sub-analysis of the CARE-HF trial demonstrated that IVMD >49 ms together with low systolic blood pressure (<117 mmHg) was predictive for hospitalization-free survival after CRT (27).

C. Tissue Doppler imaging

TDI is one of the most popular techniques for the evaluation of LV dyssynchrony. TDI includes assessment of myocardial velocity in different myocardial regions and relating the timing of myocardial velocity to electrical activity (QRS complex), providing electro-mechanical delays. Data can be acquired on-line using pulsed-wave TDI or reconstructed off-line using color-coded TDI.

1. Pulsed-wave TDI

Initially, pulsed-wave TDI was used to assess cardiac dyssynchrony. A sample can be placed in the region of interest using 2D TDI images. This allows for quick online evaluation of regional synchronicity by measuring the time to onset of mechanical contraction in the ejection phase (Figure 5). This approach has shown a relationship between improvement in cardiac function after CRT and baseline LV dyssynchrony (28,29). Penicka et al measured time intervals in the 4 basal LV segments and in the basal segment of the free wall of the right ventricle (12). The authors reported a cut-off value of >102 ms for dyssynchrony (defined as the sum of LV and interventricular delay) for the prediction of improved LV function after CRT, yielding a sensitivity of 96% and a specificity of 77% (Table 2).

The restricted assessment of only one sample area at a time constitutes a major disadvantage of this method, whereas color-coded TDI permits simultaneous examination of multiple myocardial segments, thereby avoiding potential errors from differences in cardiac frequency. Furthermore, the timing of the LV ejection phase is very difficult to superimpose on the pulsed-TDI spectral Doppler waveform, which is another limitation (Table 3).

Table 3. Advantages and limitations of the main echocardiographic techniques for assessment of LV dyssynchrony for prediction of response to CRT

Technique	Advantages	Limitations
M-mode	Widely available Rapid assessment	Low feasibility / reproducibility in patients with ischemic cardiomyopathy and extensive scar tissue
Pulsed-wave TDI	Widely available	Difficult acquisition / time-consuming Susceptible to influences of breathing, patient motion and changes in heart rate Off-line analysis not possible Angle-dependent Cannot differentiate passive motion from active deformation
Color-coded TDI	Off-line rapid analysis	Requires specialized equipment High image quality needed Angle-dependent Cannot differentiate passive motion from active deformation
TSI	Rapid analysis Complete analysis of all LV segments Attractive Visual presentation	Requires specialized equipment High image quality needed Angle-dependent Cannot differentiate passive motion from active deformation
TDI-strain	Can differentiate passive motion from active deformation	Requires specialized equipment Significant operator experience needed Time-consuming Angle-dependent
2D-strain	Automated tracking algorithm Can differentiate passive motion from active deformation No angle-dependency	Requires specialized equipment Significant operator experience needed Time-consuming
VVI	Automated tracking algorithm Can differentiate passive motion from active deformation No angle-dependency	Requires specialized equipment Significant operator experience needed Time-consuming
RT3DE	Complete analysis of all LV segments	Requires specialized equipment Significant operator experience needed Time-consuming Lower spatial and temporal resolution

Abbreviations as in Table 2.

2. Color-coded TDI

A major advantage of color-coded TDI is the ability of off-line analysis. Importantly, the size and the positioning of the samples (region of interest) can be adjusted manually within the LV wall to identify where the peak systolic velocity is most reproducible.

In the early color-coded TDI studies of LV dyssynchrony, sample volumes were placed in the basal septal and lateral segments (apical 4-chamber view). By measuring the time to peak systolic velocity of the individual segments with reference to the QRS complex, the time difference between 2 segments was calculated (Figure 6). A "septal-to-lateral delay" of ≥60 ms appeared to be predictive of an immediate response after CRT (30). Subsequently, a 4-segment model was proposed including 4 basal segments (septal, lateral, inferior, and anterior) and a delay

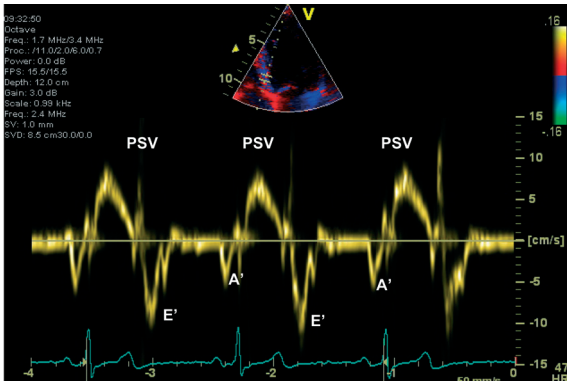


Figure 5. Pulsed-wave tissue Doppler imaging of a normal individual

The pulsed-wave sample is placed on-line in the region of interest and the myocardial velocity curve is derived. (PSV = peak systolic velocity, E' and A' are early and late diastolic velocities).

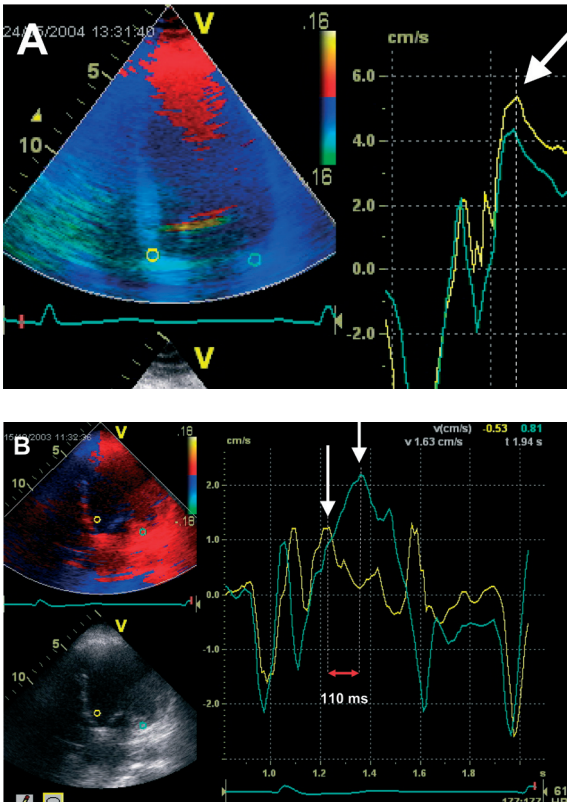


Figure 6. Color-coded tissue Doppler imaging

Color-coded 4-chamber TDI image in the upper left panel with off-line post-processing velocity tracings at the right side. A. Example of synchronous contraction without delay in peak systolic velocities. The peak systolic velocities of the septum (yellow) and the lateral wall (green), as indicated by the white arrow, occur at the same time. B. Example of severe LV dyssynchrony as indicated by the time delay in peak systolic velocity of the septum (arrow yellow curve) compared with the lateral wall (arrow green curve) of 110 ms.

of ≥65 ms was predictive of both clinical (sensitivity/specificity 80%) and echocardiographic improvement (sensitivity/specificity 92%) after 6 months of CRT (Table 2) (31).

Other studies used a "multi-segment model" to determine LV dyssynchrony to predict a favorable CRT response. A 12-segment model was proposed by Yu et al including 6 basal and 6 mid myocardial segments to assess LV dyssynchrony (32). The authors proposed to calculate a dyssynchrony index (Ts-SD) by using the standard deviation of all 12 time intervals. Initial work in 30 patients reported a Ts-SD of ≥32.6 ms to be predictive of LV reverse remodeling after CRT (33). The same group performed subsequent studies in larger patient groups comparing

multiple TDI-derived parameters, however, all studies showed best predictive value for Ts-SD-12 (see Table 2) (34-36). For instance, a recent study in 256 CRT patients showed that LV reverse remodeling after CRT (defined as a reduction of ≥15% in LVESV) could be predicted by 4 different TDI dyssynchrony parameters; a cut-off value of 33 ms for Ts-SD was able to predict response to CRT with a sensitivity of 93% and specificity of 78% (36).

Notabartolo et al measured the time to peak systolic velocity in the 6 basal segments (septal, lateral, anterior, inferior, anteroseptal and posterior) in 49 patients undergoing CRT (37). The peak velocity difference (PVD) was measured as the time difference between the earliest and latest contracting segment. A PVD of ≥110 ms at baseline was predictive of LV reverse remodeling at the 3-month follow-up (sensitivity 97%, specificity 55%). In addition, Knebel et al measured the maximal delay between the 6 opposing basal segments, and found a delay of ≥105 ms predictive for response to CRT (38).

Recently, it has become possible to acquire a tri-plane dataset (3D) and color-coded TDI of the LV simultaneously. The advantage of the tri-plane method is that acquisition of a single tri-plane dataset allows simultaneous comparison of 12 LV segments during the same heartbeat whereas the 2D method requires at least 3 acquisitions. During post-processing, this technique presents the timing of peak systolic velocities in a color-map in the apical 4-, 2-, and 3-chamber views. Furthermore, a 3D volume can be generated semi-automatically by tracing the endocardial

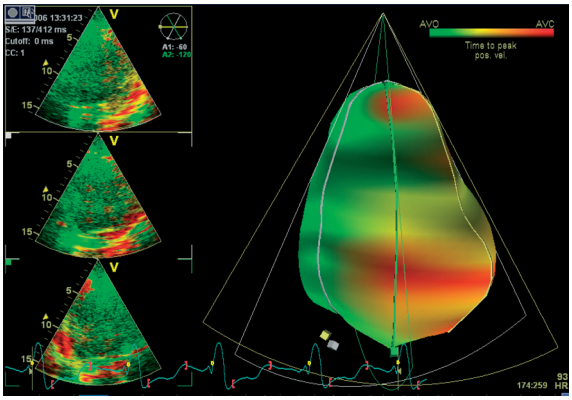


Figure 7. Tissue synchronization imaging

Using a tri-plane probe, color-coded tissue Doppler data from the apical 4-,2- and 3-chamber views are recorded simultaneously during the same heartbeat. During post-processing a 3D volume of the left ventricle is generated. The colors represent mechanical activation times. The orange-yellow color indicates later activation of the anterolateral wall compared to the septum (green).

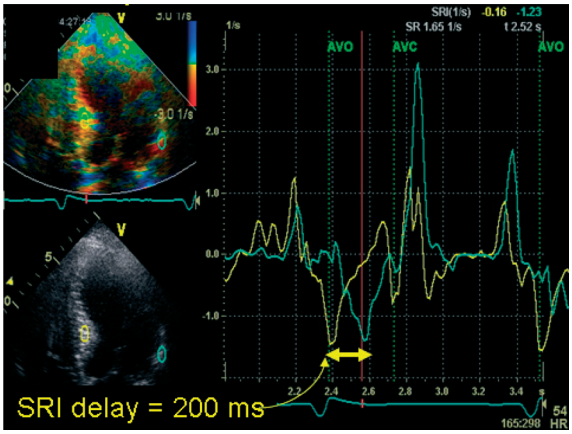


Figure 8. Strain rate imaging

Strain rate tracings obtained from the basal septum (yellow) and lateral wall (green) indicate a delay of 200 ms.

borders manually. Van de Veire and colleagues applied this technique in 60 patients and calculated dyssynchrony as the standard deviation of time to peak systolic velocity of the 12 LV segments (Ts-SD-12) (39). Patients showing LV reverse remodeling after 6 months of CRT had higher baseline values of Ts-SD-12 as compared to non-responders (42±14 ms vs. 22±12 ms, $p<0.05$). As a result, a cut-off value of ≥33 ms was able to predict response with a sensitivity of 90% and a specificity of 83% (Table 2). This cutoff value of 33 ms obtained with tri-plane TDI is similar to the cutoff value proposed by Yu et al when single-plane TDI was used (33).
Accordingly, a wide variety of TDI-based approaches has been developed recently to quantify LV dyssynchrony ranging from 2- to 12-segmental models (Table 2).

D. Tissue synchronization imaging

Tissue synchronization imaging (TSI) is another evolving technique. This technique can color-code the myocardium based on automated time-to-peak systolic longitudinal velocity of each segment. The resultant color-coded images permit a quick visualization of the earliest activated segments (displayed in green) and the latest activated segments (displayed in red) (Table 3). In addition, quantitative assessment is possible using myocardial velocity curves (similar to TDI). Van de Veire et al defined LV dyssynchrony as the time difference between basal septum and lateral wall, which was automatically calculated by the software (40). An excellent correlation was found between manually and automatically derived LV dyssynchrony ($r=0.95$, $p<0.0001$). In addition, TSI was able to predict LV reverse remodeling after 6 months of CRT (sensitivity 81%, specificity 89%, Table 2) using a cut-off value of 65 ms (similar to TDI).
More recently, TSI has been used in combination with tri-plane (3D) imaging, which permits for quick visualization of the most delayed LV segment (Figure 7). Nevertheless, long-term data using TSI are lacking and its superiority over standard 2D color-coded TDI has not been demonstrated.

E. TDI-derived strain (rate) imaging and tissue tracking

Strain imaging can be performed by off-line analysis of color-coded TDI images. In contrast to TDI, which only measures myocardial velocities, strain imaging is able to measure the percentage of myocardial deformation during systole using the Doppler velocity gradients (Figure 8). Negative strain values represent active contraction whereas positive values represent relaxation or lengthening, thereby differentiating active myocardial contraction from passive displacement. In addition, the rate of myocardial deformation, or strain rate, can be calculated. Strain imaging has been suggested to reflect myocardial dyssynchrony by measuring the time delays of time-to-peak systolic strain (comparable to TDI) (41,42). Initial studies applied strain imaging on the apical views, thereby measuring longitudinal strain, and reported low reproducibility due to the relatively high operator and angle dependency (41) (Table 3). Possibly related to these limitations, longitudinal strain appears a relatively poor predictor of CRT response as compared to TDI (34,35). Recently, Yu et al evaluated the value of TDI-derived longitudinal strain as compared to TDI in 256 CRT patients (36). The standard deviation of 12 LV segments of time to peak systolic velocity was significantly higher in responders as compared to non-responders (46±13 ms vs. 29±11 ms, $p<0.001$), whereas the standard deviation of 12 LV segment of time to peak myocardial strain was not different between responders and non-responders (65±31 ms vs. 67±28 ms, NS). Consequently, longitudinal strain was not able to predict response to CRT in this particular study.

Another study applied strain imaging on the short-axis views thereby measuring radial strain showing better results. Dyssynchrony was defined as the time difference of peak radial strain in the septum versus the posterior wall, and was significantly greater in patients with acute hemodynamic responses to CRT. Patients with dyssynchrony of ≥130 ms revealed an immediate improvement in stroke volume (sensitivity 95% and specificity 88%) (43).

Tissue tracking (TT) describes the systolic longitudinal motion or displacement and allows identification of delayed longitudinal contraction (DLC). To date, only few studies used this technique to quantify LV dyssynchrony. Yu et al evaluated 55 HF patients prior to implantation and calculated 6 different TT-derived measurements (34). A cut-off value of ≥75 ms for SD of time to peak displacement of 12 LV segments yielded a sensitivity of 66% and specificity of 73% to predict response (see Table 2). TT was also used by Sogaard et al who focused on the DLC during post-systole in order to assess LV dyssynchrony (44). LV dyssynchrony can be determined by calculating the number of myocardial segments with peak systolic excursion after aortic valve closure and by measuring the magnitude of the delay for each segment. In patients with ≤2 segments displaying DLC (n = 11) the acute improvement in LVEF after CRT initiation was significantly lower as compared to patients with >2 segments (n = 14) (10±7% vs. 32±15%, p<0.01). Also, subsequent studies by the same group with longer-term follow-up showed predictive value for the extent of myocardium showing DLC (45,46).

F. 2D derived strain imaging

A new echocardiographic technique, speckle tracking, can calculate myocardial strain from conventional 2D echocardiography. The main advantage of speckle tracking over TDI-derived strain is its lack of angle dependency (Figure 9, Table 3). Currently, only few studies involved this technique for assessment of LV dyssynchrony (38,47-50).

Suffoletto et al applied speckle tracking to routine mid ventricular 2D short-axis images in 48 patients undergoing CRT and time to peak radial strain was calculated from the 6 LV segments. Using a cut-off value of ≥130 ms for LV dyssynchrony (time difference in peak anteroseptal wall-to-posterior wall strain) yielded a sensitivity of 91% and a specificity of 75% to predict an immediate increase ≥15% in stroke volume. Long-term response (≥15% in LV ejection fraction) could be predicted with similar sensitivity and specificity (Table 2) (47). Importantly, speckle tracking analysis was possible in 96% of the patients with high reproducibility.

Recent work by Delgado et al evaluated all 3 forms of deformation using speckle tracking analysis including radial, circumferential and longitudinal strain in 161 HF patients undergoing CRT (50). Only radial strain was able to predict response to CRT; a cut-off value of 130 ms for the anteroseptal wall-to-posterior wall strain delay was able to predict LV reverse remodeling after 6 months of CRT (see Table 2).

G. Velocity vector imaging

VVI can also be applied to routine 2D images and allows measurement of myocardial velocity with an automated tracking algorithm. Cannesson et al applied this method to 23 CRT candidates. Tissue velocities were determined from standard apical 4-chamber, 2-chamber and long-axis views with high reproducibility. The greatest opposing wall peak longitudinal velocity delay from the 3 views indicates LV dyssynchrony. A baseline dyssynchrony of ≥75 ms predicted response to CRT (Table 2) (51).

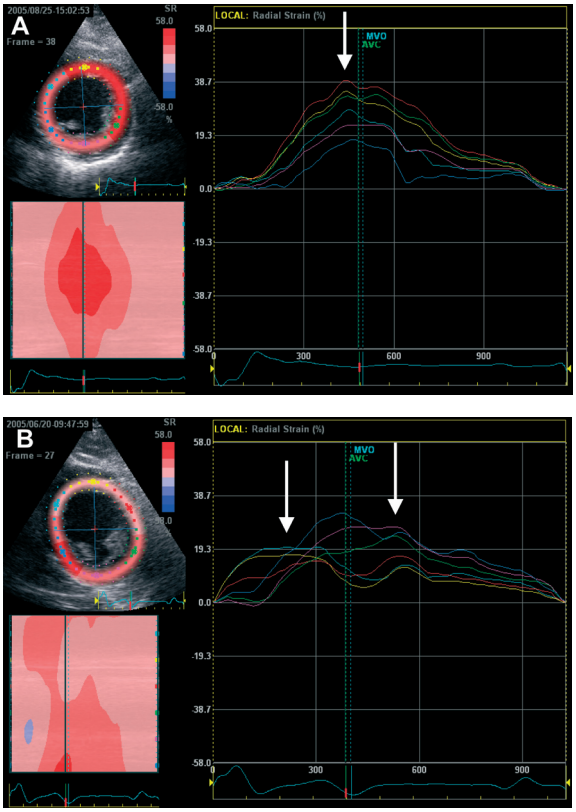
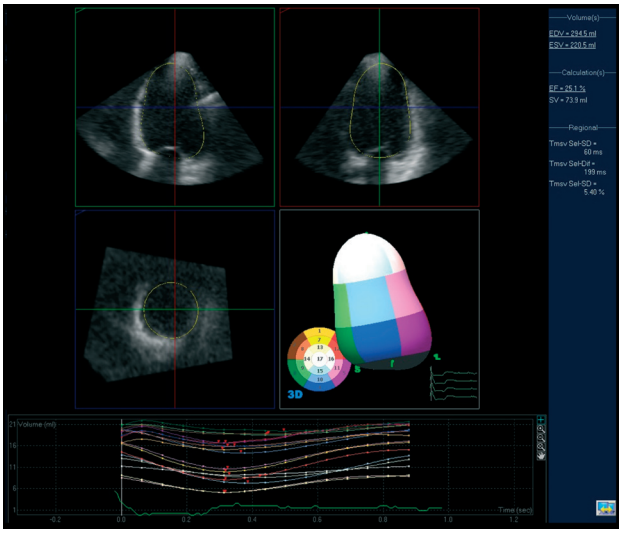


Figure 9. 2D-derived strain imaging or speckle tracking

A. Speckle tracking derived radial strain imaging in the parasternal short-axis view at the mid LV level. In this example peak radial strain (arrow) occurs simultaneously in all 6 segments, indicating a synchronous LV contraction (the curves are color-coded in accordance with the segments on the short-axis view). B. Example of radial time-strain curves from speckle tracking in a HF patient with LV dyssynchrony. The septal regions reach peak strain early in systole (blue/yellow curves), whereas the lateral segments reach peak strain late in systole (red/green curves, arrows indicate peak systolic strain).

Figure 10. Real-time 3D echocardiography

Example of LV dyssynchrony analysis from a RT3DE data set using parametric images. The global time from onset of QRS to mean systolic volume is used as timing reference; early segments are coded in blue, whereas late segments are coded in red. A. Before CRT, the postero-lateral segments are activated last (indicated in red). Substantial dyssynchrony is present as indicated by a systolic dyssynchrony index (SDI) of 9.7%. B. After 6 months of CRT the overall green color indicates absence of regions with delayed activation, indicating resynchronization after CRT implantation (SDI 1.1%).



H. Real-time 3D echocardiography

Real-time 3D echocardiography (RT3DE) is another new technique which determines dyssynchrony in 16 LV segments by color-coding each segment and quantifying regional function and change in volumes for each segment during systole and diastole. The degree of dispersion in the timing of minimal volume for each segment reflects the extent of LV dyssynchrony (Figure 10). The systolic dyssynchrony index (SDI) is used as a marker for global LV dyssynchrony and is defined as the standard deviation of the timing for each segment. In addition, the area of latest activation can be identified.

This method can rapidly quantify LV dyssynchrony as demonstrated by Kapetanakis et al who evaluated 174 unselected patients referred for routine echocardiography (52). Also, Zhang et al evaluated 13 patients with RT3DE during a 15-min interruption of CRT and reported an increase of SDI, with an increase in LV volumes and a decrease in LVEF (53). Only 1 study currently addressed the predictive value of RT3DE for acute response after CRT (54); Ajmone et al found that a SDI of 5.6% was predictive for an immediate decrease in LVESV of ≥15% (sensitivity 88% and specificity 86%, Table 2). Currently, no data are available on the prediction of long-term CRT response using this technique. However, limitations include low frame rates of 20 to 30 frames/sec for image acquisition and the inability to differentiate between passive motion and active deformation.

As discussed, several echocardiographic methods have been proposed for the quantification of LV dyssynchrony in HF patients; e.g. TDI using differences in myocardial velocities, strain using differences in myocardial deformation and 3D-echocardiography using differences in volume changes within the LV. To date there is no consensus on which technique best predicts response to CRT. Furthermore, numerous definitions of LV dyssynchrony have been advanced with varying numbers of LV segments to be evaluated and different cutoff values. Importantly, a compromise is necessary between the optimal method for detection of LV dyssynchrony and the feasibility in daily practice (Table 3). Most performed studies are small, single center, non-randomized studies with short-term follow-up. Furthermore, interpretation is confounded by varying definitions of response to CRT and availability of direct comparisons is lacking. At present, only 11 studies compared 2 or more echo techniques for prediction of response; 2 studies compared M-mode with TDI (23,55), 1 study compared TSI with TT (56), 4 studies compared several TDI-derived strain imaging parameters with TDI (34-36,57) and another 4 studies compared 2D-derived strain imaging parameters with TDI (38,47,49).[45]. Interestingly, in these studies TDI emerged as best in predicting response to CRT despite varying numbers of LV segments included in the assessment of LV dyssynchrony. Of note, 3 recent studies that applied 2D radial strain imaging demonstrated promising results with comparable (or even higher) predictive values for anteroseptal wall-to-posterior wall strain delay as compared to TDI (Table 2).

Larger multi-center studies are needed to identify the most useful technique, with the optimal number of segments to evaluate and the optimal extent of LV dyssynchrony, to select patients with a high likelihood of CRT response. Thus far, one prospective, multi-center study has been reported. The PROSPECT trial compared various echocardiographic techniques to assess LV dyssynchrony and predict response to CRT (20). The results however demonstrated that all echocardiographic techniques had limited predictive value for response to CRT. Major limitations included the limited assessability of LV dyssynchrony from the various echo techniques, but

also the poor inter-observer agreement for assessment of LV dyssynchrony. In addition to these technical shortcomings, pathophysiological issues may also have influenced response to CRT, including the presence of extensive scar tissue, limited venous anatomy and suboptimal LV lead position, which will be discussed below.

THE VALUE OF MAGNETIC RESONANCE IMAGING

The use of MRI for selecting patients for CRT is increasing. Cardiac MRI can provide a detailed morphological and functional evaluation of the heart irrespective of the patient's anatomy

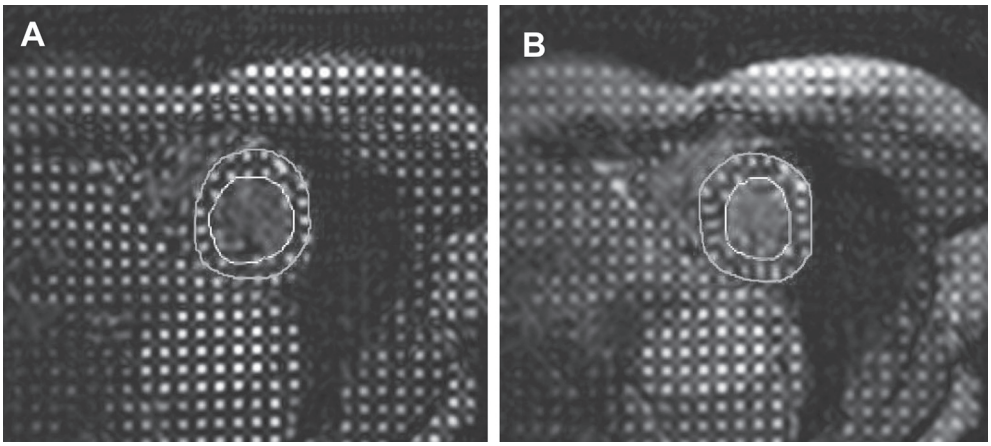
Table 3. Advantages and limitations of the main echocardiographic techniques for assessment of LV dyssynchrony for prediction of response to CRT

Technique	Advantages	Limitations
M-mode	Widely available Rapid assessment	Low feasibility / reproducibility in patients with ischemic cardiomyopathy and extensive scar tissue
Pulsed-wave TDI	Widely available	Difficult acquisition / time-consuming Susceptible to influences of breathing, patient motion and changes in heart rate Off-line analysis not possible Angle-dependent Cannot differentiate passive motion from active deformation
Color-coded TDI	Off-line rapid analysis	Requires specialized equipment High image quality needed Angle-dependent Cannot differentiate passive motion from active deformation
TSI	Rapid analysis Complete analysis of all LV segments Attractive Visual presentation	Requires specialized equipment High image quality needed Angle-dependent Cannot differentiate passive motion from active deformation
TDI-strain	Can differentiate passive motion from active deformation	Requires specialized equipment Significant operator experience needed Time-consuming Angle-dependent
2D-strain	Automated tracking algorithm Can differentiate passive motion from active deformation No angle-dependency	Requires specialized equipment Significant operator experience needed Time-consuming
VVI	Automated tracking algorithm Can differentiate passive motion from active deformation No angle-dependency	Requires specialized equipment Significant operator experience needed Time-consuming
RT3DE	Complete analysis of all LV segments	Requires specialized equipment Significant operator experience needed Time-consuming Lower spatial and temporal resolution

Abbreviations as in Table 2.

Figure 11. Tagged magnetic resonance imaging

MRI tissue tagging in a healthy volunteer. The tags appear as a grid superimposed on the short-axis view at the mid ventricular level. These taglines can be traced during the contraction (A end-diastolic, B end-systolic), enabling strain rate analysis on global and regional level during the cardiac cycle.



in any arbitrary orientation (58). Furthermore, MRI is particularly useful in patients with a suboptimal acoustic window. Both LV and interventricular delay in ventricular contraction patterns can be studied using 3 different applications of cardiac MRI.

A. Strain rate analysis from MRI tissue tagging

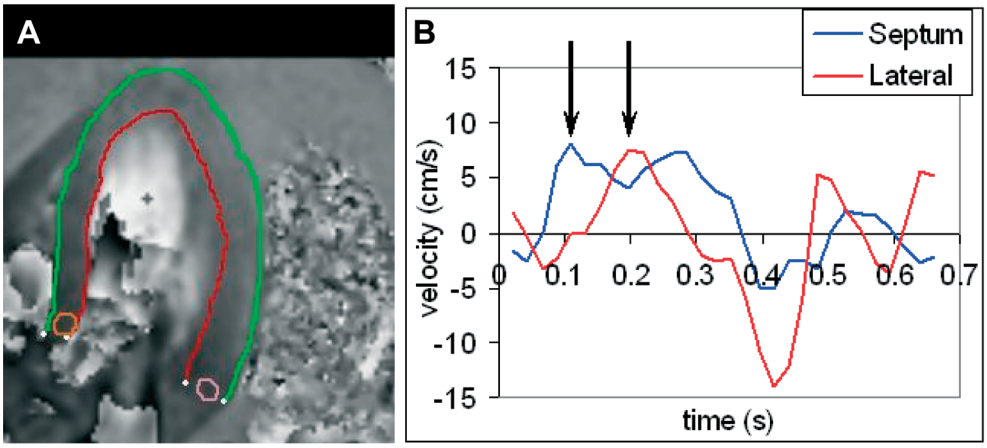
MRI tissue tagging labels the myocardium by selective saturation prepulses applied in a specific orientation perpendicular to the desired imaging plane. The tags appear as horizontal or vertical lines, or as a grid of both, superimposed on the image (4-chamber or short-axis view). These taglines can be traced during the contraction, enabling strain rate analysis on a global and regional level during the cardiac cycle. 3D MR tissue tagging has been used for studying LV dyssynchrony (59): in animal models with left bundle branch block-induced HF, an acute improvement in hemodynamic parameters as well as an acute improvement in intraventricular delay were noted after establishing mechanical synchrony by left atrial and biventricular pacing (60,61). In humans, the feasibility of assessing LV dyssynchrony with tagged MRI has been demonstrated in healthy volunteers (62) as well as in patients with ischemic and non-ischemic cardiomyopathy (63), but further testing is needed in CRT candidates (Figure 11). Still, this method is technically difficult which limits its routine use.

B. Velocity-encoded MRI

Phase-contrast velocity encoded MRI (64), when applied for myocardial wall motion measurement, allows evaluation of the myocardial velocity during contraction in any arbitrary orientation, such as the longitudinal, radial or circumferential contraction. Westenberg et al recently applied velocity-encoded MRI in HF patients with low LVEFs and wide QRS complexes, by measuring the longitudinal LV contraction and compared their results directly with TDI (65). The authors noted an excellent agreement between both modalities for classification according to the severity (minimal, intermediate or extensive dyssynchrony) of LV dyssynchrony (Figure 12). Similar results were demonstrated by Delfino et al, who reported excellent correlations for

Figure 12. Velocity-encoded magnetic resonance imaging

Velocity-encoded MRI and velocity graphs are presented in respectively the left and right panel, demonstrating extensive LV dyssynchrony with a septal-to-lateral delay of 116 ms. Adapted from Westenberg et al (65).



peak velocities (r=0.86) and time to peak velocities (r=0.97) as measured with TDI and MRI (66). Besides measuring the longitudinal myocardial wall velocities (basal-to-apex contraction and relaxation) in the 4-chamber orientation, MRI can also provide the radial, circumferential or longitudinal myocardial wall velocity acquired in a short-axis orientation (67). Regional analysis along the circumference of this short-axis, by measuring the time of peak systolic velocity, can indicate the site of latest activation.

C. Regional wall motion analysis from LV short-axis cine MRI

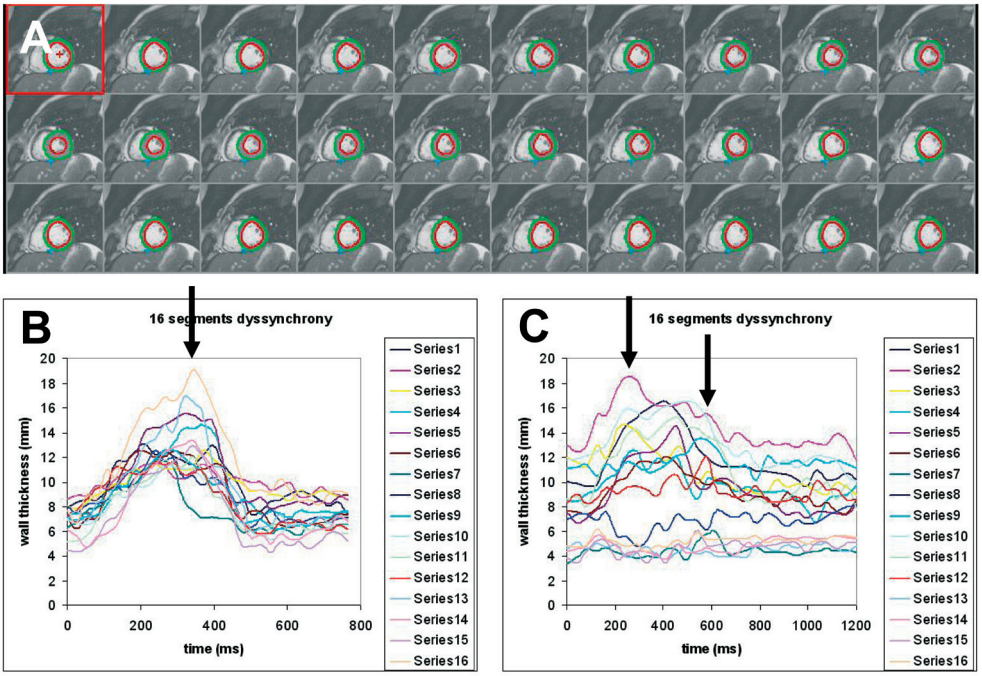
LV dyssynchrony can also be determined from regional wall motion analysis in 3 cine short-axis MRI slices. The standard 16-segment model is applied: 6 segments at basal level, 6 segments at mid ventricular level and 4 segments at apical level. In all phases, endocardial contours are determined at these 3 levels (68). Regional wall motion analysis for each of the 16 segments provides 16 individual graphs for wall motion. The standard deviation between the values of peak wall motion or peak wall thickness is an indicator of the extent of LV dyssynchrony (Figure 13).

Other information derived from MRI

Cardiac MRI is also of interest for evaluation of potential candidates for CRT, because other factors (apart from LV dyssynchrony) are important in patient selection. These factors include the size, shape and function of the LV (volumes, LVEF, sphericity) and the presence and transmurality of scar tissue at the site of LV lead placement. MRI can provide all this information with high accuracy due to high spatial and temporal resolution. With contrast-enhancement MRI, precise delineation of scar tissue is possible (69,70). Regions with scar tissue have large interstitial spaces between the collagen fibres, resulting in slower outwash of gadolinium-based contrast agent compared to regions of healthy myocardium. This is presented by an increased hyperenhancement on inversion-recovery MRI, as the T1 of the gadolinium-based

Figure 13. Wall motion analysis with magnetic resonance imaging

A. Regional wall motion analysis of short-axis MR slices at 3 different levels in a healthy volunteer. In all phases epicardial (red) and endocardial borders (green) are determined and a 16-segment model of de LV is applied: 6 segments at basal level, 6 segments at mid ventricular level and 4 segments at apical level. The standard deviation between the values of peak wall motion is an indicator of the amount of LV dyssynchrony. B. Example of complete synchrony in a healthy volunteer. C. Example of a patient with ischemic cardiomyopathy showing a differences in timing of peak wall motion (see arrows), indicating LV dyssynchrony.



contrast is much shorter than that of myocardial tissue. Bleeker et al applied this technique and recently demonstrated that patients with transmural scar tissue in the posterolateral region (the preferred region for the LV pacing lead) do not respond to CRT despite the presence of baseline LV dyssynchrony (71) (Figure 14). In addition, not only the location of scar but also the extent of scar tissue ("scar burden") is important. Two studies addressed this issue and demonstrated that the more scar burden, the less improvement in LV function after CRT (72,73).

Lastly, recent small observations demonstrated feasibility of MRI to depict the coronary venous anatomy, which anatomic information can be used for LV lead positioning (74-76). However, a high spatial resolution of a 3D dataset is required to adequately depict the relatively small coronary vessels.

Thus, MRI is a method capable of simultaneously evaluating the presence of scar tissue, LV function, LV dyssynchrony and identifying a suitable vein for LV lead placement helping to better plan the CRT implantation strategy. However, the number of studies with long-term predictive value is limited.

In addition, cardiac MRI is not feasible in all patients; claustrophobia is occasionally a problem, and absolute contraindications include pacemakers (77), defibrillators, cerebral clips and

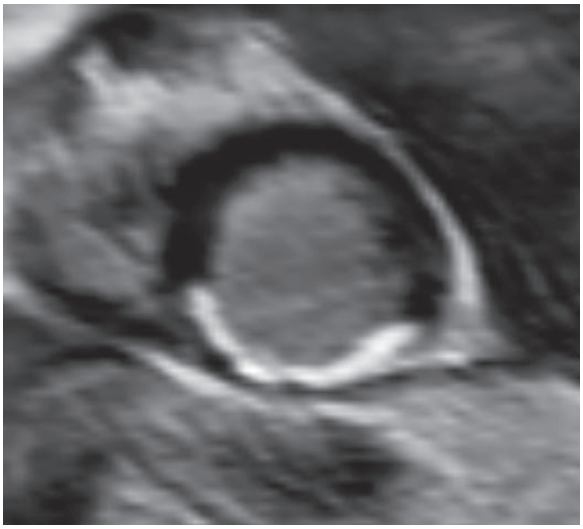


Figure 14. Contrast-enhanced magnetic resonance imaging

The presence and transmurality of scar tissue can be determined with contrast-enhanced MRI. This short-axis view demonstrates transmural scar (white area) in the postero-lateral region (preferred region of the LV pacing lead).

pregnancy. Some pacemakers and defibrillators, though, have shown MRI compatibility in experimental studies (78). Furthermore, relative precautions for contrast nephropathy should be made for patients with moderate to severe chronic kidney disease. Still, MRI is not suitable for follow-up of patients undergoing CRT. Another limitation of the MRI application in clinical routine is the time-consuming data acquisition and analysis. Image analysis software with automated segmentation algorithms are indispensable for handling large amounts of data acquired from cardiac MRI tests.

THE VALUE OF NUCLEAR IMAGING

A. Radionuclide angiography

Radionuclide angiography has been used mainly for the assessment of wall motion abnormalities and LVEF, but it can also be used for evaluation of cardiac dyssynchrony. Interventricular and LV dyssynchrony can be quantified using functional images, as assessed by Fourier analysis, with high reproducibility (79,80). Interventricular dyssynchrony is calculated as the difference between the mean phase angle of the LV and RV; LV dyssynchrony is calculated as the SD of the phase histogram. Only a few studies have used radionuclide angiography to assess LV dyssynchrony before CRT and the relationship to outcome after device implantation. One small study evaluated 13 patients and found a significant acute increase in LVEF and a significant decrease in interventricular and LV dyssynchrony during biventricular pacing, compared with normal sinus rhythm (81). Toussaint and colleagues used radionuclide angiography at baseline and 6 months after CRT implantation in 34 patients (82). The combination of a baseline LVEF >15% with interventricular delay was the best predictor of improvement in LVEF at 6 months follow-up. These results are not in line with those demonstrated with TDI (showing the greatest benefit of CRT in patients with LV rather than interventricular dyssynchrony), and further studies including comparisons with TDI are required.

B. SPECT

Recently, Chen and colleagues demonstrated in 90 normal individuals that gated SPECT imaging can also be used for the assessment of LV dyssynchrony (Figure 15) (83). These workers developed a count-based method to extract the amplitude and phase from regional LV count changes throughout the cardiac cycle. The phase information can be related to the time interval, and consequently the onset of mechanical contraction could be determined. Henneman et al correlated LV dyssynchrony as assessed with TDI with the parameters derived form gated SPECT (84). The authors analyzed 75 HF patients and demonstrated a good relationship between histogram bandwidth ($r=0.89$, $p<0.001$) and phase standard deviation ($r=0.80$, $p<0.001$). In a subsequent study the authors related both histogram bandwidth and phase standard deviation to response after 6 months of CRT (85). Cut-off values of 135° for histogram bandwidth and 43° for phase standard deviation were proposed to predict clinical response, defined as an improvement of ≥1 NYHA functional class after 6 months of CRT.

Other information derived from nuclear imaging

Similar to MRI, nuclear imaging is well-suited for assessment of viability and scar tissue. Sciagra et al demonstrated that patients were severe resting defects on ^{99m}Tc- sestamibi SPECT at baseline showed lack of response after CRT (86). Another study used ^{18}F-fluorodeoxyglucose SPECT to determine the extent of viable myocardium in 61 ischemic CRT candidates. The authors proposed a cut-off value of ≥11 viable segments (in a 17-segment model) to predict clinical response, yielding a sensitivity of 74% and a specificity of 87% (Figure 16) (87). Furthermore, scar tissue (defined as <50% tracer activity on ^{99m}Tc-tetrofosmin SPECT) in the region of the LV pacing lead prohibited both clinical and echocardiographic improvement after CRT (88). Similar results were demonstrated by Adelstein et al; higher overall scar burden, larger number of severely scarred segments, and greater scar density near the LV lead tip indicate an unfavorable response to CRT in ischemic patients (89).

THE VALUE OF COMPUTED TOMOGRAPHY

Studies on computed tomography (CT) in CRT candidates mainly focused on non-invasive visualization of the venous coronary anatomy. In clinical practice, retrograde invasive venography is used to determine venous anatomy during CRT implantation. Meisel et al evaluated the availability of veins for possible lead placement in 129 patients using CT. They reported that venous anatomy is highly variable and that not all patients are suited for endocardial (via the coronary sinus) LV lead placement (90).

Jongbloed et al demonstrated the feasibility of multislice CT (MSCT) for visualizing venous anatomy (Figure 17) (91). The same group recently demonstrated with 64-slice CT that patients with a history of extensive myocardial infarction were less likely to have a left marginal vein, which may hamper optimal LV lead positioning (Figure 18) (92).

A recent study by Aurrichio et al implemented the use of MSCT in 10 CRT recipients who presented with worsening HF symptoms (93). Besides visualization of the venous anatomy, the authors emphasized the importance of vein occlusion and proximity of the target vein to the

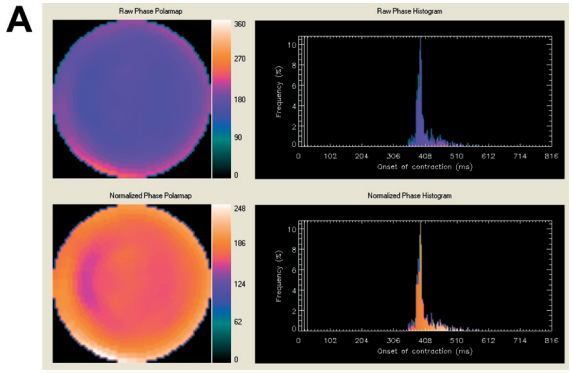


Figure 15. Phase analysis of ECG-gated myocardial perfusion SPECT imaging

A. Example of a synchronous contraction; the histogram shows a narrow and peaked distribution and the polar map is homogenous. B. Example of a dyssynchronous contraction; the histogram shows a wide distribution. The polar map indicates that the apex and posterior region of the myocardium show delayed contraction.

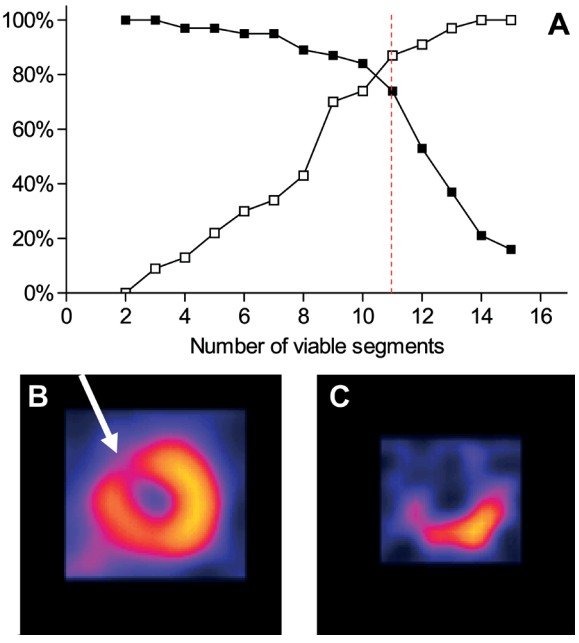


Figure 16. Viability assessment with FDG SPECT

A. Receiver-operating characteristic curve analysis on the extent of viability before CRT implantation and clinical response after 6 months of CRT, with the black line representing sensitivity and the white line representing specificity. The optimal cut-off value was identified at 11 viable segments, yielding a sensitivity of 74% and a specificity of 87%. Adapted from Ypenburg et al (87). B. Example of a responder to CRT with a small antero-septal scar (arrow) on FDG SPECT. C. Example of a non-responder with large scar formation on FDG SPECT with only few viable segments.

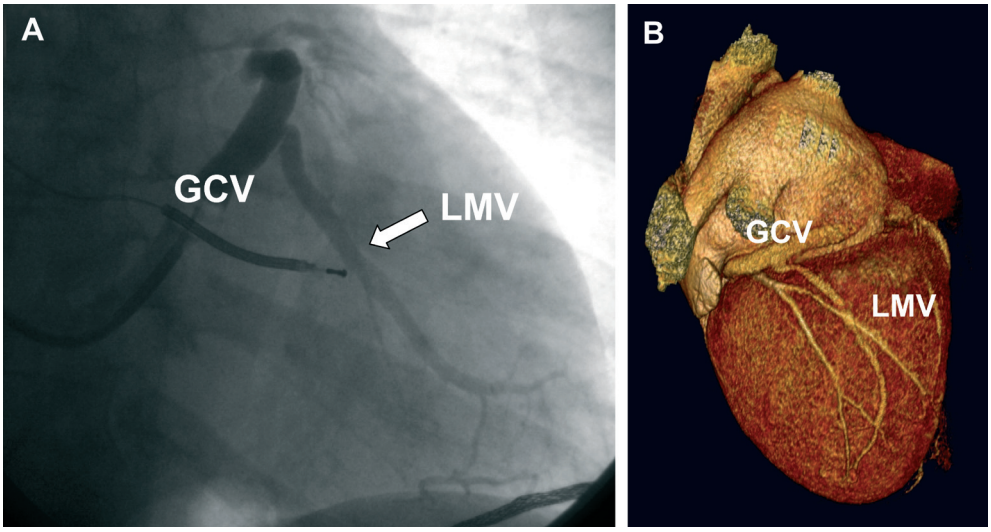
phrenic nerve or diaphragm to decide whether a transvenous or transthoracic approach may be preferred.

At present, MSCT is not routinely used to assess venous anatomy prior to CRT implantation. The main limitations include the radiation dose and the lack of information on the site of latest activation. Importantly, patient-related factors such as heart rate greater than 60 or 70 beats/min and irregular heart rhythm (atrial fibrillation or frequent atrial or ventricular extrasystoles), can interfere with the diagnostic quality of the images.

In addition, preliminary results in 21 patients showed promising results for assessment of LV function and myocardial perfusion when compared to nuclear imaging (94). Furthermore, assessment of cardiac dyssynchrony may be possible in the future with the new dual source CT due to the higher temporal resolution (95).

Figure 17. Venous anatomy using multi-slice computed tomography

Invasive venography (left panel) and 3D volume rendered reconstruction of a 64-slice CT acquisition (right panel) of the same patient with an idiopathic dilated cardiomyopathy. A large left marginal vein (LMV) is originating from the great cardiac vein (GCV).



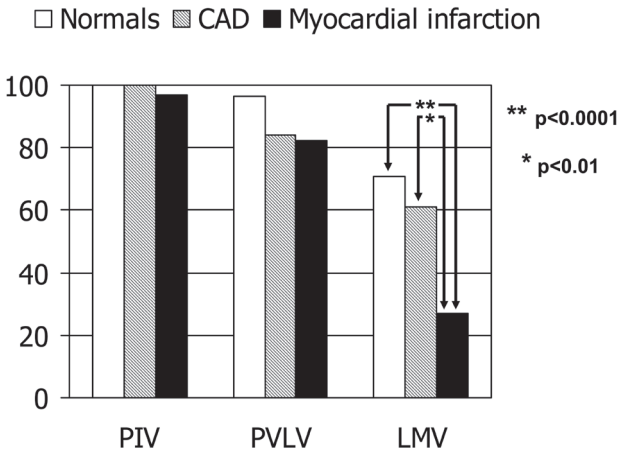


Figure 18. Venous anatomy

Prevalence – as assessed with 64-slice CT - of the posterior interventricular vein (PIV), posterior vein of the left ventricle (PVLV) and left marginal vein (LMV) in 28 normal controls, 38 patients with coronary artery disease (CAD) and 34 patients with a history of myocardial infarction. Patients with a history of myocardial infarction were less likely to have a LMV, as compared to normal controls. This may hamper left ventricular lead positioning in CRT. Adapted from Van de Veire et al (84).

BODY SURFACE POTENTIALS

Electrocardiographic imaging (ECGI) is a non-invasive cardiac electrical imaging modality that can image epicardial potentials, electrograms, and isochrones (activation sequences) using electrocardiographic measurements from body surface locations (96). Only one study applied this technique in 8 CRT candidates with LBBB using a 224-electrode vest to acquire body surface potentials at 1-millisecond intervals during the cardiac cycle (97). Electrical interventricular synchrony was quantified by the index Esyn, the mean activation time difference between the RV and LV free walls. The authors reported a wide range of electrical activation patterns with regions of delayed and/or absent conduction and development of functional lines of block. During CRT, mean Esyn improved from -76±24 to -31±-32 ms (P=0.01). Furthermore, some regions of slow conduction appeared in the LV in response to pacing, indicating functional electrical characteristics of local tissue. Still, improved Esyn did not consistently predict an improvement in LVEF during CRT, probably due to the fact that LV dyssynchrony is a better predictor than interventricular delay (19). Thus, patient-specific electrophysiologic substrate properties may determine outcome of CRT; however, its clinical role in CRT has yet to be determined.

CONCLUSIONS AND FUTURE PERSPECTIVES

Despite the impressive results of CRT in large randomized trials, 30-40% of the patients do not respond. In the search for more optimal selection criteria the presence of LV dyssynchrony at baseline appears important for clinical and echocardiographic improvement. To assess LV dyssynchrony, various non-invasive imaging techniques have been proposed. The most experience has been gathered with echocardiographic techniques, particularly color-coded TDI. Color-coded TDI has proven highly predictive for CRT response and event-free survival at 1-year follow-up in single-center studies. Other techniques including TSI, strain imaging, speckle tracking, 3D echocardiography need more investigation, but initial results are promising. Available evidence is limited on the value of non-echocardiographic imaging methods (particularly MRI and nuclear imaging) to assess LV dyssynchrony and prediction of CRT response. However, these techniques can provide other information, for instance the presence of scarred and viable myocardium and venous anatomy, potentially important for the selection of CRT candidates.

Although it is generally agreed that LV dyssynchrony is a major determinant of response to CRT, the recently published PROSPECT trial demonstrated only modest results of echocardiography to predict response to CRT (20). The major limitations, as outlined above, were non-assessability in a high percentage of patients, with low inter-observer agreement. On the other hand, the trial was also not ideal, since a substantial percentage of patients had LVEF >35%, without significant LV dilatation; in other words, these patients could not reverse remodel after CRT (which was one of the major endpoints in the trial). In addition, pathophysiological issues (scar tissue, venous anatomy, LV lead position) are important in the response to CRT and may need to be assessed before CRT implantation.

Accordingly, various questions may be addressed in patients considered for CRT. First, is substantial LV dyssynchrony present? Patient selection based on echocardiographic assessment showed a superior response rate compared to selection based on the current criteria, although larger studies are needed to define the best technology. Second, where is the area of latest activation for optimal positioning of the LV lead? As demonstrated by Ansalone et al, pacing in the area of latest activation results in the best clinical response compared to patients with the LV lead beyond the site of latest activation (98). Third, does the site of latest activation contain scar tissue? Recent observations showed that scar tissue in the region of the LV pacing lead resulted in CRT failure (71). But also the extent of scar tissue is important; Ypenburg et al observed that at least 11 viable LV segments (in a 16-segment model) are needed for a positive response to CRT (87). Fourth, is venous access present to the preferred location? MSCT can provide this information non-invasively (91). A surgical approach is preferred in case of absence of suitable cardiac veins.

Image-integration may answer all these questions at the same time. Goitein et al presented a method for integration of information provided by MSCT (venous anatomy) and echocardiography (LV dyssynchrony and site of latest activation) using commercially available software (99). The integrated image demonstrates an isochronal map of peak strain time derived from echocardiographic images, coronary venous anatomy, and approximate course of the left phrenic nerve (see Figure 19). These images can be used to evaluate the best LV lead position. Still, prospective large studies are needed comparing empiric and guided LV lead implantation (targeted at the site of latest activation).

In conclusion, various non-invasive imaging techniques may play a role in the selection of patients for CRT. Echocardiography still appears the technique of choice to assess LV dyssynchrony, whereas other imaging techniques may provide additional information on scar tissue and venous anatomy.

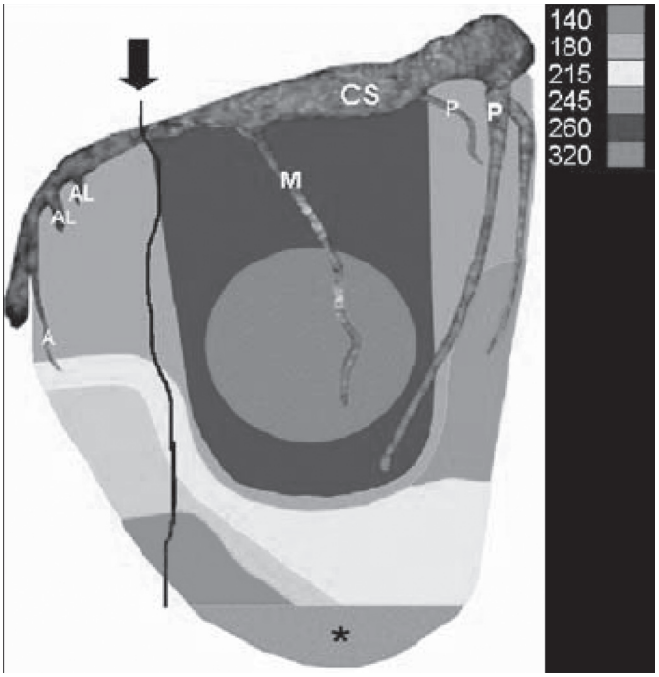


Figure 19. Image-integration

Integrated image demonstrating isochronal map of peak strain time derived from echocardiographic images (colorscale in ms referenced to QRS complex shown on right), coronary venous anatomomy, and approximate course of the left phrenic nerve. The gray region (*) could not be assayed echocardiographically because of transducer angulation limitations. CS: coronary sinus, M: marginal branch, P: posterior branch, A: anterior branch, AL: anterolateral branch. Adapted from Goitein et al (99).

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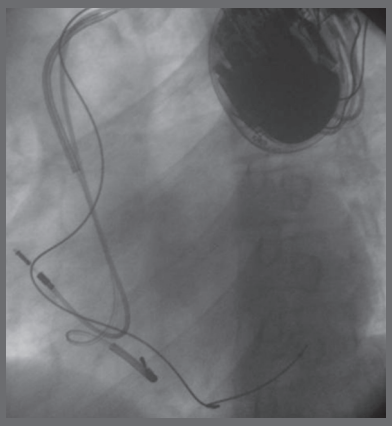
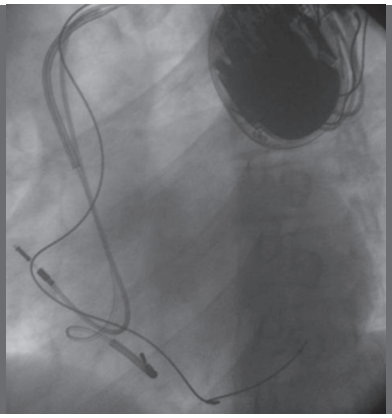


Part II

ISSUES AFTER DEVICE IMPLANTATION

Chapter 10



Long-term prognosis after cardiac resynchronization therapy is related to the extent of left ventricular reverse remodeling at mid-term follow-up

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Submitted

ABSTRACT

Objectives Aim of the current study was to evaluate the relation between the extent of left ventricular (LV) reverse remodeling and clinical/echocardiographic improvement after 6 months of cardiac resynchronization therapy (CRT) as well as long-term outcome.

Background Despite the current selection criteria, individual response to CRT varies significantly. Furthermore, it has been suggested that reduction in LV end-systolic volume (ESV) after CRT is related to outcome.

Methods A total of 302 CRT candidates were included. Clinical status and echocardiographic evaluation were performed before implantation and after 6 months of CRT. Long-term follow-up included all-cause mortality and hospitalizations for heart failure.

Results Based on different extents of LV reverse remodeling, 22% of patients were classified as super-responders (decrease in LVESV ≥30%), 35% as responders (decrease in LVESV 15-29%), 21% as non-responders (decrease in LVESV 0-14%) and 22% negative-responders (increase in LVESV). More extensive LV reverse remodeling resulted in more clinical improvement, with larger increase in LV function and more reduction in mitral regurgitation. In addition, more LV reverse remodeling resulted in less heart failure hospitalizations and lower mortality during long-term follow-up (22±11 months); 1- and 2-year hospitalization-free survival rates were 90% and 70% in the negative-responder group, as compared to 98% and 96% in the super-responder group (logrank p-value <0.001).

Conclusion The extent of LV reverse remodeling at mid-term follow-up is predictive for long-term outcome in CRT patients.

INTRODUCTION

Current selection criteria for cardiac resynchronization therapy (CRT) include severe heart failure (New York Heart Association class [NYHA] III or IV), depressed systolic function (left ventricular ejection fraction [LVEF] <35%) and wide QRS complex (>120 ms) (1). CRT not only improves clinical status (NYHA class, quality-of-life and exercise capacity) but also LV function, with reverse LV remodeling and decreases hospitalization and mortality rates (2-7). Despite the impressive results of CRT in the large clinical trials, response to CRT varies significantly among individuals; some patients exhibit significant improvement in clinical status with extensive LV reverse remodeling and almost normalization of LV function, whereas other patients show deterioration of both clinical and functional parameters despite CRT. Furthermore, preliminary results demonstrated a relation between the magnitude of LV reverse remodeling and long-term survival benefit after CRT (8).

Therefore, the aims of the current study were 1) to evaluate the relation between the extent of LV reverse remodeling and the improvement in clinical and echocardiographic parameters after 6 months of CRT and 2) to evaluate the relation between the extent of LV reverse remodeling and long-term outcome. To permit subgroup analysis, the patients will be arbitrarily divided into 4 groups, based on the extent of LV reverse remodeling after 6 months of CRT.

METHODS

Patients and study protocol

The study population consisted of 302 consecutive heart failure patients who were scheduled for CRT device implantation. The selection criteria for CRT included advanced heart failure (NYHA class III or IV), LVEF <35%, and wide QRS complex (1). Patients with a recent myocardial infarction (<3 months), or decompensated heart failure were excluded. Etiology was considered ischemic in the presence of significant coronary artery disease (≥50% stenosis in one or more of the major epicardial coronary arteries) and/or a history of myocardial infarction or prior revascularization.

The study protocol included baseline 2-dimensional echocardiography to measure LVEF and LV volumes as well as tissue Doppler imaging (TDI) to assess LV dyssynchrony. Clinical evaluation included assessment of NYHA class, quality-of-life (using the Minnesota Living with Heart Failure questionnaire) (9) and evaluation of exercise capacity using the 6-minute walking test (10). At 6 months follow-up, clinical status, LV volumes and LVEF were re-assessed. During long-term follow-up after implantation, survival and cardiac transplantation as well as hospitalization for decompensated heart failure were reported.

Definition of response

Patients who died, were hospitalized and/or functionally deteriorated before the 6 months follow-up were discarded from further analysis. The remaining group consists of clinically improved and unchanged patients at 6 months, and were divided into subgroups based on the reduction in LV end-systolic volume (ESV) after 6 months of CRT. The specific subgroups

are: negative-responders = patients with an increase in LVESV, non-responders = patients with a decrease in LVESV ranging from 0 to 14%, responders = patients with a decrease in LVESV ranging from 15 to 29%, super-responders = patients with a decrease in LVESV ≥30%.

Echocardiographic evaluation

Echocardiographic images were obtained with a 3.5-MHz transducer in the left lateral decubitus position using a commercially available system (Vivid Seven, General Electric-Vingmed, Milwaukee, Wisconsin). Standard 2-dimensional and color Doppler data, triggered to the QRS complex were saved in cine-loop format for off-line analysis (EchoPac 6.0.1, GE Medical systems, Horten, Norway). LV end-diastolic volume (EDV) and LVESV were derived and LVEF was calculated from the conventional apical 2- and 4-chamber images, using the biplane Simpson's technique (11).

The severity of mitral regurgitation was graded semi-quantitatively from color-flow Doppler images using the apical 4-chamber views. Mitral regurgitation was graded on a 4-point scale: none, mild (jet area/left atrial area <20%), moderate (jet area/left atrial area 20-45%), and severe (jet area/left atrial area >45%) (12).

For TDI, color-coded images of the 4- and 2-chamber apical views of 3 consecutive heart beats were stored for off-line analysis. Data were analyzed using commercially available software (Echopac version 6.0.1). To determine LV dyssynchrony, the sample volume was placed in the LV basal parts of the anterior, inferior, basal and lateral wall and per region, the time interval between the onset of QRS complex and the peak systolic velocity was derived. LV dyssynchrony was defined as the maximal delay between peak systolic velocities among the four LV walls. Based on previous data, a cut-off value of 65 ms was used as a marker of LV dyssynchrony (13).

Long-term follow-up

Chart review, device interrogation and telephone contact were assessed during long-term follow-up after device implantation. Events were defined as death (due to heart failure, other cardiac cause or non-cardiac cause) or cardiac transplantation, and hospitalization for decompensated heart failure. The composite of death, cardiac transplantation and hospitalizations for heart failure was the primary end-point of the study.

Device implantation

A coronary sinus venogram was obtained using balloon catheter, followed by the insertion of the LV pacing lead. An 8F guiding catheter was used to position the LV lead (Easytrak 4512-80, Guidant Corporation, St. Paul, Minnesota; or Attain-SD 4189, Medtronic Inc., Minneapolis, Minnesota) in the coronary sinus. The preferred position was a lateral or postero-lateral vein (14). The right atrial and ventricular leads were positioned conventionally. All leads were connected to a dual chamber biventricular ICD (Contak Renewal II or H195, Guidant Corporation; or Insync III or Insync Sentry, Medtronic Inc.).

Statistical analysis

Continuous variables are expressed as mean ± SD. Categorical data are summarized as frequencies and percentages. Differences in baseline characteristics between the 4 different subgroups were analyzed using one way analysis of variance (ANOVA) (continuous variables)

and chi-square or Fisher's exact tests (dichotomous variables) as appropriate. The paired Students t test was used to compare continuous data within the subgroups during follow-up. The McNemar test was used to compare NYHA class and severity of mitral regurgitation during follow-up within the different subgroups. Event and survival curves were determined according to the Kaplan-Meier method, with comparisons of cumulative event rates by the log-rank test. For all tests, a p-value <0.05 was considered statistically significant.

RESULTS

Patients

The study population consisted of 302 consecutive patients (253 men, mean age 66±10 years). All patients had advanced heart failure symptoms with most patients (94%) in NYHA functional class III. Underlying etiology of cardiomyopathy was ischemic in 58% of patients and idiopathic in 42%. Patients had severely depressed LV function (mean LVEF 25±8%) with extensive LV dilatation (mean LVEDV 227±78 ml and mean LVESV 172±68 ml). Mean extent of LV dyssynchrony was 78±46 ms. Medication included diuretics in 90%, ACE inhibitors in 90%, beta-blockers in 74% and spironolactone in 53% of patients. Device and lead implantation was successful in all patients without major procedure-related complications.

Follow-up after CRT

Sixteen patients were removed from further analysis at 6 months follow-up; 10 died, 5 deterioriated in functional class, and 4 were hospitalized for decompensated heart failure before the 6-month follow-up. Of the remaining 286 patients, 164 patients (57%) showed an improvement of 1 NYHA class, 34 patients (12%) showed an improvement of 2 NYHA classes, whereas 88 patients (31%) remained unchanged (P<0.001 vs. baseline) at 6 months follow-up. In addition, both quality-of-life and exercise capacity improved at 6 months (respectively from 36±19 to 25±20, and walking distance from 321±107 m to 395±111 m, both P<0.001). Furthermore, LVEF improved modestly (from 25±8% to 32±10%, P<0.001), with a reduction in LV volumes; LVEDV decreased from 226±78 ml to 200±77 ml and LVESV from 170±67 ml to 139±67 ml (both P<0.001) at 6 months. In addition, 107 patients (37%) showed a reduction in mitral regurgitation of at least one grade, 152 (53%) remained unchanged and 27 (10%) showed worsening of mitral regurgitation after 6 months of CRT (P<0.001).
During follow-up (22±11 months, range 6 to 53 months), 37 patients died (13%). Cause of death was decompensated heart failure in 26, other cardiac cause in 7, and non-cardiac cause in 4 patients. One patient underwent heart transplantation. In addition, hospitalizations for decompensated heart failure were noted in 21 patients (7%).

Subgroup analysis according to extent of LV reverse remodeling after 6 months of CRT

The extent of LV reverse remodeling after 6 months varied among patients, ranging from an increase in LVESV of 38% and a decrease in LVESV of 78%, with a mean reduction of 18±22%. Sixty-three patients (22%) showed deterioration in LVESV after 6 months of CRT and were classified as negative-responders (definitions see Methods section). Furthermore, 60 patients

(21%) showed LV reverse remodeling 0-14% and were classified as non-responders. LV reverse remodeling of 15-29% was noted in 100 and these patients were classified as responders (35%). In 63 patients (22%) extensive LV reverse remodeling ≥30% was reported and these were classified as super-responders (Figure 1).

Baseline characteristics between the 4 subgroups were comparable, except for less severe heart failure symptoms (lower NYHA class), more often non-ischemic cardiomyopathy, longer QRS duration, more often left bundle branch block (LBBB) configuration and more extensive LV dyssynchrony in super-responders (Table 1).

Table 1. Baseline characteristics of the different subgroups (defined according to the extent of LV reverse remodeling after 6 months of CRT)

Variable	NEG n=63	NON n=60	RESP n=100	SUPER n=63	P-value
Age (yrs)	65±10	65±12	66±11	67±9	0.8
Gender (M / F)	54/9	51/9	85/15	48/15	0.4
NYHA class (III / IV)	55/8	57/3	96/4	63/0	0.04
Ischemic etiology	47 (74%)	41 (68%)	51 (51%)	25 (40%)	<0.001
QRS duration (ms)	142±33	156±30	163±28	161±33	<0.001
LBBB	32 (51%)	46 (77%)	78 (78%)	49 (78%)	0.001
SR / Afib / Paced	50/9/4	47/7/6	75/8/17	49/5/9	0.4
LVEF (%)	26±8	24±8	26±8	25±8	0.2
LVEDV (ml)	215±75	233±78	224±73	231±78	0.6
LVESV (ml)	160±61	181±78	168±63	175±69	0.3
MR moderate-to-severe	12 (19%)	12 (20%)	11 (11%)	9 (14%)	<0.001
LV dyssynchrony (ms)	50±36	58±35	93±40	101±45	<0.001

Afib: atrial fibrillation; EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; LBBB: left bundle branch block; LV: left ventricular; MR: mitral regurgitation; NEG: negative-responders; NON: non-responders; NYHA: New York Heart Association; RESP: responders; SR: sinus rhythm; SUPER: super-responders.

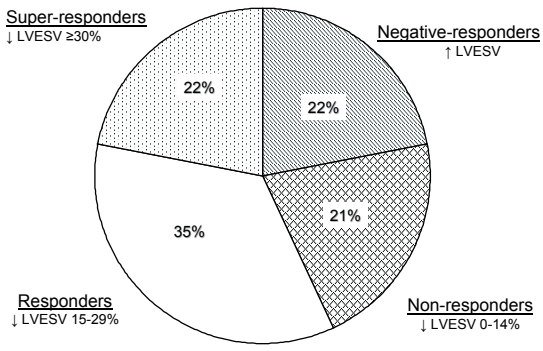


Figure 1. Extent of LV reverse remodeling after 6 months of CRT

Distribution of patients according to extent of LV reverse remodeling after 6 months of CRT.

Response to CRT versus extent of LV reverse remodeling

Mean NYHA class improved significantly in all groups at 6 months after CRT; in negative-responders from 3.1±0.3 to 2.9±0.5, in non-responders from 3.1±0.2 to 2.6±0.5, in responders

from 3.0±0.2 to 2.0±0.4 and super-responders from 3.0±0.0 to 1.7±0.5 (for all, P<0.001). Individual changes within each subgroup are presented in Figure 2.

As demonstrated in Figure 3 (panel A) super-responders showed greater improvement in quality of life score (Δ 17±13) as compared to the other subgroups (respectively Δ 8±15, 13±18 and 14±16 for negative-, non- and responders, P=0.024). In addition, a trend was noted for larger improvement in walking distance (panel B) in patients with more extensive LV reverse remodeling.

Regarding echocardiographic parameters, negative-responders showed no improvement in LVEF after 6 months of CRT (from 26±8% to 26±8%, NS), whereas the other 3 response groups showed significant improvement in LVEF; non-responders showed a mean improvement of 5±5% in LVEF, responders of 8±7% and greatest improvement was observed in super-responders (15±9%, p<0.001, Panel C). Also, super-responders showed greatest reduction in LVEDV after CRT (Panel D). Reduction in mitral regurgitation was more pronounced in patients with more LV reverse remodeling; respectively 13%, 22%, 48% and 62% of negative-responders, non-responders, responders and super-responders improved at least one grade in mitral regurgitation (P<0.001).

Figure 2. Improvement in NYHA class after 6 months of CRT

Changes in NYHA class after 6 months of CRT according to the different response groups.

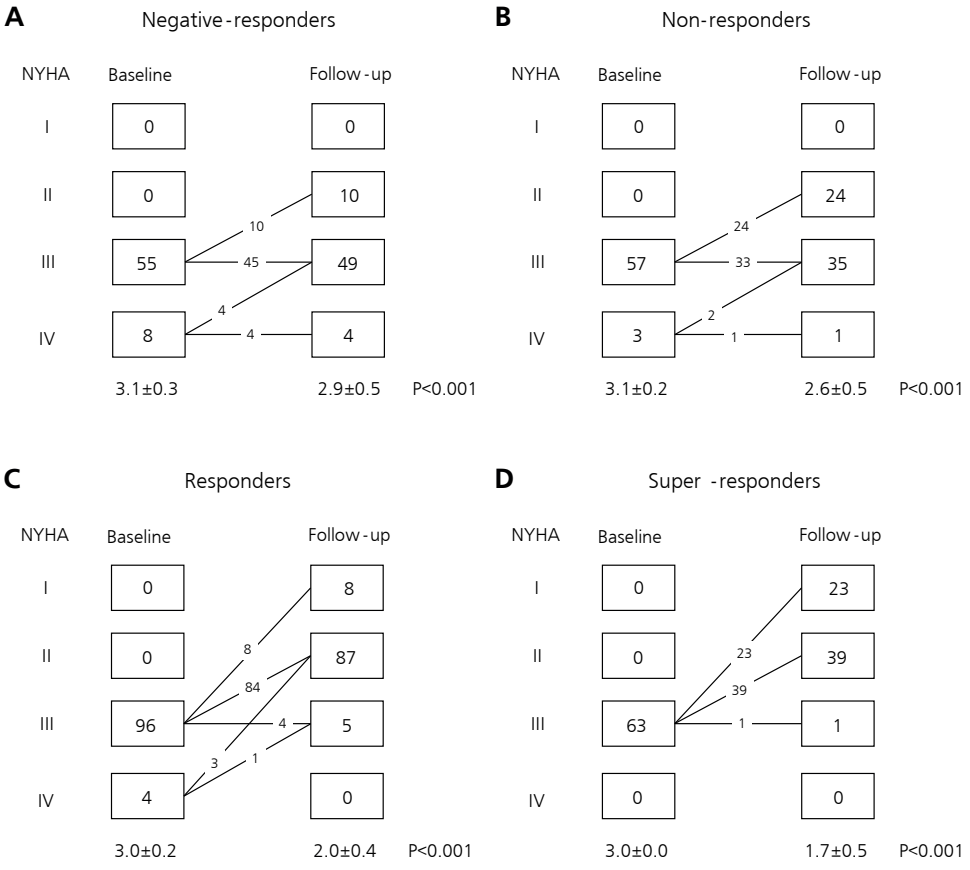
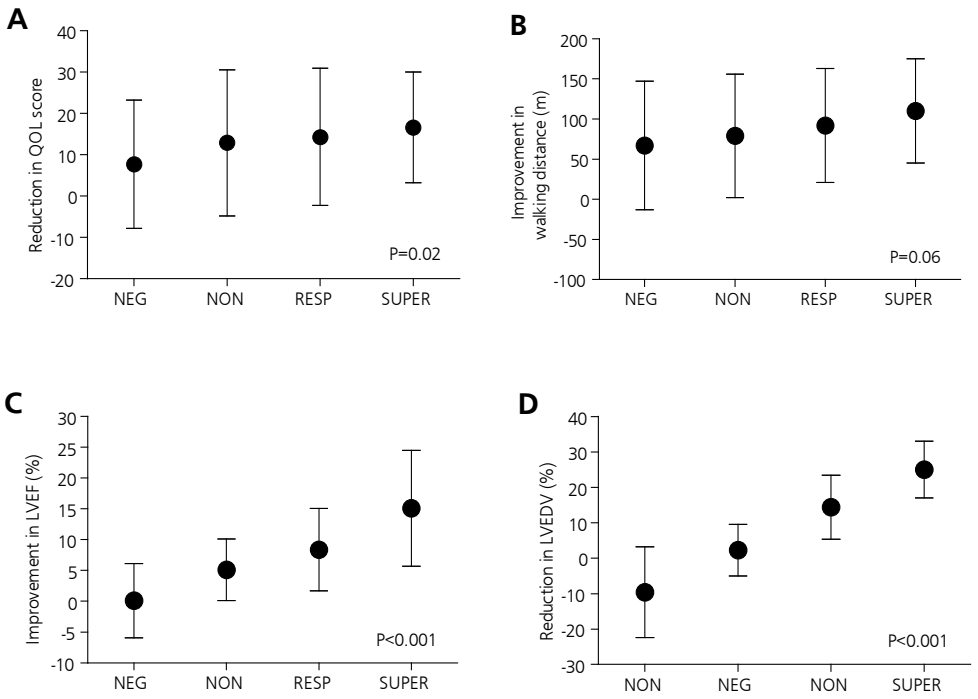


Figure 3. Clinical and echocardiographic improvement after 6 months of CRT

Improvement in clinical (A, B) and echocardiographic (C, D) parameters at 6 months follow-up in the different response groups; Negative-responders (NEG) were defined by an increase in LV-end-systolic volume, non-responders (NON) an intermediate decrease (0-14%), responders (RESP) a moderate decrease (15-29%) and super-responders (SUPER) a high decrease (≥30%) in LV end-systolic volume after 6 months of follow-up.



Long-term follow-up after CRT according to extent of LV reverse remodeling

Mortality rates decreased in parallel to the extent of LV reverse remodeling, with only one death in the super-responder group (P<0.001, Table 2). One-year survival rates were 92% in the negative-responder group, 95% in the non-responder group, 97% in the responder group and 100% in the super-responder group, respectively (log-rank P<0.001, Figure 4A). The same trend was noted for the number of patients hospitalized for decompensated heart failure (Figure 4B).

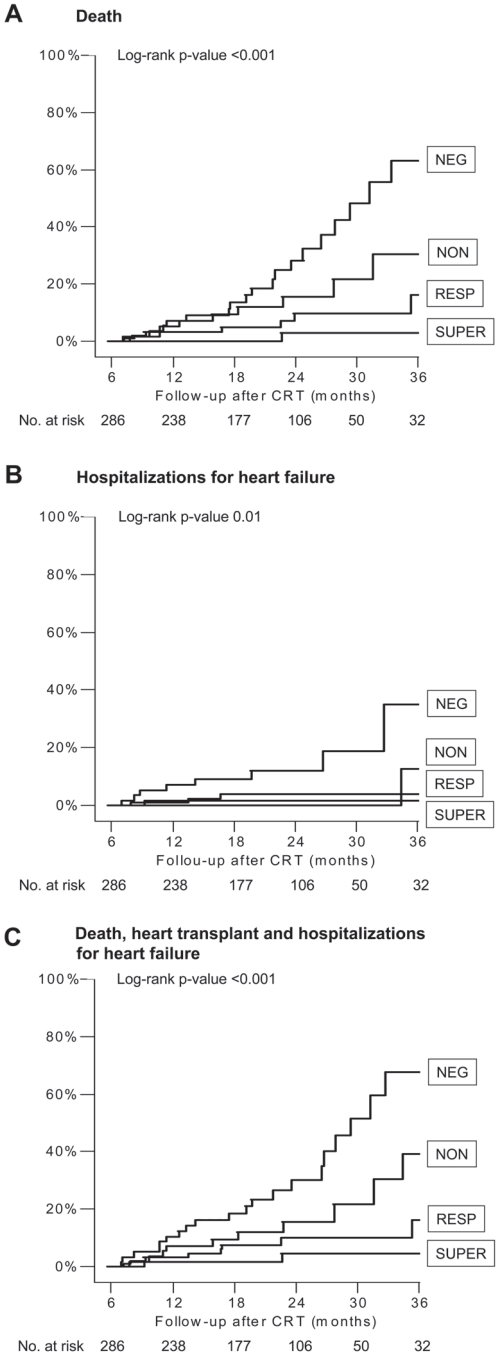
Table 2. Events during long-term follow-up according to the extent of LV reverse remodeling after CRT

	NEG n=63	NON n=60	RESP n=100	SUPER n=63	P-value
Follow-up (months)	21±10	21±10	22±12	25±10	0.1
Death	18 (29%)	10 (17%)	8 (8%)	1 (2%)	<0.001
Hospitalizations for HF	11 (17%)	3 (5%)	6 (6%)	1 (2%)	0.05
Death, HTX and hospitalizations for HF	23 (37%)	13 (22%)	12 (12%)	2 (3%)	<0.001

Abbreviations as in Table 1. HF: heart failure; HTX: heart transplantation.

Figure 4. Long-term outcome after CRT according to the extent in LV reverse remodeling

Event curves for all-cause mortality (A), hospitalizations for heart failure (B) and primary combined end-point of death and hospitalizations for heart failure (C) for the different CRT response groups.



In addition, 1- and 2-year hospitalization-free survival rates were respectively 90% and 70% in the negative-responder group, 93% and 84% in the non-responder group, 97% and 90% in the responder group and 98% and 96%in the super-responder group (log-rank P<0.001, Figure 4C). Separate comparisons revealed significant differences in hospitalization-free survival between super-responders and negative-responders (P<0.001 vs. super-responders) and non-responders (P<0.001 vs. super-responders) and a trend for better outcome when compared to responders to CRT (P=0.06 vs. responders).

DISCUSSION

The findings in the current study can be summarized as follows 1) the extent of reverse LV remodeling varies significantly among patients undergoing CRT, and 22% can be considered as super-responders, 2) more extensive LV reverse remodeling was related to greater clinical and functional improvement after 6 months of CRT and 3) more LV reverse remodeling resulted in better survival and less hospitalization for decompensated heart failure after CRT.

Differences in magnitude of response to CRT – previous studies

At present, only one group reported on 'super-response' after CRT (15,16). Blanc et al investigated 29 patients with non-ischemic dilated cardiomyopathy, LBBB and mean LVEF of 21% (15). After 12 months of CRT, 5 patients (17%) exhibited normalization in LVEF (>50%) associated with clinical improvement to NYHA class I-II; these patients were defined as 'super-responders'. A subsequent study in 84 CRT candidates (with ischemic and non-ischemic

cardiomyopathy) reported an incidence of super-responders of 13% (16). Super-responders showed an increase in LVEF from 25±8% to 60±6% (P=0.001), whereas the remaining patients showed only a modest improvement in LVEF (from 21±8% to 25±10%, P=0.004).
However, data on the magnitude of LVESV changes after CRT are lacking. Reverse remodeling may be more important than the increase in LVEF, since reduction in LVESV appeared the best predictor for long-term outcome after CRT (8).

Also of interest are the baseline characteristics of super-responders. In the present study, super-responders more frequently had non-ischemic etiology of heart failure, longer QRS duration, more often LBBB configuration, less severe mitral regurgitation, and more extensive LV dyssynchrony (Table 2). Similarly, Castellant et al suggested that super-response only occurred after CRT in non-ischemic patients with LBBB (16). The study by Blanc et al reported no differences in baseline characteristics between the super-responders and the remaining patients (15); however, this particular study included only non-ischemic patients with LBBB. In addition, various studies suggested a relationship between LV reverse remodeling after CRT and etiology (17-19). These differences in baseline characteristics help to validate the current patient selection criteria that include a wider QRS complex, particularly with LBBB configuration. Furthermore patients with more extensive LV damage from ischemic heart disease tend to respond less than patients with non-ischemic cardiomyopathy. Furthermore, from several studies it has become clear that LV dyssynchrony is important for response to CRT; in the current study, patients with extensive LV dyssynchrony had a high likelihood of response, whereas patients without LV dyssynchrony did not respond to CRT (13,20).

Extent of LV reverse remodeling in CRT – Impact on prognosis

Besides clinical end-points such as NYHA class, quality-of-life score and 6-minute walking distance, echocardiographic end-points have been used in heart failure trials (21). Importantly, reversal of LV remodeling in heart failure patients by either pharmacological or interventional therapies is proposed as a surrogate for improved outcome (22).
For instance, in the SOLVD trial, patients who were randomized to enalapril showed a decrease in LVESV after 1 year follow-up (from 106±42 ml/m^2 to 93±37 ml/m^2, P=0.01) whereas patients treated with placebo showed an increase in LVESV at 1 year follow-up (from 103±24 ml/m^2 to 116±24 ml/m^2, P=0.08) (23,24). Since enalapril usage was associated with a 16% reduction in mortality during 33 months of follow-up, it is reasonable to conclude that the LV reverse remodeling effect is associated with favourable outcome. Similar findings on the remodeling process have been reported after the use of carvedilol in patients with chronic LV dysfunction late after myocardial infarction (25,26) as well as metoprolol in patients with mild-to-moderate heart failure and chronic LV dysfunction (27).
These data from pharmacological heart failure trials emphasize the importance of LV reverse remodeling and consequently long-term prognosis. Currently, only one study related the extent of reverse remodeling after CRT to outcome; Yu and coworkers evaluated 141 patients and related the extent of reduction in LVESV to long-term clinical outcome (mean follow-up 695±491 days) (8). Receiver operating characteristic curve analysis showed that a reduction of >10% in LVESV had a sensitivity and specificity of 70% in predicting all-cause mortality. In addition, the change in LVESV was the best predictor for long-term outcome, whereas clinical parameters showed no predictive value.

In the present study, 286 patients were categorized according to reduction in LVESV after 6 months of CRT; 22% were classified as super-responders (decrease in LVESV ≥30%), 35% as responders (decrease in LVESV 15-29%), 21% as non-responders (decrease in LVESV 0-14%) and 22% negative-responders (increase in LVESV). Expanding the results of Yu et al (8), an inverse relation between the extent of LV reverse remodeling and outcome was noted. Negative responders had a high event rate (37%) for combined death and heart failure hospitalizations, as compared to 22% in non-responders, 12% in responders, and only 3% in super-responders. Importantly, super-responders exhibited a superior 1- and 2-year hospitalization-free survival of 98% and 96% respectively.

Conclusions

The extent of LV reverse remodeling after CRT varies significantly among individuals, with 22% considered super-responders to CRT. Importantly, the extent of reverse remodeling after 6 months is related to clinical improvement and survival during long-term follow-up.

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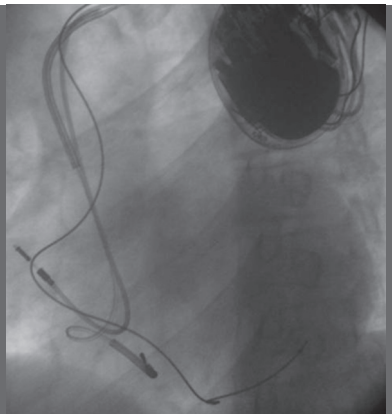
Chapter 11



Effects of interruption of long-term cardiac resynchronization therapy on left ventricular function and dyssynchrony

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ABSTRACT

Interruption of short-term cardiac resynchronization therapy (CRT) has shown to acutely worsen left ventricular (LV) function, mitral regurgitation as well as LV dyssynchrony. The present study aims to assess whether LV reverse remodeling influences interruption of CRT; and more practically, whether long-term continuous pacing is necessary in patients with reverse LV remodeling. A total of 135 CRT recipients were selected after showing LV reverse remodeling defined as a decrease in LV end-systolic volume ≥15% after 6 months of CRT ('responders'). Echocardiography was performed at baseline and after 6 months with CRT on and off. LV dyssynchrony was determined using tissue Doppler imaging. During interruption of CRT, an acute deterioration in LV function, mitral regurgitation and LV desynchronization were noted in responder patients. Of note, worsening of these echocardiographic parameters was observed, but they did not return to baseline values. For comparison, 100 non-responder patients (without LV reverse remodeling) showed no significant echocardiographic changes during interruption. In conclusion, despite the presence of LV reverse remodeling, interruption of CRT resulted in worsening of LV function and desynchronization. Therefore, continuous long-term pacing is warranted to maintain the beneficial effects.

INTRODUCTION

Cardiac resynchronization therapy (CRT) has become an established therapy in patients with advanced drug-refractory heart failure. Several studies have demonstrated acute hemodynamic improvement, long-term clinical and functional improvement and reduced mortality and hospitalizations after CRT (1-4). These benefits are attributed to a more synchronous contraction, augmented left ventricular (LV) systolic function and consequently reverse LV remodeling (5). The question has been raised whether continued biventricular pacing is needed when LV function has improved and reverse LV remodeling has occurred after 6 months of CRT. It is currently unknown if interruption of long-term CRT would acutely worsen dyssynchrony in a reverse remodeled LV, and whether LV function would acutely deteriorate. Recent data in a small patient group with significant mitral regurgitation showed an immediate reduction in regurgitation after CRT initiation, followed by acute worsening of regurgitation during interruption of long-term CRT (6). The effects of interruption of CRT after 6 months pacing will be evaluated in a large group of responders to CRT (defined as significant reverse LV remodeling at 6 months follow-up). For comparison, the effects of interruption of CRT in non-responders will also be evaluated.

METHODS

Patients

A total of 250 consecutive patients received a CRT device according to the current guidelines: advanced heart failure (New York Heart Association [NYHA] class III or IV), depressed LV ejection fraction (EF, <35%) and wide QRS complex (>120 ms) (7). Clinical status was assessed at baseline and after 6 months of CRT, including assessment of NYHA class, quality-of-life score (using the Minnesota Living with Heart Failure questionnaire) (8) and evaluation of exercise capacity using the 6-minute walking test (9). The echocardiographic analysis included evaluation at baseline and at 6-months follow-up. After data acquisition at 6-months follow-up, CRT was interrupted to perform echocardiography during intrinsic conduction or in right ventricular pacing in patients without intrinsic conduction. One-hundred and thirty-five (54%) were classified as echocardiographic responders after showing a reduction in LV end-systolic volume (ESV) of ≥15% after 6 months of CRT (10,11). These 135 patients formed the main focus of the current study, but the echocardiographic effects of CRT interruption in non-responders were also evaluated.

Echocardiography

All echocardiographic studies were performed the day before device implantation and at 6 months follow-up with CRT on and off. The CRT device was turned off for 5 min before the "off" acquisition started (6). Echocardiographic images were obtained with a 3.5-MHz transducer in the left lateral decubitus position using a commercially available system (Vivid Seven, General Electric-Vingmed, Milwaukee, Wisconsin). Standard 2-dimensional and color Doppler data, triggered to the QRS complex were saved in cine-loop format for off-line analysis

(EchoPac 6.0.1, GE Medical systems, Horten, Norway). LV volumes were derived and LVEF was calculated from the conventional apical 2- and 4-chamber images, using the biplane Simpson's technique (12). The severity of mitral regurgitation was graded semi-quantitatively from color-flow Doppler images using the apical 4-chamber views. Mitral regurgitation was graded on a 3-point scale: mild (jet area/left atrial [LA] area <20%), moderate (jet area/LA area 20-45%), and severe (jet area/LA area >45%) (13). In addition, the maximal rate of LV systolic pressure increase (LV dP/dt) was estimated from the steepest rising segment on the continuous wave Doppler regurgitant jet (14).

Tissue Doppler imaging was performed using the apical 4- and 2-chamber views as previously described (11). Views were optimized for pulse repetition frequency, color saturation, sector size and depth, allowing the highest possible frame rate. At least 3 consecutive beats were stored and images were analyzed off-line (Echopac 6.0.1). The sample volumes were placed in the basal portions of the septum, lateral, anterior and inferior walls; and per region, the time interval between the onset of QRS and the peak systolic velocity was derived. LV dyssynchrony was calculated as the maximum delay between peak systolic velocities among the 4 walls (most frequently observed between the septum and the lateral wall).

Device implantation

Device implantation started with obtaining a coronary sinus venogram with a balloon catheter, followed by the insertion of the LV pacing lead. An 8F guiding catheter was used to position the LV lead (Easytrak 4512-80, Guidant Corporation, St. Paul, Minnesota; or Attain-SD 4189, Medtronic Inc., Minneapolis, Minnesota) in the coronary sinus. The preferred position was a lateral or postero-lateral vein (15). The right atrial and ventricular leads were positioned conventionally. All leads were connected to a dual chamber biventricular ICD (Contak Renewal II or H195, Guidant Corporation; or Insync III or Insync Sentry, Medtronic Inc.).

Statistical analysis

Continuous variables are expressed as mean ± SD. Categorical data are summarized as frequencies and percentages. Differences in baseline characteristics between responders and non-responders were analyzed using unpaired Students t tests (continuous variables) and chi-square or Fisher's exact tests (dichotomous variables) as appropriate. The paired Students t test was used to compare continuous data within the subgroups during follow-up. For all tests, a P-value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the 135 echocardiographic responders (102 men, mean age 67±10 years) included in this study are summarized in Table 1. Patients had severely depressed LV function, with a mean LVEF of 26±7%. Substantial LV dyssynchrony was present, as indicated by a mean delay of 96±37 ms. Device implantation was successful in all patients and no procedure-related complications were reported.

Table 1. Baseline characteristics in responders (n=135) and non-responders (n=100) to cardiac resynchronization therapy

	Responders	Non-responders	P-value
Age (yrs)	67±10	64±11	0.011
Gender (M/F)	102/33	82/18	0.2
Ischemic etiology	70 (52%)	73 (73%)	<0.001
QRS duration (ms)	160±32	143±31	<0.001
NYHA class (II/III/IV)	14/117/4	9/82/9	0.1
Quality-of-life score	34±17	38±21	0.1
Six-minute walking distance (m)	300±127	326±93	0.1
LVEF (%)	26±7	27±9	0.8
LVEDV (ml)	216±63	219±80	0.7
LVESV (ml)	160±53	163±72	0.7
Mitral regurgitation (moderate-to-severe)	25 (19%)	16 (16%)	0.2
LV dyssynchrony (ms)	96±37	52±38	<0.001

EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; LV: left ventricular; NYHA: New York Heart Association.

Clinical and echocardiographic follow-up at 6 months

After 6 months of CRT, 123 patients (91%) showed an improvement of at least 1 NYHA functional class (105 patients showed an improvement of 1 NYHA class, 18 patients showed an improvement of 2 NYHA classes, P<0.001 vs. baseline). The quality-of-life score improved from 34±17 to 19±18 (P<0.001) and exercise capacity improved as indicated by an increase in 6-minute walking distance from 298±126 m to 420±170 m (P<0.001). In addition, LVEF improved from 26±7% to 38±9% (P<0.001), with a reduction in LV end-diastolic volume (EDV, 216±63 ml to 165±56 ml, P<0.001) and LVESV (160±53 ml to 104±44 ml, P<0.001). Furthermore, severity in mitral regurgitation decreased as demonstrated by a reduction in jet area/LA area from 16±16% to 8±10% (P<0.001) as well as an increase in LV dP/dt from 708±304 mmHg/s to 1136±429 mmHg/s (P<0.001). Also, 6 months of CRT resulted in a significant decrease in LV dyssynchrony from 96±37 ms to 32±29 ms (P<0.001).

Interruption of CRT

As demonstrated in Figure 1, interruption of CRT resulted in an acute deterioration of all echocardiographic parameters; LVESV increased to 116±47 ml and LVEF decreased to 32±9% (both P<0.001 as compared to 6 months follow-up). In addition, acute worsening of severity in mitral regurgitation was noted (jet area/LA area increased from 8±10% to 12±14% and LV dP/dt from 1136±429 mmHg/s to 757±259 mmHg/s, both P<0.001). Also, the extent of LV dyssynchrony acutely increased to 60±37 ms (P<0.001). Of interest, although worsening of these parameters was observed, the different parameters did not return completely to baseline values (see Figure 1).

Interruption of CRT in non-responders

Of note, 15 patients died within the 6 month follow-up and 100 patients showed a reduction in LVESV of less than 15%, and were thus classified as non-responders. Baseline characteristics

Figure 1. Echocardiographic parameters at baseline (PRE), 6-months follow-up (FUP) and during interruption of CRT (OFF) in 135 CRT responders

EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; LA: left atrial; LV: left ventricular. * PRE vs. FUP, P<0.001; † FUP vs. OFF, P<0.001

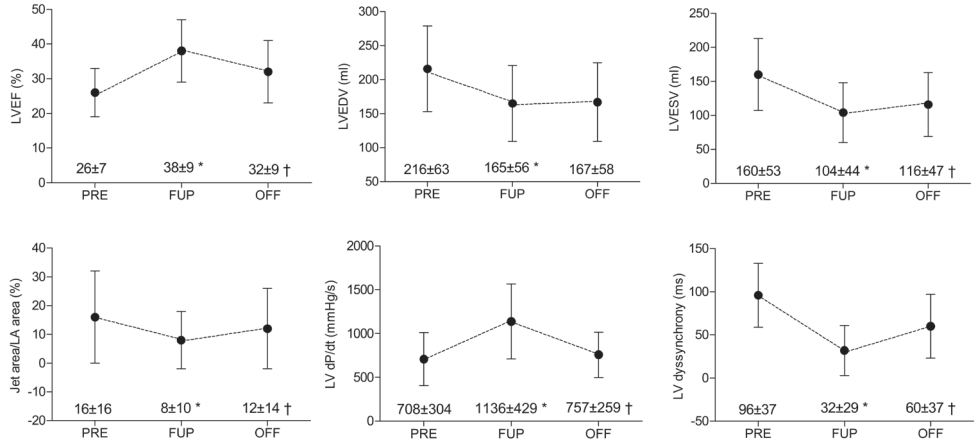

Table 2. Echocardiographic parameters in 100 non-responders to cardiac resynchronization therapy at follow-up at 6 months and during interruption of pacing

	Follow-up	Interruption of pacing	P-value
LVEF (%)	27±8	27±8	0.5
LVEDV (ml)	223±79	225±79	0.1
LVESV (ml)	116±69	167±67	0.1
Jet area / LA area (%)	14±16	14±16	0.5
LV dP/dt (mmHg/s)	733±289	644±202	<0.001
LV dyssynchrony (ms)	45±35	50±37	0.1

Abbreviations as in Table 1. LA: left atrial

between responders and non-responders were comparable except that responders had higher age, longer QRS duration, more extensive LV dyssynchrony and less often ischemic cardiomyopathy (Table 1). Of interest, interruption of CRT in non-responders did not cause immediate significant deterioration of LV function, LV dyssynchrony nor severity in mitral regurgitation (Table 2).

DISCUSSION

The results of the present study can be summarized as follows (1) interruption of long-term CRT resulted in acute deterioration of LV function, mitral regurgitation and LV desynchronization in CRT responder patients, (2) although worsening of these echocardiographic parameters was observed, the values did not return to baseline and (3) non-responder patients did not show significant echocardiographic changes during interruption.

Interruption of CRT – previous studies

CRT studies in the acute setting have demonstrated that CRT abruptly improves hemodynamics and LV function (1,16). Importantly, this effect disappears immediately when the device is turned off again (17). However, only few small studies report on the effects of interruption of long-term CRT and its effect on LV function, severity of mitral regurgitation and LV dyssynchrony. Yu et al performed serial echocardiographic examinations in 25 CRT recipients (5). After 3 months of continuous CRT, interruption caused immediate worsening of LV function (LVEF decreased from 40.0±14.7% to 33.6±13.2%, P<0.01), however no significant changes in LV volumes were observed. In addition, worsening of mitral regurgitation was noticed as demonstrated by an increase in jet area/LA area (from 18±15% to 28±16%) and LV dP/dt (from 912±229 mmHg/s to 676±152 mmHg/s, both P<0.05). Regarding LV dyssynchrony, Yu et al used tissue Doppler imaging to calculate the standard deviation of the time delays of 12 LV segments (Ts-SD). The authors demonstrated that after 3 months of pacing Ts-SD was significantly shorter as compared to baseline (37.7±10.9 ms vs. 29.3±8.3 ms P<0.05). When pacing was stopped Ts-SD increased immediately to 41.1±11.8 ms (P<0.01 vs. 3 months). Another small study by Brandt et al focused on the hemodynamic effects of temporary interruption of CRT after a mean of 427 days (18). Withdrawal of CRT resulted in a decline of LV dP/dt (from 711 mmHg/s to 442 mmHg/s, P<0.001) and an increase in mitral regurgitation (jet area/LA area 13.8% to 20.3%, P=0.004). In addition, an acute deterioration of LV function and LV volumes was noted. Lastly, Ypenburg and colleagues evaluated a selected group of 25 patients who demonstrated an acute reduction in mitral regurgitation after CRT initiation (jet area/LA area from 40±13% to 25±11%, P<0.001) (6). Interruption of CRT after 6 months resulted in acute worsening of mitral regurgitation as well as LV function. Importantly, dyssynchrony involving the papillary muscles showed similar deterioration during CRT withdrawal.

Influence of LV reverse remodeling

The present study is the first to evaluate the effect of CRT withdrawal in a reverse remodeled LV in a large group of patients. The current data demonstrate that withdrawal of CRT, even after long-term CRT with clear evidence of LV reverse remodeling, resulted in acute deterioration of LV function and mitral regurgitation. Importantly, this deterioration is accompanied by a more dyssynchronous contraction as demonstrated by an acute increase in LV dyssynchrony. This implies that the beneficial effect of LV reverse remodeling is pacing dependent and that continuous pacing is warranted. However, the parameters did not return to baseline levels, probably as a result of LV remodeling. Preliminary data suggested indeed that long-term withdrawal of CRT may result in return to baseline values (5). Furthermore, the current study evaluated the interruption effect after 6 months of CRT; it is currently unknown if this deterioration would be less during off state after e.g. 12 months or even disappear at some time. Further study is warranted to evaluate the precise effects of CRT over time.

The current data are supported by the findings in the non-responders patients; non-responder patients did not show echocardiographic improvement after CRT and consequently did not show deterioration during withdrawal of CRT.

Conclusions

Despite the presence of LV reverse remodeling, interruption of long-term CRT resulted in recurrence of LV dyssynchrony as well as deterioration of LV function and mitral regurgitation. Therefore, continuous long-term biventricular pacing is warranted.

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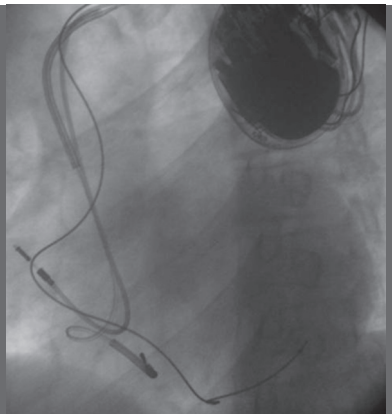
Chapter 12



Changes in global left ventricular function in heart failure patients undergoing cardiac resynchronization therapy using novel automated function imaging

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ABSTRACT

Background Global longitudinal strain reflects the longitudinal shortening of the left ventricle (LV) and can be assessed by novel 2-dimensional strain echocardiographic technique, automated function imaging (AFI).

Objectives To evaluate the acute and late effects of cardiac resynchronization therapy (CRT) on LV global longitudinal strain.

Setting and Patients 141 consecutive heart failure patients from two tertiary hospitals referred for CRT device implantation.

Main outcome measures Global peak longitudinal systolic strain (GLPSS Avg) was quantified before device implantation, immediately after and at 3- to 6-month follow-up. Moreover, the acute effects on GLPSS Avg were evaluated after interrupting CRT at 3- or 6-month follow-up. Response to CRT was defined as a decrease in LV end-systolic volume ≥15%.

Results Responders (57%) and non-responders (43%) showed similar values for GLPSS Avg at baseline (7.9 ± 2.7% vs. 7.7 ± 3.1%, NS). However, during follow-up, responders showed a significant improvement in GLPSS Avg (from 7.9 ± 2.7% to 10.1 ± 3.8%, P<0.001), combined with significant reverse LV remodeling and improvement in LV ejection fraction, whereas in non-responders no change in GLPSS Avg or LV function was noted. Importantly, no significant changes in GLPSS Avg were observed immediately after CRT device implantation or after interruption of the device at 6 months follow-up in both groups.

Conclusions The changes in LV systolic function after CRT can be characterized by the novel technology AFI. Improvement in GLPSS Avg after CRT appears to be a long-term effect and is related to the extent of reverse LV remodeling after CRT.

INTRODUCTION

It is well established that cardiac resynchronization therapy (CRT) is an effective treatment for advanced heart failure in selected patients. The beneficial effects include improvement in clinical parameters, such as symptoms, quality of life, and exercise distance as well as reduction in hospitalizations and mortality, but also include improvement in functional parameters, including improvement in global left ventricular (LV) function, LV reverse remodeling and reduction in mitral regurgitation (1-7).

Nevertheless, a consistent proportion of patients do not respond to CRT (1,8,9). In order to understand the high prevalence of non-responders, several non-invasive imaging studies have been performed to study the exact mechanism underlying CRT (10,11).

Automated function imaging (AFI) is a novel echocardiographic technique based on 2-dimensional strain imaging that enables quantification of regional and global longitudinal strain (12-15). The major advantages of this technique are its angle-independency and its ability to differentiate between active and passive deformation of the segments, which is of special importance in ischemic patients.

In the present study, we used AFI to study the effects of CRT on global longitudinal strain. Echocardiography was performed at baseline, after CRT initiation, during follow-up and during interruption of biventricular pacing, in order to differentiate between acute and late effects.

METHODS

Study population and protocol

A total of 141 consecutive patients with chronic heart failure, scheduled for implantation of a CRT device, were included in the current study. The selection criteria for CRT included: advanced symptomatic heart failure (New York Heart Association [NYHA] functional class III or IV), LV ejection fraction [EF] ≤35% and QRS duration on surface ECG ≥120 ms) (15). Patients with recent myocardial infarction (<3 months) or decompensated heart failure were excluded. Etiology was considered ischemic in the presence of significant coronary artery disease (≥50% stenosis in one or more of the major epicardial coronary arteries) and/or a history of myocardial infarction with ECG evidence or prior revascularization.

The study protocol was as follows: before device implantation transthoracic echocardiography was performed to assess LV volumes, LVEF as well as off-line analysis to quantify global longitudinal strain (GLPSS Avg). Within 24-48h after CRT device implantation, GLPSS Avg was re-assessed to evaluate the acute effect of CRT on LV function. All echocardiographic parameters were re-assessed after 6 months of CRT. In addition, GLPSS Avg was assessed during interruption of CRT at 6 months follow-up. Finally, clinical parameters were evaluated at baseline and at 6 months follow-up.

Echocardiographic evaluation

Patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed Vivid-7, General Electric Vingmed, Milwaukee, Wisconsin). Data acquisition

was performed with a 3.5-MHz transducer at a depth of 16 cm in the parasternal and apical views (standard apical long-axis, 2- and 4-chamber images). Standard 2-dimensional images were stored in cineloop format from 3 consecutive beats and were transferred to a workstation for further off-line analysis (Echopac 6.1, GE Medical Systems, Horten, Norway).
LV end-diastolic (EDV) and end-systolic volumes (ESV) were derived and LVEF was calculated from apical 2- and 4-chamber views by Simpson's rule (17). Patients who showed a decrease of ≥15% in LVESV at follow-up were classified as echocardiographic responders to CRT (17).
In addition, LV dyssynchrony was evaluated with tissue Doppler imaging as previously described (18). The sample volume was placed in the basal portions of the LV septum and lateral wall, obtaining the peak systolic velocities. Time differences between septal and lateral peak systolic velocities were calculated to define LV dyssynchrony.

Automated function imaging to assess global LV longitudinal strain

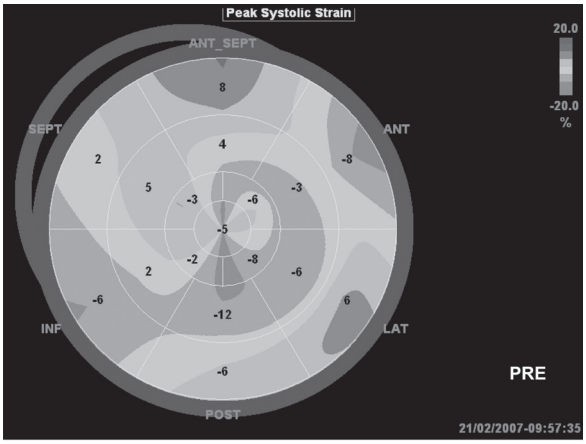
Global longitudinal strain was quantified using the novel AFI technique based on 2D strain imaging (13). The software analyzes motion by tracking speckles (natural acoustic markers) in two dimensions. The frame-to-frame changes of the speckles are used to derive motion and velocity. For this purpose, one single cardiac frame is needed form each apical view (apical long-axis, 4- and 2-chamber views) using a mean frame rate of 70 fps (range 40-100 fps).
First, the LV end-systolic frame is defined in the apical long-axis view. The closure of the aortic valve is marked and the software measures the time interval between the R wave and aortic valve closure. This interval is used as a reference for the 4- and 2-chamber view loops. After defining the mitral annulus and the LV apex with 3 index points at the end-systolic frame in each apical view, the automated algorithm traces 3 concentric lines on the endocardial border, the mid-myocardial layer and epicardial border, including the entire myocardial wall. The tracking algorithm follows the endocardium from this single frame throughout the cardiac cycle, and allows for a further manually adjustment of the region of interest to ensure that all the myocardial regions are included throughout the cardiac cycle. The LV is divided in 6 segments in each apical view and the tracking quality is validated for each segment. Then, the myocardial motion is analyzed by speckle-tracking within the region of interest.
Finally, the automated algorithm, using a 17-segment model, provides the peak systolic longitudinal strain for each segment in a "bull's eye" display, with the average value of peak systolic longitudinal strain for each view and the averaged global longitudinal peak systolic strain (GLPSS Avg) for the complete LV (Figure 1). Of note, the GLPSS Avg can only be calculated when at least 4 segments in each apical view have a valid tracking. Generally, longitudinal strain values are presented as negative values, and a larger negative value indicates larger longitudinal strain. However, for the purpose of the present study, the global strain values are presented as positive values.
In the present study, GLPSS Avg was assessed at baseline, 24-48h after device implantation and at 6-month follow-up. After data acquisition at 6-month follow-up, CRT was interrupted to perform echocardiography during intrinsic conduction or in right ventricular pacing in patients without intrinsic conduction.

Clinical evaluation

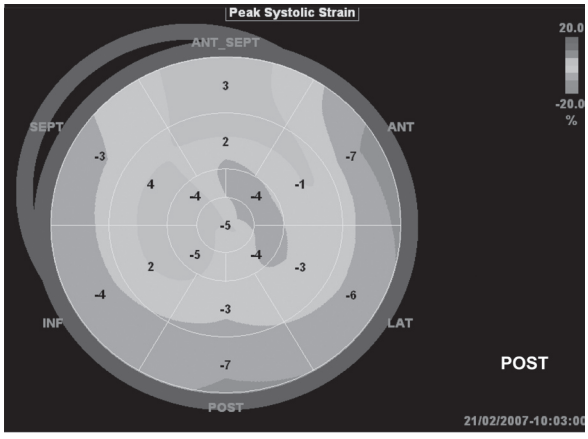
Clinical evaluation included evaluation of heart failure symptoms using New York Heart Association functional class, quality-of-life by the Minnesota Living with Heart Failure

Figure 1. Changes in global longitudinal strain after CRT device implantation

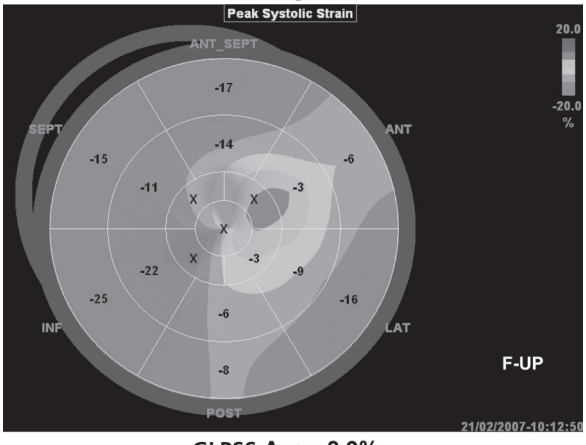
Example of a 17-segment "bull's eye" display of the LV of a responder to CRT. A red color indicates normal strain values, whereas a red and blue colors indicate lower strain values. From left to right are provided bull's eye displays at baseline (PRE, left), immediately after CRT implantation (POST, middle) and at follow-up (F-UP, right). An improvement in global longitudinal strain (GLPSS Avg) is shown at follow-up, with an increase in the homogeneous red color-coded area.



GLPSS Avg : 4.1%



GLPSS Avg : 4.8%



GLPSS Avg : 8.9%

Table 1. Baseline characteristics (n=141)

Age (yrs)	66±11
Gender (M/F)	115/26
Ischemic etiology	84 (60%)
QRS duration (ms)	143±36
Sinus rhythm (%)	121 (86%)
NYHA functional class	3.0±0.4
Quality-of-life score	35±18
6-minute walking distance (m)	313±114
LVEF (%)	25±7
LVEDV (ml)	207±71
LVESV (ml)	156±62
LV dyssynchrony (ms)	74±44
Medical therapy	
ACE-inhibitors	121 (86%)
Diuretics	126 (89%)
Beta-blockers	96 (68%)
Spironolactone	35 (25%)

ACE: angiotensine-converting enzyme; EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; LV: left ventricular; NYHA: New York Heart Association.

questionnaire (19), and exercise tolerance using 6-minute walking distance (20). QRS duration was measured in all patients from the surface electrocardiogram, using the widest QRS complex from the leads II, V1 and V6. The electrocardiograms were recorded at 25 mm/sec and were evaluated by two independent observers without knowledge of the clinical status of the patient.

Device implantation

The right atrial and right ventricular leads were positioned conventionally. To insert the LV lead, first a venogram from the coronary sinus was obtained using a guiding balloon catheter. Thereafter, an 8F guiding catheter was used to position the LV lead (Easytrak 4512-80, Guidant Corporation, St. Paul, Minnesota; or Attain-SD 4189, Medtronic Inc., Minneapolis, Minnesota) into the coronary sinus. The preferred position was a lateral or postero-lateral vein. All leads were connected to a dual-chamber biventricular ICD (Contak CD or TR, Guidant Corporation; or Insync III or CD, Medtronic Inc.).

Statistical analysis

Continuous variables were presented as mean values ± SD and were compared with 2-tailed Student t test for paired and unpaired data. Categorical data were presented as number and percentage and compared with χ^2-test.

Differences in GLPSS Avg over time between responders and non-responders were evaluated with analysis of the variance for repeated measurements. In addition, for overall population and within the same group of patients, GLPSS Avg values were compared at 3 different stages: 1) baseline values vs. values immediately after implant, 2) Baseline values vs. 6-month

follow-up data and 3) 6-month follow-up values vs. values after the interruption of the CRT device. To adjust for inflation of the type I error with multiple tests, we applied a posthoc Bonferroni correction; consequently, a P value < 0.017 was considered significant (0.05 divided by 3 different stages). Furthermore, relation between change in GLPSS Avg and change in LV volumes and LV ejection fraction was assessed by linear regression analysis.
All statistical analyses were performed with SPSS software (version 12.0, SPSS Inc., Chicago, Illinois). A P value <0.05 was considered statistically significant.

RESULTS

Study population

Baseline characteristics of the 141 patients included (mean age 66±11 years, 82% men) are summarized in Table 1. Patients had severe heart failure (mean NYHA class 3.0 ± 0.4), with severe LV dysfunction (mean LVEF 25±7%) and wide QRS complex (mean 143±36 ms). Ischemic etiology of heart failure was present in 84 patients (60%). All patients had optimized medical therapy, including angiotensin-converting enzyme inhibitors, beta-blockers and diuretics, at maximum tolerated dosages. CRT implantation was successful in all patients and no complications were observed.

Changes in clinical status after 6 months of CRT

At 6-month follow-up, a significant improvement in all clinical parameters was observed in the overall population. Mean NYHA class improved from 3.0±0.4 to 2.0±0.6 (P<0.001), the quality-of-life score improved from 35±18 to 22±20 (P<0.001) and the 6-minute walking distance increased from 313±114 m to 374±121 m (P<0.001).

Changes in LV function after 6 months of CRT

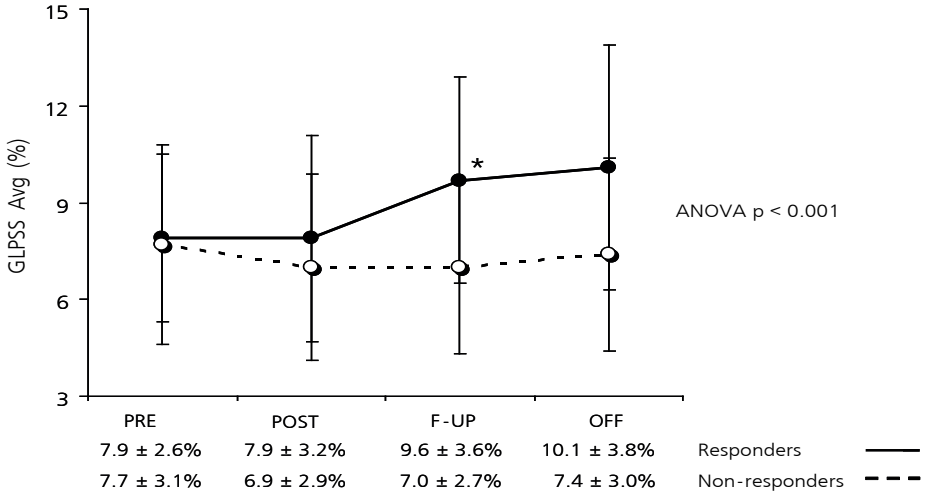
After 6 months of CRT, improvement in LV function and reverse remodeling was noted; LVESV decreased from 156±62 ml to 125±60 ml (P<0.001), LVEDV decreased from 207±71 ml to 181±69 ml (P<0.001) and LVEF increased from 25±7% to 33±10% (P<0.001).
Furthermore, baseline mean value of GLPSS Avg was 7.8±2.8% (range 1.1% to 15.2%). Immediately after CRT initiation no change in GLPSS Avg was observed (7.5±3.1%, NS vs. baseline). However, at 6-month follow-up a significant improvement in GLPSS Avg was noted to 8.5±3.5% (P=0.01 vs. baseline). Interruption of CRT did not induce any change in the value of GLPSS Avg at 6-month follow-up (8.9±3.7%, NS) (Figure 1).
Finally, linear regression analysis demonstrated a direct relationship between change in GLPSS Avg and LV reverse remodeling after 6 months of CRT (Figure 2 A-C).

Responders vs. non-responders

Based on a reduction in LVESV of ≥15% after CRT, 80 (57%) patients were classified as responders. There were no differences in baseline characteristics between responders and non-responders, except for significantly more male patients, more ischemic patients, shorter QRS duration and less LV dyssynchrony in the non-responders (Table 2). At follow-up, responders showed (by definition) significant LV reverse remodeling; LVESV decreased from 157±63 ml

Figure 2. Relation between change in global longitudinal strain and change in LV volumes and function after CRT

Relation between absolute change in global longitudinal strain (GLPSS Avg) and the absolute change in LV ejection fraction (LVEF, A), the relative change in LV end-systolic volume (LVESV, B) and the relative change in LV end-diastolic volume (LVEDV, C) respectively.



to 101±52 ml and LVEDV decreased from 209±74 ml to 160±67 ml (both P<0.001). As a consequence a significant improvement in LVEF was observed (from 26 ± 6% to 38 ± 8%; P<0.001) (Figure 3). In non-responders no significant changes in LV volumes or LVEF were observed.

Moreover, values of baseline GLPSS Avg were similar between responders and non-responders (7.9±.7% vs. 7.7±3.1%, NS; Figure 4). In responders no acute change in GLPSS Avg was noted, but a significant improvement was demonstrated at 6-month follow-up. This value remained

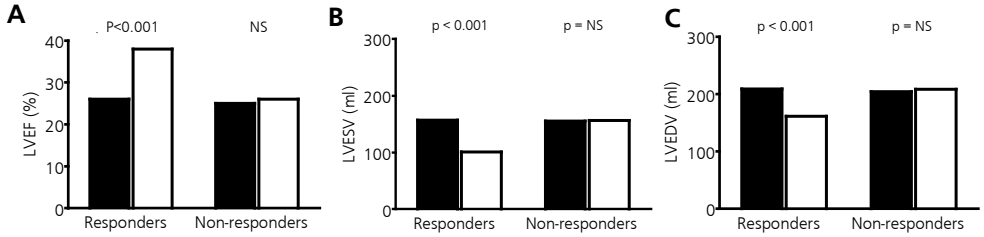
Table 2. Baseline characteristics in responders (n=80) and non-responders (n=61)

	Responders	Non-responders	P value
Age (yrs)	67±9	64±13	0.1
Gender (M/F)	60/20	55/6	0.02
Ischemic etiology	40 (50%)	44 (72%)	0.01
QRS duration (ms)	150±37	135±33	0.01
Sinus rhythm	67 (84%)	54 (88%)	0.7
NYHA functional class	3.0±0.4	3.0±0.4	0.3
Quality-of-life score	33±16	37±19	0.2
6-minute walking distance (m)	323±108	300±121	0.3
LVEF (%)	26±7	25±7	0.4
LVEDV (ml)	209±74	204±68	0.6
LVESV (ml)	157±63	155±61	0.8
LV dyssynchrony (ms)	90±40	51±37	<0.001

Abbreviations as in Table 1.

Figure 3. Changes in echocardiographic parameters after CRT in responders and non-responders

A LV ejection fraction (LVEF); B LV end-systolic volume (LVESV); C LV end-diastolic volume (LVEDV). Black bars represent baseline parameters whereas the white bars represent follow-up parameters.



stable during interruption of biventricular pacing. Conversely, the value of GLPSS Avg did not improve at 6-month follow-up in non-responders.

DISCUSSION

This study provides new insights about the effects of CRT on LV function using the novel echocardiographic AFI technique. The main findings can be summarized as follows: 1) CRT initiation or withdrawal did not induce any acute changes in global longitudinal strain, however a significant increase in GLPSS Avg was noted at long-term follow-up, 2) changes in GLPSS Avg were related to the extent of LV reverse remodeling after CRT and consequently 3) improvement in GLPSS Avg during follow-up was only noted in responder patients, whereas non-responders did not show any change in GLPSS Avg.

Changes in longitudinal function after CRT

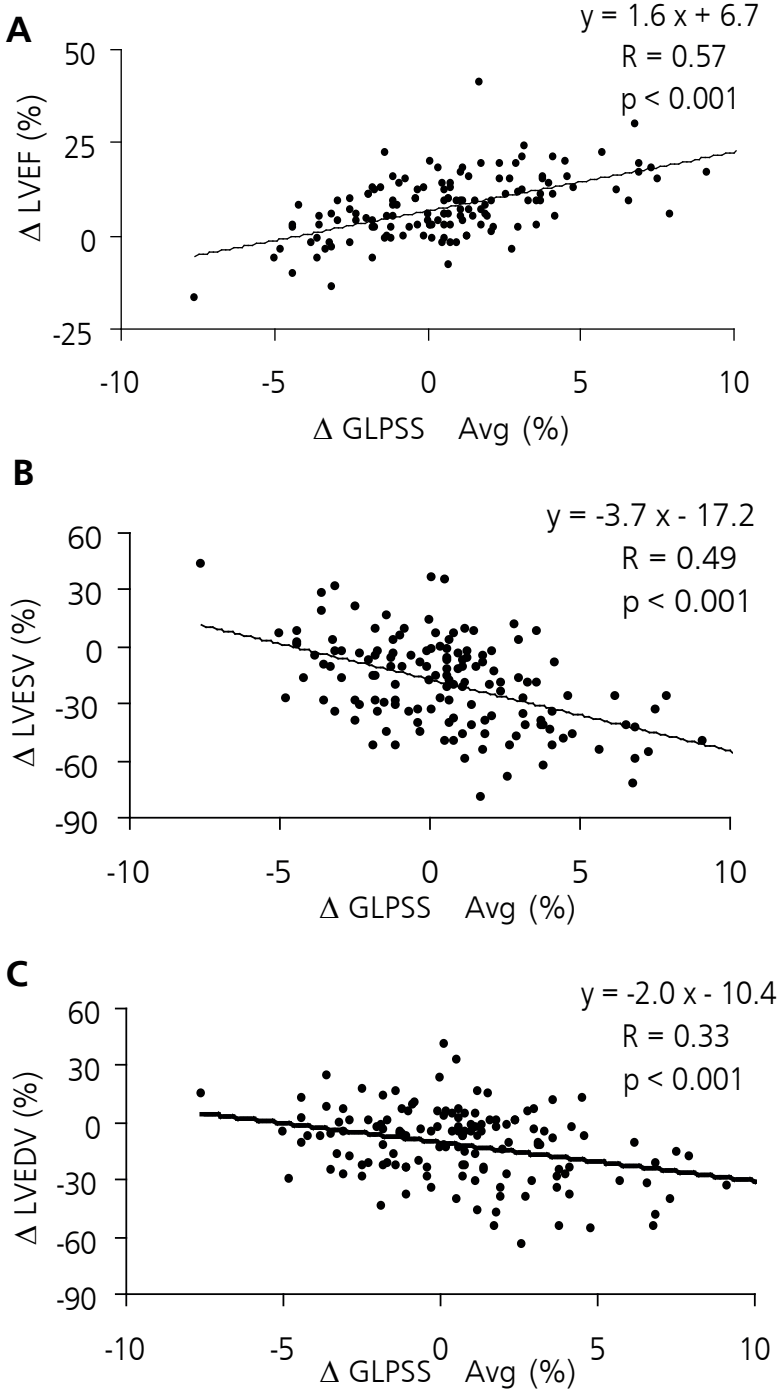
Despite the dramatic improvement in LV function and reduction in LV volumes after CRT demonstrated in large studies, information regarding changes in longitudinal function is limited. Only few small studies used echocardiography with tissue Doppler imaging to examine the longitudinal function (9,21-23). Bax et al studied the acute effects of CRT in 22 heart failure patients and demonstrated a significant improvement in peak systolic velocities in the basal septum (from 2.1±1.3 to 3.9±1.8 cm/s) as well as the basal lateral wall (from 2.4±1.7 to 4.5±1.5 cm/s) (21). However, Yu et al reported no significant change in peak systolic velocities in the basal segments in 25 CRT patients after 3 months of follow-up (9). To date, only one study reported on the changes in global longitudinal strain after CRT. Becker et al studied 47 heart failure patients using 2D speckle tracking strain analysis applied to 4- and 2-chamber views and demonstrated a significant increase in global longitudinal strain after 3 months of CRT (24). The current findings similarly revealed a significant improvement in GLPSS Avg from 7.8±2.8% to 8.5±3.5% (P<0.001) after 6 months of CRT.

Relation between changes in global LV longitudinal strain and LV reverse remodeling after CRT

The effects of CRT can be divided into acute and chronic effects (10). Studies evaluating the acute effects have demonstrated that CRT abruptly enhances LV systolic function by an

Figure 4. Changes in global longitudinal strain after CRT according to response

Average global longitudinal strain (GLPSS Avg) in responder and non-responder patients at baseline (PRE), at 24-48h after pacemaker implantation (POST) and at 6 months follow-up with the device turned on (F-UP) and turned off (OFF). (*paired t-test for comparisons within the same group (P<0.001).



increase in stroke volume, a reduction in LVESV, and a rise in LV pressure (6,9). These beneficial hemodynamic effects are the result of the more coordinated (synchronized) contraction of the LV immediately after CRT initiation. Of note, these results are rapidly reversed when CRT is interrupted, and underscore that the acute effect of CRT is related to enhanced and more coordinated (synchronized) LV function (9). At 6 months follow-up however, the hemodynamic benefits are more related to structural reverse remodeling of the LV (25,26). Various echocardiographic studies have shown a reduction in LV volumes associated with an increase in LVEF, but also a reduction in LV mass (6,9,26).

The present study evaluated the acute and late effects of CRT on GLPSS Avg. In the overall population, no significant changes were observed immediately after CRT initiation. At 6 months follow-up however, a significant increase in GLPSS Avg was observed in the entire population, which was not reversed after CRT withdrawal at 6 months. Furthermore, a linear relation was found between the change in GLPSS Avg after 6 months of CRT and the extent of LV reverse remodeling. These observations suggest that the increase in GLPSS Avg is related to structural reverse remodeling, rather than to acute pacing effects, in particularly since CRT withdrawal did not affect the increase in GLPSS Avg. When patients were divided into responders and non-responders, this effect was even more pronounced with a larger increase in GLPSS Avg at 6 months, without decrease when CRT was turned off.

CONCLUSIONS

Automated function imaging is a novel technology that enables quantification of LV systolic function and characterization of its changes after CRT. Improvement in global longitudinal strain after CRT appears a long-term effect and is related to the extent of reverse LV remodeling after CRT.

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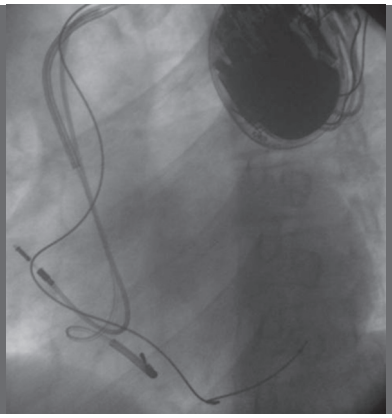
Chapter 13



Acute effects of initiation and withdrawal of cardiac resynchronization therapy on papillary muscle dyssynchrony and mitral regurgitation

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ABSTRACT

Objectives The purpose of this study was to evaluate the relation between dyssynchrony involving the mitral valve apparatus and the improvement in mitral regurgitation (MR) acutely after cardiac resynchronization therapy (CRT). The effect of interruption of CRT at 6 months follow-up on dyssynchrony and MR was also evaluated.

Background MR may improve acutely after CRT, but the precise mechanism is not fully understood.

Methods Out of 63 consecutive patients with baseline MR, 25 patients showed an acute reduction in MR severity immediately after CRT. This selected group of 25 patients (age 68±10 years, left ventricular ejection fraction 23±8%) was evaluated in the current study. Echocardiography including speckle tracking strain analysis was performed at baseline, after CRT initiation and during interruption of CRT at 6 months of follow-up to study the relation between dyssynchrony between the papillary muscles and severity of MR.

Results According to the inclusion criteria, all patients showed an immediate improvement in MR after CRT (vena contracta width decreased from 0.54±0.15 cm to 0.39±0.13 cm, $P<0.001$), accompanied by an improvement in mitral deformation indices. Furthermore, dyssynchrony between the papillary muscles decreased from 169±69 ms to 25±26 ms ($P<0.001$). Importantly, these beneficial effects were maintained at 6 months follow-up, but acute loss of resynchronization (from 26±28 ms to 134±51 ms, $P<0.001$) was observed after interruption of CRT, with an acute recurrence of MR and worsening in mitral deformation indices.

Conclusion CRT can acutely reduce MR in patients with dyssynchrony involving the papillary muscles; interruption of CRT at 6 months follow-up however, resulted in acute loss of resynchronization with recurrence of MR.

INTRODUCTION

Recent studies have demonstrated that cardiac resynchronization therapy (CRT) may improve functional mitral regurgitation (MR) acutely (1-3). However, the exact mechanism underlying the reduction in MR following CRT remains unclear. Preliminary results suggested that the acute improvement in MR may be related to improved coordination of papillary muscle contraction (2).

In this context, we hypothesized that patients with dyssynchrony between the anterior and posterior papillary muscle (APM – PPM dyssynchrony) will exhibit an acute reduction in MR after CRT, due to resynchronized papillary muscle contraction. Furthermore, it was hypothesized that deactivating CRT after 6 months would cause loss of resynchronization and acute recurrence of MR.

Accordingly, the study population consisted of selected patients with moderate-severe MR who showed an immediate reduction in MR after CRT initiation. Extensive echocardiographic evaluations were performed including speckle tracking radial strain analysis to asses APM – PPM dyssynchrony. Patients were evaluated before and immediately after CRT, and again evaluated after 6 months with CRT on and off.

METHODS

Patients, study protocol

Between January 2005 and July 2006, 186 patients received a CRT device according to the current guidelines: New York Heart Association (NYHA) class III or IV, depressed LV function (LV ejection fraction (EF) <35%), and wide QRS complex (≥120 ms) (4). Sixty-three of these patients had significant MR at baseline, with 25 patients showing an acute improvement in MR severity acutely after CRT initiation. These 25 patients formed the focus of the current study.

The study protocol included echocardiography at baseline, the day after implantation and at 6 months follow-up. After data acquisition at 6 months follow-up, CRT was interrupted to perform echocardiography during intrinsic conduction or in right ventricular pacing in patients without intrinsic conduction. Furthermore, assessment of clinical status was performed at baseline and after 6 months of CRT.

Echocardiography

All patients underwent standard transthoracic 2-dimensional (2D) echocardiography, including quantification of MR, LV function, global and local LV remodeling, assessment of mitral valve deformation indices and speckle tracking strain analysis to assess APM – PPM dyssynchrony. All echocardiographic studies were performed the day before implantation, the day after implantation, at 6 months follow-up with CRT on and off. The CRT device was turned off for 5 minutes before the acquisition started. Patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed Vivid Seven, General Electric-Vingmed, Milwaukee, Wisconsin, USA). Images were obtained using a 3.5 MHz transducer, at a depth of 16 cm in the parasternal and apical views (standard long-axis and 2- and 4-chamber

images). Standard 2D and color Doppler data, triggered to the QRS complex, were saved in cine-loop format. For each measurement, ≥3 cardiac cycles were averaged. Investigators were not blinded for the pacemaker settings.

Quantification of MR and mitral deformation indices. The severity of MR was measured from the apical 4-chamber view, by measuring the width of the vena contracta (5). Left atrial (LA) area and regurgitant jet area were measured by planimetry from the apical 4-chamber view, allowing calculation of the ratio of regurgitant jet area to LA area (6). The severity of MR was graded mild (vena contracta width <0.3 cm, LA area <4cm^2 or jet area/LA area <20%), moderate (vena contracta width 0.3-0.7 cm, jet area/LA area 20-40%) or severe (vena contracta width >0.7 cm, jet area/LA area >40%) as recommended by the ACC/AHA 2006 guidelines (6,7).

The maximal rate of LV systolic pressure increase (LV dP/dt) was estimated from the steepest rising segment on the continuous wave Doppler regurgitant signal (8). The valvular tenting area was obtained from the parasternal long-axis view at mid-systole and was measured as the area enclosed between the annular plane and mitral leaflets. Displacement of mitral coaptation (coaptation height) towards the LV apex was measured by the distance between leaflet coaptation and the mitral annulus plane in the apical 4-chamber view. Mitral annulus diameter was measured at end-systole and end-diastole in the 4-chamber view. Annular contraction was calculated as (end-diastolic diameter – end-systolic diameter) / end-diastolic diameter (9).

Gobal and local LV remodeling. LV volumes (end-diastolic volume (EDV), end-systolic volume (ESV)) and LVEF were calculated from the conventional apical 2- and 4-chamber images, using the biplane Simpson's technique (10). The distance between the posterior papillary muscle head and the intervalvular fibrosa (PPM-fibrosa) in the long-axis view measured the apical displacement of the posterior papillary muscle (9).

Speckle tracking strain analysis. Radial strain was assessed on LV short-axis images at the papillary muscle level, using speckle tracking analysis (11-13). Time-strain curves for all the 6

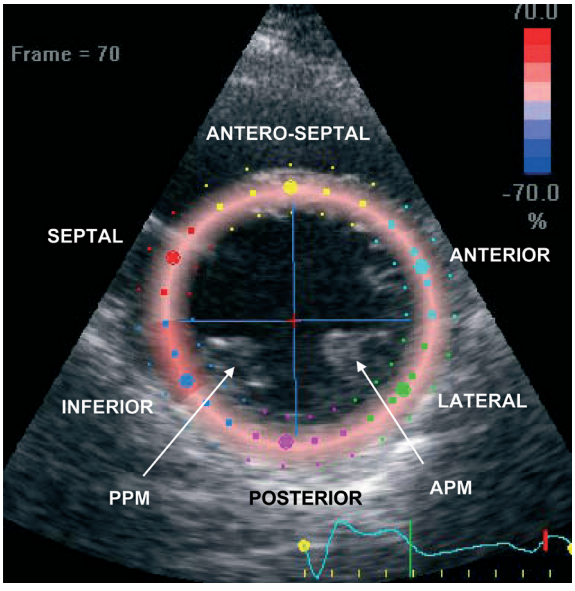


Figure 1 . Example of position of the papillary muscles

Short-axis of the left ventricle at the level of the papillary muscles, with reconstruction of the 6 LV segments. In this patient the anterior papillary muscle (APM) was located adjacent to the lateral LV segment (green) and the posterior papillary muscle (PPM) was located adjacent to the inferior LV segment (dark blue).

LV segments (septal, antero-septal, anterior, posterior, lateral and inferior) were constructed. The segments adjacent to the papillary muscles were noted (Figure 1). Peak radial strain and time from QRS onset to peak radial strain for the LV segments were obtained, and the severity of dyssynchrony between the anterior and posterior papillary muscle could be determined (Figure 2). Radial strain measurements were reproducible and showed minimal variability (interobserver correlation coefficient r=0.94, intraobserver correlation coefficient r=0.96).

CRT implantation

A coronary sinus venogram was obtained using balloon catheter, followed by the insertion of the LV pacing lead. An 8F guiding catheter was used to position the LV lead (Easytrak 4512-80, Guidant Corporation, St. Paul, Minnesota; or Attain-SD 4189, Medtronic Inc., Minneapolis, Minnesota) in the coronary sinus. The preferred position was a lateral or postero-lateral vein (14). The right atrial and ventricular leads were positioned conventionally. All leads were connected to a dual chamber biventricular ICD (Contak Renewal II or H195, Guidant Corporation; or Insync III or Insync Sentry, Medtronic Inc.).

Clinical evaluation at 6 months follow-up

Clinical evaluation was performed before implantation and after 6 months of CRT. NYHA functional class was used to evaluate heart failure symptoms and scored by an independent physician, who was blinded to all other patient data. Quality-of-life score was assessed using the Minnesota Living with Heart Failure questionnaire (15). Exercise tolerance was assessed using the 6-minute walk test (16). In all patients, QRS duration was measured from the surface ECG using the widest QRS complex from the leads II, V1 and V6, at baseline and after implantation.

Statistical analysis

Continuous variables are expressed as mean ± SD. Categorical data are summarized as frequencies and percentages.

Clinical parameters were assessed at baseline and at 6 months follow-up. Comparison of these data during follow-up was performed with the paired student t test (continuous variables) and McNemar test (NYHA class, MR severity). A P-value of 0.05 was considered statistically significant.

All echocardiographic studies were performed the day before implantation, the day after implantation, at 6 months follow-up with CRT on and off. Comparison of these data during follow-up was performed by applying the statistical tests as mentioned earlier. Baseline parameters were compared with parameters immediately after implant, parameters immediately after implant with 6 months follow-up data, and 6 months follow-up data with the interruption parameters. Therefore, to adjust for inflation of the type I error with multiple tests, we applied a Bonferroni correction and considered a P-value of <0.017 (0.05/3) statistically significant.

RESULTS

Patients

Baseline characteristics of the 25 patients (16 men, age 68±10 years) are summarized in Table 1. A total of 19 patients (76%) had moderate MR and 6 patients (14%) had severe MR before CRT implantation. Speckle tracking radial strain analysis showed that dyssynchrony between the anterior and posterior papillary muscle was present in all patients (169±69 ms, range 92 ms to 254 ms). In 18 patients (72%) the APM was located adjacent to the lateral LV segment and in the remaining patients (28%) adjacent to the anterior LV segment (Figure 2). Furthermore, the PPM was located adjacent to the inferior LV segment in 22 patients (88%) and adjacent to the posterior LV segment in 3 patients (12%).

Device implantation was successful in all patients and no procedure-related complications were observed. One patient died of worsening heart failure before the 6-month follow-up evaluation.

Table 1. Patient characteristics (n=25)

Age (yrs)	68±10
Gender (M/F)	16/9
NYHA class (III/IV)	24/1
Ischemic etiology	16 (64%)
QRS duration (ms)	154±25
Left bundle branch block	20 (80%)
Sinus rhythm/Atrial fibrillation/Paced	21/1/3
Severity of MR (moderate/severe)	19/6
LVEDV (ml)	251±85
LVESV (ml)	196±85
LVEF (%)	23±8
APM-PPM dyssynchrony (ms)	169±69
Medication	
Anticoagulants	24 (96%)
Diuretics	23 (92%)
ACE-inhibitors	22 (88%)
Beta-blockers	20 (80%)
Spironolactone	14 (56%)

APM–PPM dyssynchrony: dyssynchrony between the anterior and posterior papillary muscles; ACE: angiotensin-converting enzyme; EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; LV: left ventricular; MR: mitral regurgitation; NYHA: New York Heart Association.

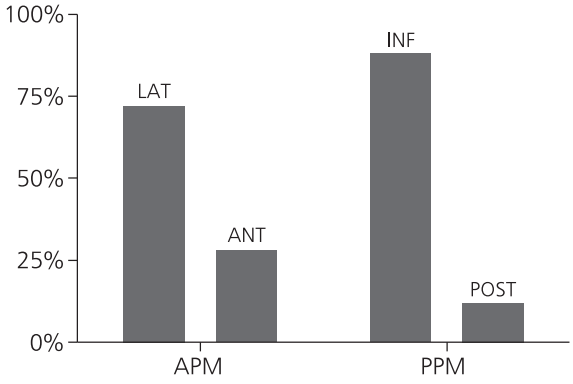


Figure 2. Position of the papillary muscles

The anterior papillary muscle (APM) was located adjacent to the lateral LV segment in 18 patients (72%) and adjacent to the anterior LV segment in 7 patients (28%); the posterior papillary muscle (PPM) was located adjacent to the inferior LV segment in 22 patients (88%) and adjacent to the posterior LV segment in 3 patients (12%).

Changes in MR, mitral deformation indices and LV function

According to the inclusion criteria, all patients showed an immediate reduction in severity of MR after CRT; vena contracta width decreased from 0.54±0.15 cm to 0.39±0.13 cm (P<0.001). Importantly, this reduction in MR was maintained at 6 months follow-up (vena contracta width 0.37±0.11 cm, NS, vs. immediately after CRT), followed by an immediate increase of MR when the pacemaker was turned off at 6 months (Table 2, Figure 3).

Table 2. Echocardiographic parameters at baseline (PRE), immediately after CRT implantation (POST), at 6 months follow-up (6 MO) and during interruption of CRT at 6 months follow-up (OFF)

	PRE	POST	6 MO	OFF	P-value PRE vs. POST *	P-value POST vs. 6 MO *	P-value 6 MO vs. OFF *
Severity in MR							
- No MR/mild/moderate/severe	0/0/19/6	0/10/15/0	3/8/13/0	2/2/17/3	<0.001	1.0	<0.001
- Vena contracta width (cm)	0.54±0.15	0.39±0.13	0.37±0.11	0.47±0.16	<0.001	0.57	0.003
- Jet area (cm^2)	7.7±3.1	4.6±2.4	4.1±2.1	6.5±3.2	<0.001	0.33	<0.001
- Jet area / LA area (%)	40±13	25±11	25±10	39±13	<0.001	0.96	<0.001
- LV dP/dt (mmHg)	702±344	1153±620	1160±625	847±517	<0.001	0.68	0.002
LV remodeling							
- LVESV (ml)	196±85	183±85	145±89	163±88	<0.001	<0.001	<0.001
- LVEDV (ml)	251±85	249±87	205±97	210±101	0.51	<0.001	0.17
- LVEF (%)	23±8	28±9	33±10	29±10	<0.001	0.006	<0.001
- PPM-fibrosa (cm)	6.7±0.5	6.4±0.6	6.1±0.6	6.3±0.6	<0.001	0.004	<0.001
Mitral deformation indices							
- Tenting area (cm^2)	7.8±1.0	7.2±1.0	6.7±1.2	6.9±1.3	<0.001	0.002	0.001
- Coaptation height (cm)	1.94±0.28	1.84±0.17	1.79±0.14	1.84±0.18	<0.001	0.23	<0.001
- MA contraction (%)	15±4	19±4	22±4	19±5	<0.001	0.017	0.009
Dyssynchrony							
- APM-PPM dyssynchrony (ms)	169±69	25±26	26±28	134±51	<0.001	0.91	<0.001

Abbreviations as in Table 1. LA: left atrial. * Bonferroni correction: a P-value of <0.017 was considered statistically significant.

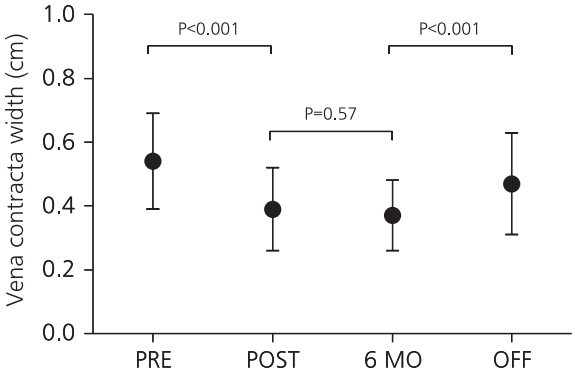


Figure 3. Severity of mitral regurgitation after CRT

Severity of mitral regurgitation (expressed in mean vena contracta width) at baseline (PRE), immediately after CRT implantation (POST), at 6 months follow-up (6 MO) and during interruption of CRT at 6 months (OFF).

The acute improvement in MR after CRT implantation was accompanied by an immediate improvement in LV dP/dt, a reduction in LVESV, and a deterioration of LV function. LVEDV did not change acutely. At 6 months follow-up, the improvement in LV volumes and LV function was even more pronounced with evidence of significant LV reverse remodeling. An acute deterioration of these parameters, except for LVESV, occurred during interruption of CRT at 6 months follow-up.

Furthermore, acute local remodeling after initiation of CRT was noted, as demonstrated by an acute reduction in PPM-fibrosa distance from 6.7±0.5 cm to 6.4±0.6 cm (P<0.001), with a further reduction to 6.1±0.6 cm at 6 months follow-up (P=0.004 vs. after CRT initiation).

Finally, acute reduction in MR was accompanied by an acute improvement in mitral deformation indices. An acute improvement in tenting area was observed (from 7.8±1.0 cm^2 to 7.2±1.0 cm^2, P<0.001), with reduction in coaptation height (from 1.94±0.18 cm to 1.79±0.14 cm, P<0.001) and improvement in mitral annular contraction (from 16±4% to 20±4%, P<0.001). This improvement was maintained or even further improved after 6 months of CRT, followed by an acute deterioration of these parameters after interruption of CRT.

Changes in dyssynchrony between the papillary muscles

Speckle tracking analysis was possible in all patients; however 31 of the 588 evaluated segments (5%) had to be eliminated because of negative strain values. In case of very low but positive strain values the segment was included when appearing hypo- or dyskinetic on the short-axis views.

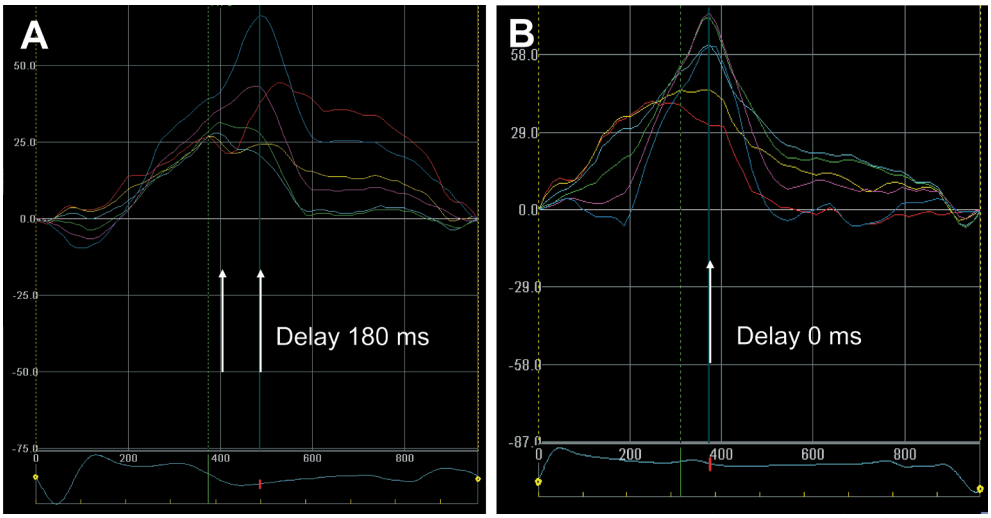
CRT initiation exhibited resynchronization of the papillary muscles as demonstrated by a decrease in APM – PPM dyssynchrony from 169±69 ms to 25±26 ms (P<0.001, see example Figure 4). This reduction in dyssynchrony was maintained at 6 months follow-up (25±26 ms immediately after CRT vs. 26±28 ms at 6 months of follow-up, NS). However, during interruption of CRT, APM – PPM dyssynchrony increased acutely to 134±51 ms (Figure 5).

Clinical evaluation at 6 months follow-up

After 6 months of CRT, 18 patients improved 1 NYHA class and 3 patients improved 2 NYHA classes (P<0.001). The quality-of-life score decreased from 35±17 to 19±14 (P<0.001). In addition, a significant increase in 6-minute walking distance was noted (from 296±101 m to 395±95 m, P<0.001).

Figure 4. Patient example

Time-strain curves of the 6 LV segments at the level of the papillary muscles. At baseline, the delay between peak radial strain of the anterior papillary muscle (APM, adjacent to the lateral LV segment, green curve) and the posterior papillary muscle, (PPM, adjacent to the inferior LV segment, dark blue curve) was 180 ms (A). After initiation of CRT, the dyssynchrony between the papillary muscles disappeared (B).



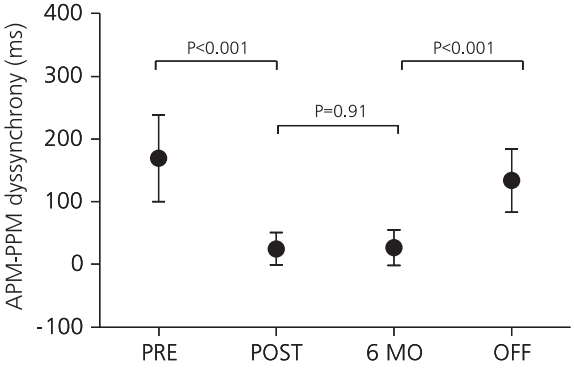


Figure 5. Papillary muscle dyssynchrony after CRT

Dyssynchrony between the papillary muscles at baseline (PRE), immediately after CRT implantation (POST), at 6 months follow-up (6 MO) and during interruption of CRT at 6 months follow-up (OFF).

Patients without reduction of MR after CRT

Of note, analysis of the 38 patients who did not show an immediate reduction in MR severity after CRT revealed that these patients have minimal dyssynchrony between the papillary muscles at baseline as compared to the patients who did show an immediate reduction after CRT initiation (38 ± 55 ms vs. 169 ± 69 ms, P<0.001).

DISCUSSION

The results of the present study illustrate that the mechanism underlying acute improvement in MR after CRT may be attributable to resynchronized contraction of the papillary muscles.

Interruption of CRT at 6 months follow-up resulted in acute loss of APM – PPM resynchronization with an acute deterioration of MR. Furthermore, the acute improvement in MR was accompanied by an improvement in mitral deformation indices, whereas CRT interruption at 6 months follow-up was associated with an acute deterioration of these parameters.

CRT and reduction in MR

As demonstrated in various randomized trials, CRT in patients with moderate-to-severe heart failure results in a sustained improvement in symptoms and LV systolic function and reverse remodeling (17-21). Furthermore, CRT may also reduce MR (19,21-24). For instance, the MIRACLE trial reported a significant reduction in MR in the CRT group after 6 months (MR jet area decreased from 7.31±6.14 cm^2 to 4.81 cm^2, P<0.01) (21). This reduction in MR has been attributed to LV reverse remodeling, with a secondary reduction in mitral annular diameter and as a consequence restored mitral valve closure, which is a long-term effect of CRT.

However, other studies reported an immediate improvement in MR severity after CRT initiation (1,2). Breithardt and colleagues studied 24 heart failure patients (LVEF 21±6%), and demonstrated that the severity of MR improved immediately after CRT, with a reduction in effective regurgitant orifice area from 25±19 mm^2 to 13±8 mm^2 (P<0.01) (1). A similar acute reduction in MR severity was demonstrated by Kanzaki and colleagues; the regurgitant volume decreased from 40±20 ml to 24±17 ml (P<0.01) (2). In line with these results, the present study showed an immediate reduction in MR severity after CRT in all patients (vena contracta width from 0.54±0.15 cm to 0.39±0.13 cm, P<0.001). This improvement was accompanied by a significant decrease in LV end-systolic volume, an increase in LV dP/dt and LV function, similar to the previous studies (1,2). Furthermore, as demonstrated in Table 2, mitral deformation indices and local LV remodeling showed an acute improvement after CRT.

Relation between MR and dyssynchrony

Preliminary results suggested that the immediate reduction in MR may be caused by resynchronization of the papillary muscles (2). Furthermore, increased closing force of the mitral leaflets may also be important for the improvement in MR (1). The present findings further support this hypothesis.

Firstly, LV dP/dt almost doubled after CRT initiation (702±344 mmHg to 1153±620 mmHg, P<0.001), with an improvement in LVEF (from 23±8% to 28±9%, P<0.001) which counteracts effectively on the increased tethering forces (with a decrease in tenting area reduced from 7.8±1.0 mm^2 to 7.2±1.0 mm^2, P<0.001). Breithardt and colleagues showed a somewhat similar increase in LV dP/dt acutely after CRT (1).

Furthermore, all 25 included patients showed an immediate reduction in dyssynchrony between the papillary muscles (from 169±69 ms to 25±26 ms, P<0.001) accompanied by a reduction in MR severity. A similar reduction in time delay between the papillary muscles after CRT initiation was demonstrated by Kanzaki and colleagues (106±74 ms to 39±43 ms, P<0.001) who evaluated 26 heart failure patients (LVEF 24±6%, 73% ischemic cardiomyopathy) with at least mild MR before and after CRT using mechanical activation strain maps (2).

Importantly, assuming that the improvement in MR is biventricular pacing dependent, it could be anticipated that interruption of biventricular pacing would lead to an immediate desynchronization of the papillary muscles with acute deterioration of MR. Indeed, all acute improvements in echocardiographic parameters maintained or some even more improved

during follow-up, in particular MR severity (vena contracta width 0.39±0.13 cm after CRT to 0.37±0.11 cm after 6 months, NS) and dyssynchrony between the papillary muscles (25±26 ms to 26±28, NS) showed no changes. During interruption of biventricular pacing however, both MR severity and dyssynchrony showed an acute worsening of mitral deformation indices and parameters reflecting global and local remodeling. Brandt and colleagues focused specifically on the hemodynamic consequences of temporary interruption of CRT in 20 patients after a median duration of biventricular pacing of 427 days and demonstrated similar results (25); withdrawal of CRT resulted in a decline in LV dP/dt and an increase in MR (median MR jet area from 4.1 mm^2 to 5.9 mm^2, P=0.002). However, markers of dyssynchrony were not reported in that study.

Clinical implications

Given the rapid increase in patients with dilated cardiomyopathy and secondary MR on the one hand, and the poor survival of these patients on the other hand, treatment of MR is an important issue (26-28). At present, surgical valve repair or replacement is the therapy of choice, but surgery is associated with relatively high risk for (peri-)operative morbidity and mortality and alternative treatment options are considered in patients who are not amenable for surgery (29,30). In this perspective, the findings of the current study are relevant, since these observations suggest that CRT may be considered as a potential alternative treatment of MR in patients who cannot undergo surgery. In particular, CRT may reduce MR if dyssynchrony involves the posterior papillary muscle.

Still, it is important to emphasize that the current patients represent a highly selected cohort; 60% of patients with baseline MR did not show an acute improvement in MR. Importantly however, these patients without an acute reduction in MR after CRT initiation had minimal dyssynchrony between the papillary muscles. Future prospective studies are needed to further elucidate the relation between LV dyssynchrony and reduction in MR after CRT.

CONCLUSION

CRT can acutely reduce MR in patients with dyssynchrony involving the papillary muscles; interruption of CRT at 6 months follow-up however, resulted in acute loss of resynchronization with recurrence of MR.

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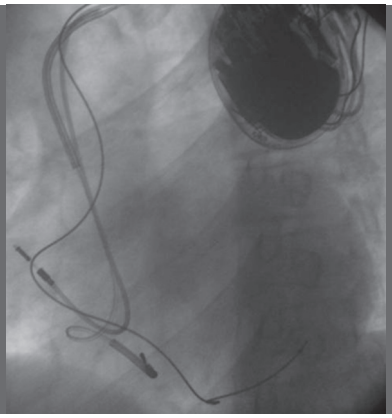
Chapter 14



Mechanism of improvement in mitral regurgitation after cardiac resynchronization therapy

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ABSTRACT

Aims The aim of the current study was to evaluate the relationship between the presence of LV dyssynchrony at baseline and acute versus late improvement in mitral regurgitation (MR) after cardiac resynchronization therapy (CRT).

Methods and Results Sixty-eight patients consecutive (LV ejection fraction 23±8%) with at least moderate MR (≥grade 2+) were included. Echocardiography was performed at baseline, one day after CRT initiation and at 6 months follow-up. Speckle tracking radial strain was used to assess LV dyssynchrony at baseline. The majority of patients improved in MR after CRT, with 43% improving immediately after CRT and 20% improving late (after 6 months) after CRT. Early and late responders had similar extent of LV dyssynchrony (209±115 ms vs. 190±118 ms, NS); however, the site of latest activation in early responders was mostly inferior or posterior (adjacent to the posterior papillary muscle), whereas the lateral wall was the latest activated segment in late responders.

Conclusion The current data suggest that the presence of baseline LV dyssynchrony is related to improvement in MR after CRT. LV dyssynchrony involving the posterior papillary muscle may lead to an immediate reduction in MR, whereas LV dyssynchrony in the lateral wall resulted in late response to CRT.

INTRODUCTION

Mitral regurgitation (MR) is a common finding in patients with dilated cardiomyopathy and depressed left ventricular (LV) function. Progressive remodeling and dilation of the LV may lead to annular enlargement and papillary muscle displacement resulting in functional MR.
Since the number of these patients is increasing rapidly and the presence of MR is associated with reduced survival (1-3), treatment of MR is an important issue. Recent studies have demonstrated that cardiac resynchronization therapy (CRT) may result in improvement in MR (4-6). However, the mechanism of this improvement in MR following CRT is not yet fully understood. LV dyssynchrony involving the posterior mitral leaflet appeared to be a determinant for the presence of MR (7). In addition, preliminary data suggested that CRT can acutely reduce MR in patients with dyssynchrony between the papillary muscles (8). Besides the acute effect, reduction in MR has also been shown at long-term follow-up after CRT, and is most likely secondary to LV reverse remodeling (9,10).
In this context, we assumed that patients with late activation (dyssynchrony) of the myocardial segments adjacent to posterior papillary muscle will respond acutely in MR after CRT initiation, whereas patients with late activation (dyssynchrony) of the lateral LV segments will show late improvement in MR due to LV reverse remodeling. Lastly, patients without dyssynchrony will show neither an acute or chronic improvement in MR nor reverse remodeling. To evaluate the role of dyssynchrony in reduction of MR, we evaluated 68 consecutive patients with at least moderate MR who underwent CRT. Transthoracic echocardiography was used to assess indices of MR and off-line analysis with speckle tracking radial strain was used to assess LV dyssynchrony.

METHODS

Patients

Between January 2005 and September 2006, 68 patients with at least moderate MR (≥grade 2+) were selected from 206 patients eligible for CRT in Leiden University Medical Center. Eligibility for CRT was based on the current guidelines; moderate to severe heart failure (New York Heart Association [NYHA] class III or IV), depressed LV function (LV ejection fraction [EF] <35%) and wide QRS complex (≥120 ms) (11). Twenty-five patients were included in a previous paper (8). Patients with a recent myocardial infarction (<3 months), previous mitral valve surgery, or decompensated heart failure were excluded. Etiology was considered ischemic in the presence of significant coronary artery disease (≥50% stenosis in one or more of the major epicardial coronary arteries) and/or a history of myocardial infarction with ECG evidence, prior PCI or prior CABG.

Study protocol

Clinical status was assessed at baseline and after 6 months of follow-up, including assessment of NYHA class, quality of life (using the Minnesota Living with Heart Failure questionnaire) (12), and evaluation of exercise capacity using the 6-minute hall walk test (13). Echocardiography was performed at baseline, the day after implantation and at 6-months follow-up.

Echocardiographic evaluation

All patients underwent standard transthoracic 2D echocardiography, including quantification of MR, LV function, global and local LV remodeling, and mitral valve deformation. All measurements were performed the day before implantation (PRE), the day after implantation (POST) and after 6 months of CRT (6 MO). Measurements of dyssynchrony were only performed at baseline. Patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed Vivid Seven, General Electric-Vingmed, Milwaukee, Wisconsin, USA). Images were obtained using a 3.5 MHz transducer, at a depth of 16 cm in the parasternal and apical views (standard long-axis and two- and four-chamber images). Standard 2D and color Doppler data, triggered to the QRS complex, were saved in cine-loop format. For each measurement, ≥3 cardiac cycles were averaged. All echocardiographic measurements were obtained by 2 independent observers.

The severity of MR was graded semi-quantitatively from color-flow Doppler images using the apical 4-chamber views. Left atrial (LA) and regurgitant jet area were measured by planimetry, allowing calculation of the ratio of the jet area to the LA area (14,15). In addition, vena contracta width was measured (16). The severity of MR was graded on a 4-point scale: mild = 1+ (jet area/LA area <10%), moderate = 2+ (jet area/LA area 10-20%, vena contracta <0.3 cm), 3+ = moderately severe (jet area/LA area 20-45%, vena contracta 0.3–0.7 cm), 4+ = severe (jet area/LA area >45%, vena contracta >0.7 cm) (17). Inter- and intraobserver agreement for jet area/LA area showed a mean value of differences of respectively 1.6% (95% limits of agreement from -7.2% to 10.3%) and 0.1% (95% limits of agreement -2.9% to 3.1%) and for vena contracta -0.03 cm (95% limits of agreement from -0.21 cm to 0.16 cm) and 0.01 cm (95% limits of agreement from -0.07 cm to 0.10 cm). The maximal rate of LV systolic pressure increase (LV dP/dt) was estimated from the steepest rising segment on the continuous wave Doppler regurgitant jet (18).

Mitral deformation indices included valvular tenting area, coaptation height and mitral annular contraction. The valvular tenting area was obtained from the parasternal long-axis view at mid-systole and was measured as the area enclosed between the annular plane and mitral leaflets. Displacement of mitral coaptation (coaptation height) towards the LV apex was measured by the distance between leaflet coaptation and the mitral annulus plane in the apical 4-chamber view. Mitral annulus diameter was measured at end-systole and end-diastole in the 4-chamber view. Annular contraction was calculated as (end-diastolic diameter – end-systolic diameter) / end-diastolic diameter (19).

LV volumes (end-diastolic volume [LVEDV], end-systolic volume [LVESV]) and LVEF were calculated from the conventional apical 2- and 4-chamber images, using the biplane Simpson's technique (20). The apical displacement of posterior papillary muscle was proposed to represent the global LV remodeling and was measured as the distance between the posterior papillary muscle head and the intervalvular fibrosa (PPM-fibrosa) in the long-axis view (19). For assessment of LA remodeling several parameters were calculated. The antero-posterior diameter was measured at end-systole on the M-mode image obtained from the parasternal long-axis view (21). Short- and long-axis of the LA were measured on apical 4-chamber views at end-systole. Furthermore, LA volumes were measured on apical 2- and 4-chamber views using the biplane Simpson's rule (22,23). LA end-systolic volume (LAESV) was defined as the largest LA volume in ventricular systole; LA end-diastolic volume (LAEDV) was defined as the smallest possible LA volume in ventricular diastole.

LV dyssynchrony was calculated using speckle tracking radial strain analysis applied to baseline LV short-axis images at the papillary muscle level (24,25). Time-strain curves for all the 6 segments (septal, anteroseptal, anterior, posterior, lateral and inferior) were constructed. Peak radial strain and time from QRS onset to peak radial strain were obtained. Consequently, the location of the earliest and latest activated segments and the heterogeneity in time-to-peak radial strain for the 6 segments were determined (26). LV dyssynchrony was defined as the maximal time difference between the earliest and latest activated segments; the site of latest activation was also noted (Figure 1). Inter- and intraobserver agreement for LV dyssynchrony showed a mean value of differences of respectively -11.5 ms (95% limits of agreement -73.5 ms to 50.4 ms) and 7.4 ms (95% limits of agreement from -10.7 ms to 25.5 ms).

Definition of response in MR after CRT

At 6-month follow-up, the patients were divided into three groups based on the improvement in MR. "Early responders" were defined as patients who improved at least one grade in MR immediately after implantation. Patients who showed an improvement of at least one grade MR after 6 months of CRT were classified as "late responders". "Non-responders" showed no improvement or even deterioration in MR during follow-up.

CRT implantation

A coronary sinus venogram was obtained using balloon catheter, followed by the insertion of the LV pacing lead. An 8F guiding catheter was used to position the LV lead (Easytrak 4512-80, Guidant Corporation, St. Paul, Minnesota; or Attain-SD 4189, Medtronic Inc., Minneapolis, Minnesota) in the coronary sinus. The preferred position was a lateral or postero-lateral vein (27). The right atrial and ventricular leads were positioned conventionally. All leads were connected to a dual chamber biventricular ICD (Contak Renewal II or H195, Guidant Corporation; or Insync III or Insync Sentry, Medtronic Inc.).

Statistical analysis

Continuous variables are expressed as mean ± SD. Categorical data are summarized as frequencies and percentages. Inter- and intraobserver agreements for severity of MR and LV dyssynchrony parameters are calculated using Bland-Altman analysis in a subset of 20 patients. The 95% limits of agreement were defined as the range of values ± 2 SDs from the mean value of differences. Patients were randomly selected and time between measurements by the same reader was >1 week. Differences in baseline characteristics between early-, late- and non-responders were analyzed using one-way analysis of variance (ANOVA) with post hoc Bonferoni testing (continuous variables) and chi-square or Fisher's exact tests (dichotomous variables) as appropriate. The relation between response-pattern and change in echocardiographic parameters over time was then studied using repeated measures two-way ANOVA. We assumed that every pair of measurements has the same correlation coefficient across subjects and that the variance and covariances are homogenous across time. This specific structure for the covariance is referred to as compound symmetry, and it is reasonable to assume such structure in view of the relatively short follow-up (6 months). The paired Students t test was used to compare continuous data within the three subgroups during follow-up. In acute responders and non-responders mitral deformation indices and parameters indicating LV function measured immediately after implant were compared with the baseline values,

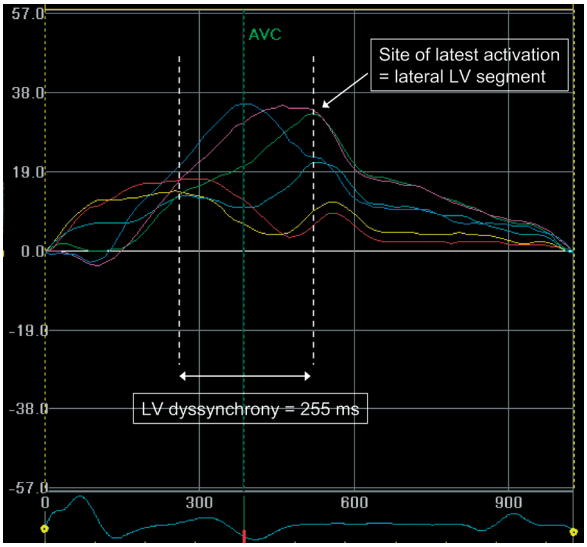


Figure 1. Example of speckle tracking analysis for dyssynchrony

Time-strain curves from the midventricular short-axis view for the 6 standard segments (yellow: antero-septal; red: anterior; green: lateral; purple: posterior; dark blue: inferior; and light blue: septal LV segment). LV dyssynchrony is present in this example as indicated by the difference in timing of peak strain between the earliest and latest activated segment of 255 ms. The latest activated segment is the lateral LV segment.

whereas in late responders and non-responders the 6 months follow-up measurements were compared with baseline. LA function and volumes measured at baseline and at 6 months follow-up were compared within all 3 groups. To adjust for inflation of the type I error with multiple tests, we applied a Bonferroni correction; for changes in mitral deformation indices and LV function we considered a P value of <0.05/4 statistically significant, for changes in LA function and volumes a P value of <0.05/3 was considered significant.

RESULTS

Patient characteristics

Baseline characteristics of the 68 consecutive patients (48 men, age 68±9 years) included in this study are summarized in Table 1. All patients had central jets, secondary to LV dilatation; 24 patients (35%) having moderate MR (grade 2+), 36 patients (53%) having moderately severe MR (grade 3+) and 8 patients (12%) had severe MR (4+) before CRT implantation. Most patients had NYHA class III (93%) and mean LVEF was 23±8%. All patients received optimized medical therapy, if tolerated. Device implantation was successful in all patients and no procedure-related complications were observed. However, 7 patients died of worsening heart failure before the 6-month follow-up evaluation.

Clinical and functional improvement after CRT

After 6 months of CRT, 40 patients improved one NYHA class and 5 patients improved two NYHA classes (McNemar test, P<0.001). The quality-of-life score decreased from 35±18 to 22±19 (P<0.001). In addition, a significant increase in 6-minute walking distance was noted (from 290±110 m to 374±127 m, P<0.001).

One day after implantation, LVESV showed a modest decrease from 197±95 ml to 190±76 ml (P<0.001) accompanied with an improvement in LVEF (from 23±8% to 25±9%, P<0.001).

Table 1. Baseline characteristics of the study population (n=68)	
Age (yrs)	68±9
Gender (M/F)	48/20
NYHA class (III/IV)	63/5
Ischemic etiology	39 (57%)
QRS duration (ms)	159±31
LBBB	52 (76%)
Sinus rhythm / atrial fibrillation / paced	55/8/5
Grade MR (2+ / 3+ / 4+)	24/36/8
LVEF (%)	23±8
LVEDV (ml)	251±80
LVESV (ml)	197±75
LV dyssynchrony (ms)	163±120
Medication	
Diuretics	63 (93%)
ACE-inhibitors	61 (90%)
Beta-blockers	52 (76%)
Spironolactone	41 (40%)

ACE: angiotensin-converting enzyme; EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; LBBB: left bundle branch block; LV: left ventricular; MR: mitral regurgitation; NYHA: New York Heart Association.

Significant reverse remodeling was observed at 6 months follow-up, as evidenced by a decrease in LVEDV from 251±80 ml at baseline to 216±89 ml (P<0.001) after 6 months of CRT. Similarly, LVESV decreased from 197±75 ml to 155±80 ml (P<0.001). Furthermore, the LV ejection fraction improved from 23±8% to 30±10% (P<0.001).

Improvement in MR after CRT

Immediately after CRT 26 patients improved one grade in MR and 3 patients improved two grades, resulting in 29 early responders (43%). The group of late responders comprised 14 patients (20%); 12 patients showed a reduction of one grade in MR, 2 patients showed a reduction of 2 grades after 6 months. Twenty-five patients (37%) were considered non-responders, including the patients who died before 6 months of follow-up. Early responders showed an immediate reduction in severity of MR after CRT, which was maintained or even further reduced after 6 months of CRT (Figure 2, Table 2). In contrast, late responders exhibited reduction in MR only after 6 months of CRT. In the non-responder group severity of MR did not change during the entire follow-up.

Regarding mitral deformation indices, Figure 3 demonstrates significant differences in trend during follow-up between acute, late and non-responders. Acute improvement in MR was accompanied by an acute significant improvement in tenting area (from 7.8±1.0 cm^2 to 7.2±0.9 cm^2, P<0.001), coaptation height (from 1.9±0.2 cm to 1.8±0.2 cm, P<0.001) and mitral annular contraction (from 16±4% to 20±4%, P<0.001). This improvement was even more pronounced after 6 months of CRT. In the late responders these mitral deformation indices did not improve acutely after CRT, but did improve after 6 months (in all P<0.005). Lastly, the non-responder

Table 2. Effect of CRT on severity of MR and LV function and LV volumes

Effect of CRT on severity of MR and LV function and LV volumes between patients who show an acute improvement in MR (EARLY, n=29), a late improvement after 6 months of follow-up (LATE, n=14) or no improvement at all (NON, n=25). The following comparisons were made: in early responders PRE vs. POST; in late responders PRE vs. 6 MO and in non-responders both. The corresponding p-values are added between brackets. To correct for repeated measurements a P-value of <0.013 was considered statistically significant.

		EARLY	LATE	NON	P-value
MR (grade)	PRE	2.8±0.6	2.8±0.7	2.8±0.7	1.0
	POST	1.7±0.7 [P<0.001]	2.8±0.7	2.8±0.7 [P=0.7]	
	6 MO	1.6±0.8	1.7±0.7 [P<0.001]	2.9±0.8 [P=0.4]	
Jet area (cm^2)	PRE	7.1±3.2	7.9±4.0	7.0±4.7	0.7
	POST	3.5±1.9 [P<0.001]	7.9±4.0	7.8±4.2 [P=0.8]	
	6 MO	3.0±1.3	3.7±2.1[P<0.001]	8.5±4.9 [P=0.3]	
Jet area/LA area (%)	PRE	34±13	34±15	35±15	1.0
	POST	18±9 [P<0.001]	34±15	34±14 [P=0.3]	
	6 MO	17±8	20±11[P<0.001]	35±15 [P=0.7]	
Vena contracta (cm)	PRE	0.46±0.16	0.46±0.22	0.42±0.20	0.8
	POST	0.31±0.12 [P<0.001]	0.47±0.20	0.43±0.19 [P=0.7]	
	6 MO	0.31±0.10	0.27±0.14 [P<0.001]	0.44±0.18 [P=0.3]	
LV dP/dt	PRE	669±335	705±444	702±239	1.0
(mmHg/s)	POST	1134±608 [P<0.001]	851±451	714±185 [P=0.6]	
	6 MO	1123±605	1174±496 [P=0.005]	721±265 [P=0.8]	
LVEF (%)	PRE	24±8	22±7	22±8	0.5
	POST	28±9 [P<0.001]	24±9	23±8 [P=0.1]	
	6 MO	33±10	33±9 [P<0.001]	25±8 [P=0.1]	
LVEDV (ml)	PRE	251±82	241±46	256±94	0.8
	POST	249±83 [P=0.4]	243±44	259±92 [P=0.2]	
	6 MO	204±91	195±54 [P<0.001]	249±102 [P=0.9]	
LVESV (ml)	PRE	194±81	191±48	205±82	0.8
	POST	182±82 [P<0.001]	187±48	201±81 [P=0.1]	
	6 MO	142±83	134±50 [P<0.001]	189±87 [P=0.3]	

Abbreviations as in Table 1. LA: left atrial.

group showed neither improvement in MR as well as in tenting area, coaptation height, and mitral annular contraction during the entire follow-up.

Furthermore, Figure 3 also demonstrates acute local remodeling after initiation of CRT in acute responders, as demonstrated by an acute reduction in PPM-fibrosa distance from 6.7±0.5 cm to 6.4±0.6 cm (P<0.001), with a further reduction to 6.1±0.6 cm after 6 months. Local LV remodeling in late responders was noted only after 6 months (from 6.7±0.7 cm to 6.2±0.7 cm, P<0.001). The non-responders showed no change at all in local LV remodeling. Global changes in LV function were also noted in acute responders as demonstrated by an immediate improvement in LV dP/dt, a reduction in LVESV, and consequently an improvement in LVEF (all parameters P<0.001, Table 2). This improvement was maintained or even further improved after

Table 3. Effect of CRT on left atrial size and volumes between patients who show an acute improvement in MR (EARLY, n=29), a late improvement after 6 months of follow-up (LATE, n=14) or no improvement at all (NON, n=25)

		EARLY	LATE	NON	P-value
LA diameter (cm)	PRE	4.7±0.7	4.8±0.8	4.9±0.8	0.7
	6 MO	4.3±0.8*	4.5±0.8*	4.8±0.9	
LA LAX (cm)	PRE	5.2±0.4	5.3±0.7	5.3±1.1	0.8
	6 O	4.8±0.6*	5.0±0.6	5.2±0.9	
LA SAX (cm)	PRE	4.5±0.6	4.4±0.7	4.2±0.9	0.9
	6 MO	3.9±0.8*	4.0±0.8	4.2±0.9	
LAESV (ml)	PRE	63±21	70±23	66±29	0.6
	6 MO	53±22*	60±23*	69±31	
LAEDV (ml)	PRE	49±17	50±20	48±28	1.0
	6 MO	41±17*	40±21*	48±34	

Abbreviations as in Table 1 and 2. SAX: short-axis. * PRE vs. 6 MO P<0.001.

6 months of CRT, with significant LV reverse remodeling. Late responders showed a reduction in LV volumes and improvement in LV function after 6 months of follow-up (P<0.001). Non-responders in MR showed no improvement in indices of global LV remodeling during the entire follow-up. Of note, 72% of the early responders and 93% of the late responders showed >15% reduction in LVESV after 6 months as compared to only 4 patients (20%) in the non-responder group (P<0.001).

LA remodeling was only assessed at 6 months follow-up (Table 3). LA diameters showed a significant reduction during follow-up in early responders (P<0.001) with a trend for reduction in late responders (P=0.034 for LA LAX and P=0.040 for LA SAX). LA volumes however, were significantly decreased. Non-responders showed no LA reverse remodeling.

LV dyssynchrony and improvement in MR

As demonstrated in Table 4, baseline characteristics of all three patient groups were similar except for the indices of LV dyssynchrony at baseline. Of note, speckle tracking analysis was possible in all but three patients due to technically inadequate short-axis images and 18 segments (5%) of the remaining 390 segments had to be eliminated because of negative strain values.

Non-responders showed less LV dyssynchrony at baseline compared to early and late responders (99±74 ms vs. 209±115 ms vs. 190±118 ms, P<0.001). Early and late responders had similar extent of LV dyssynchrony; however, the site of latest activation in early responders was the posterior or the inferior LV segment, which is adjacent to the posterior papillary muscle, whereas in late responders the site of latest activation was the lateral LV segment (Figure 4).

In contrast, evaluation of 100 random CRT candidates without (34%) or mild MR (grade 1+, 66%) demonstrated similar extent of LV dyssynchrony as compared to patients with at least moderate MR (167±122 ms vs. 163±120 ms, P=0.8). However, different distribution of site of latest activation was noted (see Figure 5), with the lateral segment contracting latest in the majority of patients. Interestingly, only 18% of the patients demonstrated late contraction of the posterior and inferior segments.

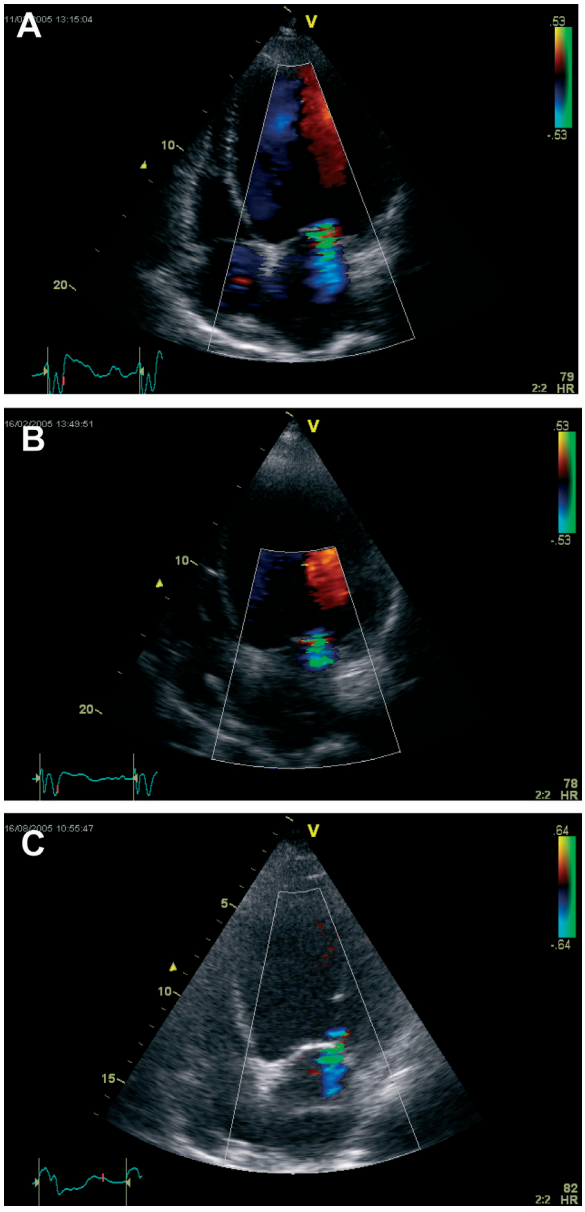


Figure 2. Color Doppler images of an "acute responder"

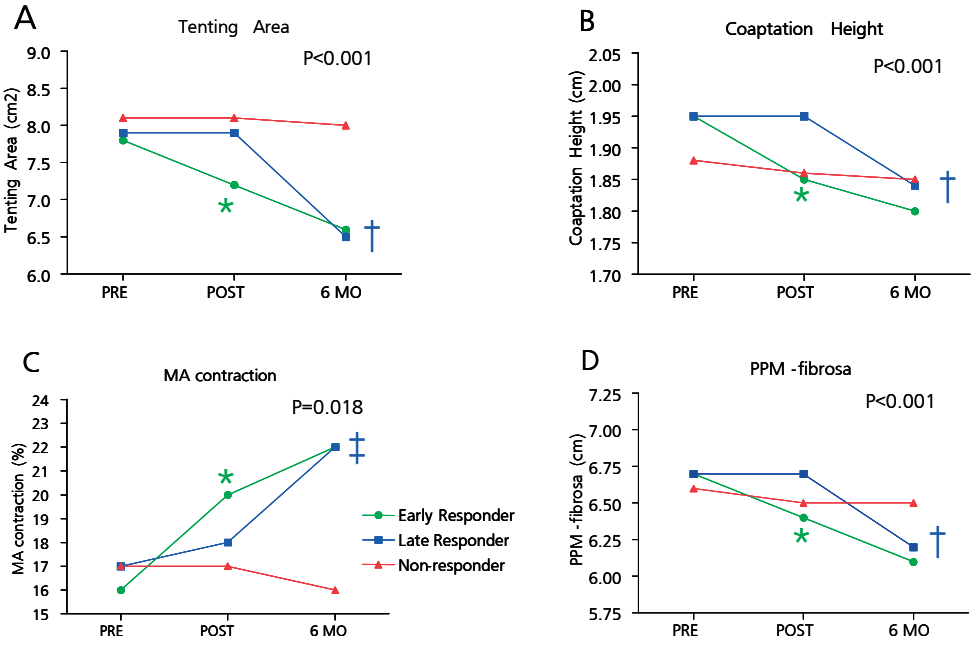
Acute reduction in MR is seen immediate after cardiac resynchronization therapy (B) compared to baseline (A). Panel C demonstrates a sustained reduction at 6-months follow-up.

DISCUSSION

The results of the current study can be summarized as follows: 1) the majority of patients included in this study improved in MR after CRT, with 43% improving immediately after CRT, and 20% improving late (at 6 months) after CRT; 2) the site of latest activation (the most dyssynchronous region) in early responders was mostly posterior or inferior (close to the posterior papillary muscle), whereas the lateral wall was the latest activated segment in late responders; 3) improvement in MR was accompanied by an improvement in mitral deformation indices, as well as in global and local LV reverse remodeling as in LA remodeling.

Figure 3. Effects of CRT on mitral deformation indices (A-C) and global LV remodeling (D) immediately after implantation (POST) and after 6 months (6 MO)

Patients are divided in early, late and non-responders according to their improvement in MR. The P-value indicates a significant difference in trend during follow-up between the three groups.
(* PRE vs. POST P<0.001; † PRE vs. 6 MO P<0.001; ‡ PRE vs. 6 MO P<0.005).



Mechanism of MR in dilated cardiomyopathy

The development of functional MR in dilated cardiomyopathy has been attributed to annular enlargement secondary to the LV dilatation and papillary muscle displacement due to LV remodeling, which results in tethering and mitral valve tenting (28,29). Boltwood and colleagues have reported that annular dilatation is the main determinant of MR in patients with dilated cardiomyopathy (30). Other studies have demonstrated that systolic mitral valve tenting is the main determinant of mitral valve incompetence (28,29,31). Lancellotti and colleagues demonstrated in 70 ischemic patients that severity of MR at rest best correlated with changes in mitral deformation (tenting area, coaptation height) during exercise. Moreover, posterior displacement of the papillary muscle was associated with severity of MR (19).

The presence of LV dyssynchrony may also contribute to MR. LV dyssynchrony decreases LV contraction efficiency and closing forces thereby impairing mitral valve tenting (4). Moreover, dyssynchrony between the LV segments supporting the papillary muscles produces uncoordinated regional LV mechanical activation in these segments, resulting in geometric changes in mitral leaflet attachments and implying tethering of the mitral leaflets (5). For instance, in previous work we measured a time delay of 169±69 ms between maximal contraction of the anterior papillary muscle and the posterior papillary muscle in 25 patients with moderate-severe MR (8).

Table 4. Baseline characteristics in patients who show an acute improvement in MR after CRT (EARLY, n=29), a late improvement after 6 months of follow-up (LATE, n=14) or no improvement at all (NON, n=25)

	EARLY	LATE	NON	P-value
Age (yrs)	68±10	71±7	66±8	0.3
Gender (M/F)	19/10	10/4	19/6	0.7
NYHA class (III/IV)	28/1	13/1	22/1	0.5
Ischemic etiology	19 (56%)	6 (43%)	14 (56%)	0.4
QRS duration (ms)	157±29	175±33	153±31	0.1
LBBB	22 (76%)	10 (71%)	20 (80%)	0.3
Sinus rhythm/atrial fibrillation/paced	25/1/3	10/2/2	20/5/0	0.4
Grade MR (2+/3+/4+)	9/18/2	5/7/2	11/12/4	0.7
LVEF (%)	24±8	22±7	22±8	0.5
LVEDV (ml)	251±82	241±46	256±94	0.8
LVESV (ml)	194±81	191±48	205±82	0.8
LV dyssynchrony (ms)	209±115	190±118	99±74	<0.001

Abbreviations as in Table 1.

Figure 4. Distribution of site of latest activation between early and late responders in improvement in MR after CRT

AS: antero-septal, ANT: anterior, LAT: lateral, POST: posterior, INF: inferior, SEPT: septal LV segment.

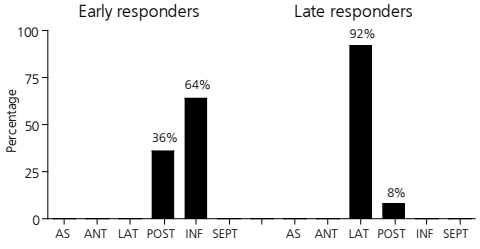
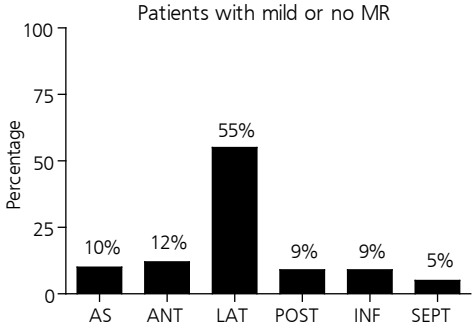


Figure 5. Distribution of site of latest activation in 100 CRT patients without significant MR at baseline

Abbreviations as in Figure 4.



Acute versus late improvement in MR

CRT has been reported to reduce MR. However, some patients exhibit immediate reduction in MR, whereas other patients show improvement only late after CRT. Indeed, several acute CRT studies reported an acute MR reduction (4-6). For instance, Lancellotti and coworkers studied 27 patients (LVEF 29±5%) with CRT on and off, and demonstrated that MR improved immediately after CRT, with a reduction in effective regurgitant orifice area from 22±10 mm^2 to 13±7 mm^2 (6). Furthermore, these changes in MR were directly related to changes in LV systolic function (LV dP/dt). The likely cause of the improvement in MR was concluded to be a decrease in LVESV and coordination of ventricular contraction, leading to restoration of mitral valve closure. Kanzaki and colleagues noted a similar reduction in MR severity and

added the role of papillary muscle resynchronization during CRT (5). Along with the reduction in MR severity, the inter-papillary muscle time delay shortened from 106±74 ms at baseline to 39±43 ms after CRT (P<0.001). Furthermore, the change in inter-papillary muscle time delay correlated well with the decrease in MR severity after CRT (r=0.77, P<0.001). Similar results from our group concerning the mechanism of acute reduction in MR after CRT were reported recently (8). At baseline, a time delay of 169±69 ms between the anterior and the posterior papillary muscle was present, that decreased immediately to 25±46 ms after CRT along with a reduction MR severity (evidenced by a reduction in vena contracta width from 0.54±15 cm to 0.39±0.13 cm, P<0.001).

Besides the acute effect of CRT on MR, reduction in MR has also been shown at long-term follow-up; data from the MIRACLE trial and other large trials have demonstrated a significant reduction in average MR jet area and MR severity after CRT (9,10). Thus, immediate reduction in MR severity can be attributed to resynchronized papillary muscle activation and improved coordination of LV contraction, which results in improved systolic function and reduced mitral leaflet tethering forces. The likely cause of late improvement in MR is LV reverse remodeling leading to a reduction in mitral annular size, with restoration of mitral valve closure. Of note, late responders in MR also show an acute improvement in LVESV probably as a result of a decrease in LV dyssynchrony with a coordinated contraction.

The current study evaluated the different mechanisms of reduction in MR after CRT. Importantly, the majority of patients (63%) demonstrated a reduction in MR severity after CRT, either acute or late. Acute improvement in MR severity was accompanied by acute improvements in mitral deformation, LV function and LA function which were maintained or improved even further during late follow-up. Late improvement in MR (after 6 months of CRT), was accompanied by LV reverse remodeling, global LV remodeling and improved mitral deformation indices. Interestingly, both acute and late responders exhibited severe baseline LV dyssynchrony, but a different location of LV dyssynchrony was noted in both groups. In acute responders the inferior or posterior segments showed the latest activation, whereas in late responders the lateral wall showed the latest activation. The posterior papillary muscles are located adjacent to the inferior or posterior LV segments, suggesting involvement of the papillary muscle in the dyssynchrony in acute responders. This hypothesis is further supported by the fact that patients without significant MR do have similar extent of LV dyssynchrony but show less often a posterior or inferior site of latest activation. Future larger studies are warranted to further elucidate the role of dyssynchrony in functional MR.

CONCLUSIONS

The observations in the present study indicate that the improvement in MR after CRT is related to the presence of LV dyssynchrony. If the LV dyssynchrony involves the posterior papillary muscle an immediate reduction in MR can be expected after CRT (secondary to resynchronization of the posterior papillary muscle), whereas in patients with LV dyssynchrony not involving the posterior papillary muscle late improvement in MR can be expected (related to LV reverse remodeling with subsequent reduction in mitral annular size and improved closure of the valve).

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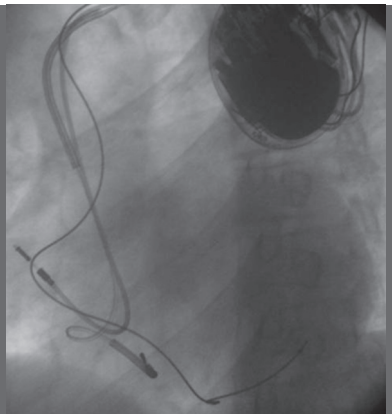
Chapter 15



Benefit of combined resynchronization and defibrillator therapy in heart failure patients with and without ventricular arrhythmias

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Abstract

Objectives To assess the efficacy of combined resynchronization-defibrillator (CRT-ICD) therapy in heart failure patients with and without ventricular arrhythmias.

Background Since CRT and ICD therapy both lower all-course mortality in patients with advanced heart failure, combination of both therapies in a single device is challenging.

Methods 191 consecutive patients with advanced heart failure, left ventricular ejection fraction <35% and a QRS duration >120 ms received a CRT-ICD. Seventy-one patients had a history of ventricular arrhythmias (secondary prevention); 120 patients did not have prior ventricular arrhythmias (primary prevention). During follow-up, ICD therapy rate, clinical improvement after 6 months and mortality rate were evaluated.

Results During follow-up (18±4 months) primary prevention patients experienced less appropriate ICD therapies than secondary prevention patients (21% vs. 35%, P<0.05). Multivariate analysis revealed however no predictors of ICD therapy. Furthermore, a similar, significant, improvement in clinical parameters was observed at 6 months in both groups. Also, the mortality rate in the primary prevention group was lower than in the secondary prevention group (3% vs. 18%, P<0.05).

Conclusions As 21% of the primary prevention patients and 35% of the secondary prevention patients experienced appropriate ICD therapy within 2 years after implant, and no predictors of ICD therapy could be identified, implantation of a CRT-ICD device should be considered in all patients eligible for CRT.

INTRODUCTION

Despite significant advances in the treatment of congestive heart failure, the 5-year mortality exceeds 50% (1,2). Although the cause of death is heart failure related in most patients with advanced symptoms, a significant proportion will die suddenly and unexpected due to ventricular arrhythmias.

Cardiac resynchronization therapy (CRT) in New York Heart Association (NYHA) class III and IV patients, with a wide QRS complex and depressed left ventricular (LV) function, has a positive effect on functional status, quality of life and LV function as demonstrated by various randomized and non-randomized studies (3-7). Furthermore, the Cardiac Resynchronization – Heart Failure (CARE-HF) study reported a positive effect of CRT on all cause mortality, as compared to optimal medical treatment alone (8). However, CRT alone will have a limited effect on the arrhythmic death rate.

Implantable cardioverter defibrillators (ICD) provide a substantial mortality benefit by preventing sudden cardiac death in patients with previous ventricular arrhythmias (9). Furthermore, the Sudden Cardiac Death in Heart Failure trial (SCD-HeFT) showed that low LV ejection fraction (EF) patients without ventricular arrhythmias, regardless of the underlying cause, benefit from an ICD on top of optimal medical therapy (10).

However, whether a combined CRT-ICD device should be implanted in all CRT candidates is still a matter of debate. The randomized Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial, showed a trend for CRT-only to decrease mortality, but reported a significant mortality effect in patients treated with a CRT-ICD device (11).

The aim of this study was to evaluate number of ICD therapies in patients eligible for CRT with and without prior ventricular arrhythmias, who received a combined CRT-ICD device, and whether predictors of VT/VF could be determined. Secondary endpoints were response to CRT and mortality differences in patients with and without prior ventricular arrhythmias.

METHODS

Patients

From 2000 to April 2004, all 195 consecutive patients eligible for CRT-ICD in our center were included in this prospective analysis. Standard therapy guidelines were applied to indicate ICD implantation (12,13). Eligibility for CRT was based on the following criteria: (1) advanced heart failure (NYHA class III or IV), (2) LVEF <35%, and (3) wide QRS complex (>120ms) with a left bundle branch pattern on the electrocardiogram.

Patients with ischemic as well as non-ischemic dilated cardiomyopathy were included. The etiology was considered ischemic in the presence of an old myocardial infarction and/or significant coronary artery disease (>50% stenosis in 1 of the major epicardial coronary arteries) on coronary angiography; whereas patients with normal coronary arteries were classified as non-ischemic. All patients underwent coronary angiography before implant. Patients with atrial fibrillation or previous implanted pacemakers were also included in this analysis.

The study protocol was as follows. Before implant patients were allocated to one of two groups according to the indication for ICD implantation: (A) CRT-ICD implantation was

considered a primary preventive intervention in patients without life-threatening sustained ventricular arrhythmias. Patients with non-sustained ventricular tachycardia (VT) on holter monitoring or syncope without inducible ventricular arrhythmias during electrophysiological testing, were also included in this **primary prevention group**. (B) CRT-ICD implantation was considered a secondary preventive intervention in sudden cardiac arrest survivors or in patients with sustained hemodynamic unstable VT, as well as in patients with syncope and inducible ventricular arrhythmia at electro-physiological testing (**secondary prevention group**).
For this analysis, follow-up was obtained up to 2 years. ICD printouts were obtained every 3 months. Clinical evaluation was assessed at baseline and after 6 months and thereafter at regular intervals.

CRT-ICD implantation

A coronary sinus venogram was obtained using a balloon catheter, followed by the insertion of the LV pacing lead into one of the postero-lateral veins through an 8F guiding catheter (Easytrak 4512-80, Guidant Corporation, St. Paul, Minnesota; or Attain-SD 4189, Medtronic Inc., Minneapolis, Minnesota). The right atrial and ventricular leads were positioned conventionally. All leads were connected to a dual chamber biventricular ICD (Contak CD or Renewal, Guidant Corporation; Insync-III or Marquis, Medtronic Inc).
Procedural success was accomplished when pulse generator and the 3 leads were positioned without complications and biventricular pacing could be installed.

ICD evaluation

During follow-up ICD printouts were obtained every 3 months. From these printouts, the incidence and type of arrhythmias, as well as the incidence of appropriate and inappropriate shocks was determined. Shocks or anti-tachycardia pacing (ATP) were classified as appropriate when they occurred in response to VT or ventricular fibrillation (VF) and as inappropriate when triggered by sinus- or supraventricular tachycardia, T-wave oversensing or electrode dysfunction. Cut-off rate of the monitor or first therapy zone was noted.

Clinical evaluation

All patients were evaluated at the outpatient clinic at baseline and at 6 months following CRT-ICD implantation. Heart failure symptoms were classified using the NYHA score. Quality of life score was assessed using the Minnesota Living with Heart Failure questionnaire (14). To ascertain biventricular pacing, a surface ECG was obtained at all visits. Exercise tolerance was evaluated using a 6-minute walk test at all visits (15). Resting 2-D echocardiography was performed at baseline and 6 months follow-up to assess LVEF. From the apical 2- en 4-chamber images, LVEF was determined using the biplane Simpson's rule (16).
After 6 months, patients were classified as responders, based on an improvement in NYHA class by ≥1 and/or an improvement by ≥25% in 6-minute walking distance, or as non-responders based on lack of improvement.
Thereafter, follow-up at the outpatient clinic was scheduled at regular intervals. Events were classified as cardiac death (e.g. arrhythmic death, sudden cardiac death, death attributable to congestive heart failure or myocardial infarction), non-cardiac death and heart transplantation.

Statistical analysis

Continuous data are presented as mean ± SD; dichotomous data are presented as numbers and percentages. Differences in baseline characteristics and 6-month follow-up between independent patient groups are evaluated using unpaired Student *t* (continuous variables) and chi-square tests as well as a Mann-Whitney test (NYHA classification). Yates correction was used in tables with a total less than 100 or with any cell containing a value less than 10. Data within patient groups (to compare the effect of CRT) were compared by the use of paired Student *t* tests (continuous variables) and Wilcoxon signed-rank tests (NYHA classification). Event and survival curves were determined according to the Kaplan and Meier method, with comparisons of cumulative event rates by the log-rank test.

Univariable and multivariable Cox' regression analysis were performed to determine a relation between potential risk factors at baseline, and the incidence of ICD therapy in primary prevention patients, secondary prevention patients and both (primary endpoint); and death from any cause during long-term follow-up (secondary endpoint). We considered the following variables: age, gender, etiology, QRS duration, LVEF, medication, previous infarction, medication and co-morbidity. Responding to CRT and the indication for ICD therapy were added in the analysis of incidence of ICD therapy in all patients. All variables entered the multivariable stage, irrespective of the results of the univariable analyses. Multivariable regression was then performed according to the principle of backward deletion. All variables with a P value of <0.25 remained in the final model. We report only adjusted hazard ratios (HR) with their corresponding 95% confidence intervals (CI).

For all tests, a P-value of <0.05 was considered statistically significant.

RESULTS

Patient characteristics

Hundred-ninety-five consecutive patients with advanced heart failure underwent CRT-ICD implantation. The procedure was successful in all patients and, except for pocket haematoma in 9 and a pneumothorax in 1, no procedure-related complications were observed. One patient died 1 day after a "rescue"- procedure due to refractory cardiogenic shock. Three patients were lost for follow-up (all primary prevention patients). Follow-up of the remaining 191 CRT-ICD patients (age 64±11 years, 153 men, Table 1) was 18 months (range 25 days to 2 years). Underlying etiology was ischemic in 107 patients (56%) and non-ischemic in 84 patients (44%). NYHA class before implant was 2.9±0.5, QRS duration was 163±30 ms and LVEF was 21±7%. According to the initial indication for ICD implantation, 120 patients (101 prophylactic, 14 patients with non-sustained VT on holter monitoring without inducible VT, 5 patients with syncope without observed or inducible VT) were allocated to the **primary prevention group** (group A); the **secondary prevention group** (group B) contained 71 patients (11 patients with inducible VT, 38 patients with spontaneous VT and 22 out of hospital cardiac arrest survivors).

Patients in the secondary prevention group were more likely to have an ischemic cardiomyopathy (70% vs. 48%, p<0.01) and a previous myocardial infarction (62% vs. 32%, P<0.01). Usage of amiodarone was significantly higher in the patients with prior ventricular arrhythmias.

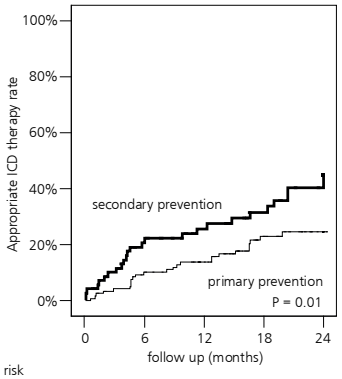
Table 1. Baseline characteristics in primary prevention patients (n=120), secondary prevention (n=71) and all (n=191)

	Primary Prevention	Secondary Prevention	All patients
Age (yrs)	64±10	66±11	64±11
Gender (M/F)	94/26	59/12	153/38
NYHA class	2.9±0.5	3.0±0.5	2.9±0.5
Ischemic etiology	57 (48%)	50 (70%)*	107 (56%)
QRS duration (ms)	163±30	164±29	163±30
Rhythm			
Sinus rhythm	87 (73%)	50 (70%)	138 (72%)
Paroxysmal atrial fibrillation	27 (22%)	15 (21%)	42 (22%)
Permanent atrial fibrillation	6 (5%)	6 (8%)	12 (6%)
Pacemaker rhythm	12 (10%)	9 (13%)	21 (11%)
LVEF (%)	22±7	20±7	21±7
CRT-ICD indication			
Prophylactic	101 (84%)	0 (0%)	101 (53%)
Non-sustained VT	14 (12%)	0 (0%)	14 (7%)
Syncope	5 (4%)	0 (0%)	5 (3%)
Inducible VT	0 (0%)	11 (15%)	11 (6%)
Spontaneous VT	0 (0%)	38 (54%)	38 (20%)
Spontaneous VF	0 (0%)	22 (31%)	22 (12%)
Cardiovascular history			
Previous infarction	38 (32%)	44 (62%)*	82 (43%)
Previous percutaneous coronary intervention	17 (14%)	16 (23%)	33 (17%)
Previous coronary artery bypass graft	28 (23%)	13 (18%)†	41 (21%)
Previous valve surgery	10 (8%)	8 (11%)	18 (9%)
Previous device (PM/ICD/CRT)	10/2/4	8/21*/0	18/23/4
Co-morbidity			
Diabetes Mellitus	24 (20%)	13 (18%)	37 (19%)
Stroke/transient ischemic attack	8 (7%)	15 (21%)*	23 (12%)
Peripheral vascular disease	11 (9%)	7 (10%)	18 (9%)
Chronic obstructive pulmonary disease	18 (15%)	7 (10%)	25 (13%)
Medication			
ACE inhibitor / ATII blocker	103 (86%)	58 (82%)	161 (84%)
Diuretics	98 (82%)	61 (86%)	159 (83%)
Spironolactone	54 (45%)	32 (45%)	86 (45%)
Betablocker (incl. Sotalol)	72 (59%)	33 (46%)	105 (55%)
Statin	50 (42%)	33 (46%)	83 (43%)
Digoxin	30 (25%)	19 (27%)	49 (26%)
Amiodarone	18 (15%)	39 (55%)*	57 (30%)
Follow-up (months)	19±6	18±7	18±6

ACE: angiotensin-converting enzyme; ATII: angiotensin-II; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; PM: conventional pacemaker; VT: ventricular tachycardia; VF: ventricular fibrillation

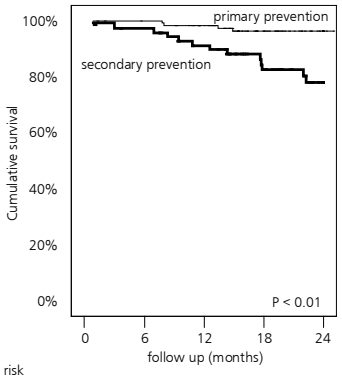
* P<0.01 compared to primary prevention group; † P<0.025 compared to primary prevention group

Figure 1. Appropriate ICD therapy rate in primary and secondary prevention patients



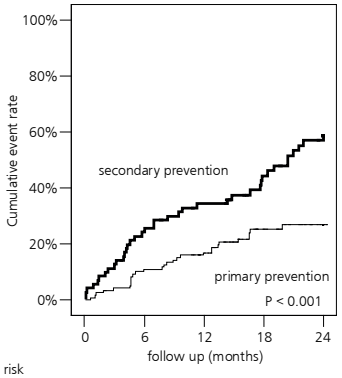
Patients at risk					
Primary prevention	120	103	89	52	36
Secondary prevention	71	49	41	31	25

Figure 2. Survival curve for primary and secondary prevention patients



Patients at risk					
Primary prevention	120	117	104	66	45
Secondary prevention	71	67	59	43	31

Figure 3. Cardiac event curve for primary and secondary prevention patients



Patients at risk					
Primary prevention	120	117	104	66	45
Secondary prevention	71	67	59	43	31

Among patients in the primary prevention group amiodarone was initiated for the suppression of atrial fibrillation (n=18, 15%), whereas among secondary prevention patients amiodarone (n=39, 55%) was used for atrial arrhythmia suppression in 4, VT suppression in 27, and both in 8 patients.

Incidence and therapy of ventricular arrhythmias

During follow-up the incidence of ventricular arrhythmias (as monitored by the device) was 24% in the primary prevention group and 39% in the secondary prevention group (P<0.05, Table 2). The first ventricular arrhythmia episode was terminated by ATP and/or shocks in 50 patients (88%). Ventricular arrhythmias (>10 beats) with a cycle length in the monitor zone received no therapy (12%). After the first episode of ventricular arrhythmias the parameter settings of the ICD were adjusted.

As expected (despite a significantly higher usage of anti-arrhythmic drugs), secondary prevention patients received more appropriate ICD therapy (n=25, 35%, 95 % CI 24-46%) than primary prevention patients (n=25, 21%, 95% CI 14-28%, P<0.05). The 1-year ICD therapy rate in the primary prevention group (although lower than the 27% event rate in the secondary prevention group, P=0.01) was 15% (Figure 1).

Of interest, the time between implant and first appropriate ICD therapy was similar in both groups (group A: 9±6 months; group B: 8±7 months, NS). Furthermore, the cycle length of the first ventricular arrhythmia triggering ICD therapy was the same in both groups (324±107 ms) and the average cut-off rate of the VT detection zone was set at 165±18 bpm in both groups.

Predictors of ICD therapy

No differences were observed in baseline clinical parameters between patients who received appropriate ICD therapy and patients who did not receive therapy. No predictors of ICD therapy

Table 2. Cardiovascular events

	Primary Prevention	Secondary Prevention	All patients
Deaths	4 (3%)	13 (18%)*	19 (9%)
Heart transplantation	1 (1%)	1 (1%)	2 (1%)
Ventricular arrhythmia (VT/VF)	29 (24%)	28 (39%)*	57 (30%)
Appropriate ICD therapy	25 (21%)	25 (35%)*	50 (26%)
Inappropriate shock	6 (5%)	8 (11%)	14 (7%)
Cycle length of first ventricular arrhythmia (ms)	313±69	335±13	324±107
Time to first appropriate ICD therapy (months)	9±6	8±7	9±7
Cut-off rate VT zone (bpm)	164±18	167±19	165±18

Abbreviations as in Table 1.
* P<0.01 compared to primary prevention group

could be identified by multivariate analysis (including etiology, sex, age, QRS duration, LVEF, medication, previous infarction and co-morbidity) in primary prevention patients. In secondary prevention patients however, age (<65 years, HR 0.249, 95% CI 0.066-0.941, P<0.05) and amiodarone usage (HR 0.150, 95% CI 0.040-0.565, P<0.05) were associated with a decreased risk of ICD therapy.

Inappropriate therapy

Fourteen patients (7%) experienced inappropriate shocks (5% primary prevention group, 11% secondary prevention group, NS). The trigger for inappropriate therapy was: atrial arrhythmia in 10 patients, sinustachycardia in 2 patients, T-wave oversensing in 1 and sensing of diaphragm potentials in 1 patient.

Clinical parameters

At baseline, no differences in NYHA class, LVEF and QRS duration were observed between primary and secondary prevention patients. After CRT implantation NYHA class improved ≥1 class in 145 patients (76%) and quality of life score changed from 40±16 to 24±19 (P<0.01). In addition, the exercise capacity improved, as reflected by an increase in 6-minute walking distance from 300±137 m to 403±144 m (P<0.01) after 6 months of CRT. There were no significant differences in clinical outcome parameters between the 2 groups (Table 3).
Accordingly, primary and secondary prevention patients responded equally to CRT therapy (75% vs. 77%, NS).
However, patients with ATP/ shocks had, in contrast to patients without ATP/shocks, a lower response rate to CRT (65% vs. 80%, P<0.025, Table 4). Vice versa, clinical response to CRT resulted in a 69% lower risk of receiving ICD therapy in both groups (HR 0.308, 95% CI 0.099-0.962, P<0.05).

Long-term follow-up

Seventeen (9%, group A: 4 (3%); group B: 13 (18%)) patients died within the 2-year follow-up period. Most deaths were due to end-stage heart failure; 1 patient died after

Table 3. Clinical parameters in primary (n=120) and secondary prevention (n=71) patients

	Primary Prevention	Secondary Prevention	All patients
NYHA class			
Baseline	2.9±0.5	3.0±0.5	2.9±0.5
Follow-up	1.9±0.6*	2.0±0.6*	1.9±0.6*
Quality of life – questionnaire			
Baseline	40±16	39±17	40±16
Follow-up	24±21*	23±16*	24±19*
6-minute hall walk test (m)			
Baseline	297±145	305±123	300±137
Follow-up	401±155*	407±123*	403±144*
Responder	90 (75%)	55 (77%)	145 (76%)

NYHA: New York Heart Association, * P<0.01 compared to baseline parameters

Table 4. Clinical parameters in patients with (n=50) and without (n=141) ICD therapy

	Patients with ICD therapy	Patients without ICD therapy
NYHA class		
baseline	3.0±0.5	2.9±0.5
follow-up	2.1±0.6*	1.9±0.6*
Quality of life - questionnaire		
baseline	41±17	40±16
follow-up	28±16*	23±20*
6 minute hall walk test (m)		
baseline	296±124	301±142
follow-up	385±146*	409±143*
Responder	32 (65%)	113 (80%)†

Abbreviations as in Table 3. * P<0.01 compared to baseline parameters; † P<0.025 compared to patients with ICD therapy

myocardial infarction. No arrhythmic deaths were observed. Two patients underwent heart transplantation.

Despite identical baseline functional status, secondary prevention patients accounted for more deaths than primary prevention patients (18% vs. 3%, P<0.05, Table 2). The 1-year survival was 91% in the secondary prevention group and 99% in the primary prevention group with a 2-year survival of respectively 96% and 79% (Figure 2).

Multivariate analysis revealed advanced age and amiodarone usage as independent predictors of death. Previous ventricular arrhythmias, etiology and response to CRT had however no influence on the relative risk of death. Importantly, ICD therapy was not correlated with lives saved (HR 1.185, 95% CI 0.305-4.598, NS).

The cumulative cardiac event rate including appropriate therapy (ATP/shock), death and heart transplantation is shown in Figure 3. The two curves (primary and secondary prevention

patients) diverge immediately after implant and continue their paths, resulting in a 1-year event rate of 17% in patients without arrhythmias and of 34% in patients with arrhythmias.

DISCUSSION

The main findings of this study were: (1) secondary prevention patients experienced more appropriate ICD therapy, however 21% of the primary prevention patients received appropriate ICD therapy; (2) no predictors of ICD therapy in primary prevention patients could be identified; (3) patients with and without previous ventricular arrhythmias had a similar clinical benefit from CRT; though long-term follow-up showed a higher mortality rate in secondary prevention patients; (4) clinical responders to CRT showed a lower number of ICD therapies compared to non-responders.

ICD therapy

Fifty patients (26%) experienced ventricular arrhythmias resulting in appropriate ICD therapy (ATP and/or shock) within 2 years after implant. As expected, and despite the higher use of amiodarone in the secondary prevention group, secondary prevention patients received significantly more ICD therapy than primary prevention patients (35% vs. 21%). However, the results obtained in the primary prevention group are in line with the results of the MADIT II study (26% ICD therapy in ischemic cardiomyopathy patients, LVEF <30%) (13,17). Also the SCD-HeFT trial (LVEF < 35%, ischemic and non-ischemic heart disease patients) reported an incidence of 21% ICD therapy, though the follow-up period was longer in SCD-HeFT (10). In a retrospective review of 978 CRT-ICD patients of the MIRACLE-ICD trial it was reported that 28% of the secondary prevention patients experienced an appropriate shock at 12 months follow-up, compared to only 14% of the primary prevention patients (18). Reported incidences of appropriate ICD therapy for secondary prevention patients vary from 53% (2-year follow-up) to 82% (10-year follow-up)(19-22). In our study 35% of the secondary prevention patients received ICD therapy within 2 years of follow-up. Furthermore, in line with previous studies, time to first appropriate therapy was similar for both primary and secondary prevention patients (9±7 months) (20,23).

Wilkoff et al reported that the cycle length of ventricular arrhythmias in primary prevention patients is shorter than the cycle length of ventricular arrhythmias in secondary prevention patients (303±54ms vs. 366±71ms, P<0.0001) (18). In part, this difference was explained by the rate-lowering effect of amiodarone, used by 44% of the secondary prevention patients and 23% of the primary prevention patients. In contrast, we found no differences in arrhythmia cycle length between the two groups. Notably, our study contained 22 survivors of ventricular fibrillation, who tended to experience arrhythmias at a faster rate than patients initially treated because of sustained VT.

In this study 23 patients with an ICD (2 primary prevention patients and 21 secondary prevention patients) received an upgrade to a CRT-ICD device. The potential beneficial effect of CRT on ventricular arrhythmias in patients with heart failure is incompletely understood. Some small studies reported a decrease of the number of ventricular arrhythmias after CRT, possibly due to LV reverse remodelling (24-27); however others reported the opposite (28,29). A recently

published meta-analysis of large randomized CRT-trials found no statistically significant effect of CRT on VT/VF occurrence compared to ICD therapy only (30). Due to the relatively small number of patients we were not able to detect a positive effect on VT/VF occurrence of CRT in the group of patients upgraded from ICD only to CRT-ICD.
As ICD therapy is costly and only 21% of the primary prevention patients received appropriate therapy, we tried to identify predictors of VT/VF in this group. However we could not identify predictors of VT/VF in primary prevention patients eligible for CRT.

Response to CRT

The baseline characteristics of both groups were (with the exception of the higher number of ischemic heart disease patients in the secondary prevention group and higher amiodarone usage in this group) more or less identical. Furthermore the efficacy of CRT, as reflected by the improvement of functional status, was similar in both groups, which is in line with the results of larger randomized trials (3,4,6,7,11).
As reported by others, not all patients (46 patients, 24%) responded to CRT. This relatively high number reflected the inability to predict a positive outcome by applying the current inclusion criteria and warrants a further refinement of these criteria (3,31,32). Of interest, response to CRT was associated with a lower risk of receiving ICD therapy.

Mortality

Two-year mortality was 9%. No arrhythmic deaths were observed and most deaths were hear failure related. Large randomized heart failure trials in patients without ventricular arrhythmias reported 2-year mortality rates between 12% and 30%, which is much higher compared to the 4 primary prevention patients who died in this study (2-year mortality rate 4%, Figure 2) (8,10,11,13). Notably, sudden cardiac death accounted for 35% of all deaths in the CARE-HF study (8).
In contrast, the 18% mortality rate observed in secondary prevention patients was comparable to the mortality rate reported by some secondary sudden cardiac death prevention trials (9). Secondary prevention patients were more likely to have ischemic heart disease, more previous myocardial infarctions, more ventricular arrhythmias and a higher amiodarone usage: in other words comprise a sicker patient group. As expected, high age (>65 years) was associated with a higher mortality rate. Furthermore, amiodarone usage was also found to be an independent predictor of death. This is in line with a recent study by Kies et al, who evaluated 300 sudden cardiac death survivors with an ischemic cardiomyopathy. They also reported that amiodarone was associated with a higher mortality (33).

Limitations of the study

This was a non-randomized observational study performed to evaluate outcome differences between different ICD-indication groups which however reflect daily clinical practice. A control group would have underlined our results, however all patients had an LVEF <35% and therefore an indication for ICD implant, as well as an indication for CRT. The primary and secondary prevention groups were not entirely comparable; the secondary prevention group accounted for much more ischemic patients. However, etiology was not identified as an independent predictor for ICD therapy or death.

Power calculation was not performed in this prospective study, because the incidence of ICD therapy in patients with and without prior ventricular arrhythmias was unknown at the start of the study. The sample size of 191 patients may be too small to identify predictors of VT/VF, and explains its inability to predict them. Also, assumption of the clinical efficacy of ICD therapies is needed, since the number of ICD therapies are not correlated with the number of lives saved from SCD. Larger studies are needed to further evaluate these issues.

Conclusions

Despite a higher incidence of VT/VF episodes in secondary prevention patients, 21% of the primary prevention patients did receive appropriate ICD therapy during follow-up and no predictors could be identified before implant. Furthermore, CRT is effective in heart failure patients with and without prior ventricular arrhythmias. Interestingly, patients responding to CRT received less ATP or shocks.

These data suggest that a combined CRT-ICD device should be implanted in all patients eligible for CRT. However, the data also suggest that specificity of the selection criteria for ICD therapy is low and efforts should be made to increase the number of patients who will truly benefit from combined CRT-ICD therapy.

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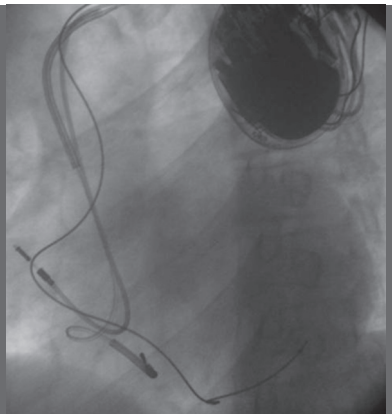
Chapter 16



Intrathoracic impedance monitoring to predict decompensated heart failure

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Based on Am J Cardiol 2006;99:554-7

ABSTRACT

Intrathoracic impedance measurement has been introduced in the Insync Sentry biventricular implantable cardioverter-defibrillator (ICD; Medtronic Inc.), and may permit early identification of pulmonary fluid accumulation secondary to left-sided heart failure. An audible alarm (OptiVol alert) can be triggered when the impedance index rises above a predefined level of 60 Ω·day. The aim of this study was to evaluate the clinical value of OptiVol alert and its prediction for decompensated heart failure. We included 115 consecutive patients (New York Heart Association [NYHA] class 2.8±0.5 and LV ejection fraction 26±8%) who received an Insync Sentry biventricular ICD. When presenting with OptiVol alert, current hemodynamic status was evaluated. During follow-up (9±5 months), there were 45 presentations with OptiVol alert in 30 patients. Only in 15 cases (33%) clinical signs and symptoms of heart failure were present, whereas in the remaining patients clinical signs of heart failure were absent ($P<0.05$). ROC curve analysis showed that increasing the threshold for OptiVol alarm provided a substantial increase in specificity for detection of heart failure, with the optimal cut-off value identified at 120 Ω·day, yielding a sensitivity of 60% with a specificity of 73%. In conclusion, intrathoracic impedance measurement as present in the Insync Sentry biventricular ICD may be a useful tool for monitoring pulmonary fluid status. The proposed threshold for OptiVol alert of 60 Ω·day is very sensitive but not specific for assessment of heart failure; adjustment of threshold settings may yield a superior balance between sensitivity and specificity.

INTRODUCTION

The number of patients with heart failure is increasing exponentially. Much of the medical costs in these patients is related to (re-)hospitalization for decompensated heart failure (1). Therefore, monitoring pulmonary fluid status may be valuable to detect early decompensation, and adjustment of medical therapy may prevent hospitalization. The new generation cardiac resynchronization therapy (CRT) devices (Insync Sentry biventricular ICD, Medtronic Inc, Minneapolis, Minnesota, USA) permit intrathoracic impedance measurements to detect changes in pulmonary fluid status. The feasibility of this device was recently reported by Yu et al. demonstrating an inverse correlation between intrathoracic impedance and pulmonary capillary wedge pressure and fluid balance (2); moreover a decrease in impedance was noted before the onset of patient symptoms and hospital admission for pulmonary fluid overload. Furthermore, an audible alarm (OptiVol alert) can be triggered when a decrease in intrathoracic impedance indicates pulmonary fluid accumulation secondary to left-sided heart failure. Accordingly, these new devices may detect heart failure in the preclinical phase, which may potentially allow adjustment of therapy to prevent heart failure hospitalization. However, the clinical value of this monitoring function has not been shown yet. Therefore, the aim of the study was to evaluate the clinical value of this alarm and its prediction for decompensated heart failure.

METHODS

Patients

One-hundred and fifteen consecutive patients with severe heart failure received an Insync Sentry biventricular ICD. Patients were selected according to the traditional criteria for CRT: advanced heart failure (New York Heart Association [NYHA] class III or IV), depressed left ventricular ejection fraction (LVEF, <35%) and prolonged QRS duration (>120 ms). Patients with atrial fibrillation or previously implanted pacemakers were included.

The study protocol was as follows: before implantation clinical status was assessed and echocardiography was performed to measure LVEF. During follow-up standard out-patient clinic visits and biventricular ICD printouts were scheduled every 3 months. Patients were instructed to visit the hospital in case of OptiVol alert.

Device implantation

A coronary sinus venogram was obtained using a balloon catheter, followed by the insertion of the LV pacing lead. An 8F guiding catheter was used to position the LV lead (Attain-SD 4189, Medtronic Inc., Minneapolis, Minnesota, USA) in the coronary sinus. The preferred position was a lateral or postero-lateral vein (3). The right atrial and ventricular leads were positioned conventionally. All leads were connected to a dual chamber biventricular ICD (Insync Sentry, Medtronic Inc.).

Intrathoracic impedance monitoring

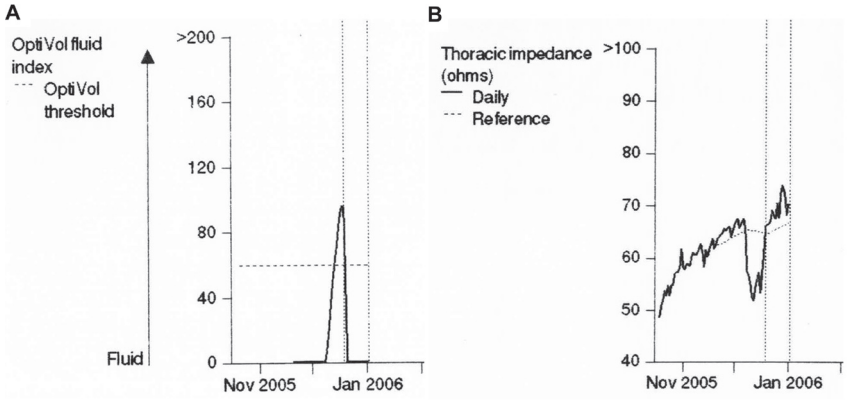
OptiVol fluid status monitoring works by measuring intrathoracic impedance every 20 minutes between 12 a.m. and 5 p.m., using an electrical impulse vector that travels between a lead in the right ventricle of the heart and the pulse generator. As a result the electrical impulse passes through lung tissue. By comparing the daily average impedance values with a reference impedance line, a trend-line can be assessed in the OptiVol fluid index chart (example see Figure 1). Since the device is part of the impedance measurement vector, fluid accumulation in the pacemaker pocket can influence readings; therefore, OptiVol fluid status monitoring is initialized 30 days after device implantation to allow for wound healing.

As fluid accumulates in the patient's lungs, the OptiVol fluid index increases. If the condition is not resolved, and the OptiVol Index crosses a predefined threshold, an observation will be triggered. If enabled, an OptiVol alert will also be audible from the implanted device at a programmed time. When the fluid buildup has been resolved, and the daily impedance value is trending at or above the reference impedance values, the OptiVol fluid index will return to zero.

The OptiVol threshold can be programmed at device implant or at follow-up device checks. In our analysis, the threshold was programmed at the default value of 60 Ω·day, based on clinical data for optimal sensitivity and low false positive rates (4).

Figure 1. Example of OptVol fluid index

Crossing the OptiVol threshold of 60 Ω·day triggers the alert (A). The OptiVol fluid index is calculated by comparing the daily average impedance values with a reference impedance line (B). The impedance decreases prior to the alert and increases after increasing diuretics. If the daily impedance moves above the reference trend, the OptiVol fluid index will reset.



Clinical and biventricular ICD monitoring

During follow-up clinical status and biventricular ICD check up were performed every 3 months in the out-patient clinic. From the biventricular ICD print-outs, OptiVol index trend and thoracic impedance could be determined. Additional visits were planned in case of OptiVol alert. When presenting with OptiVol alert, current hemodynamic status was evaluated by history, drug use, physical examination, laboratory tests and chest X-ray. An alert was assigned as true positive in case of significant heart failure needing medical adjustment and follow-up visits were planned.

Table 1. Patient characteristics (n=115)	
Age (years)	65±11
Gender (M/F)	95/20
NYHA functional class	2.8±0.5
Ischemic etiology (%)	79 (69%)
QRS duration (ms)	151±35
Rhythm (SR/AF/Paced)	97/11/7
LVEF (%)	26±8
LVEDV (ml)	212±77
LVESV (ml)	160±75
Serum-creatinine (µmol/L)	123±47
Medication	
Diuretics	108 (94%)
ACE-inhibitors	105 (91%)
Beta-blockers	81 (70%)
Spironolactone	42 (37%)
Digoxin	26 (23%)

ACE: angiotensin-converting enzyme; AF: atrial fibrillation; EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; LV: left ventricular; NYHA: New York Heart Association; SR: sinus rhythm.

Statistical analysis

Continuous data are presented as mean ± SD; dichotomous data are presented as numbers and percentages. Comparison of data was performed using the unpaired Students *t* test for continuous variables and Fisher's exact test for proportions. The optimal threshold needed to predict decompensated heart failure was determined by receiver operator characteristic (ROC) curve analysis. For all tests, a P-value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

One-hundred and fifteen patients were included in this study (95 men, age 65±11 years). Baseline patient characteristics are summarized in Table 1. Device and lead implantation were successful in all patients without major complications. All OptiVol thresholds were set at 60 Ω·day and an audible alarm was enabled in all patients.

Optivol alert

During follow-up (9±5 months, range 2 to 19 months), there were 49 presentations with OptiVol alert in 33 patients. Two patients had an alert shortly after LV lead repositioning; one patient had a very high index during a pocket infection and one patient presented with an alert 43 days after implant due to slow wound healing. The remaining 45 OptiVol alerts in 30 patients were analyzed. Baseline characteristics between patients with and without (n=85)

Figure 2. Maximum OptiVol Fluid Index (Ω·day) in patients with OptiVol alert with and without signs of decompensated heart failure

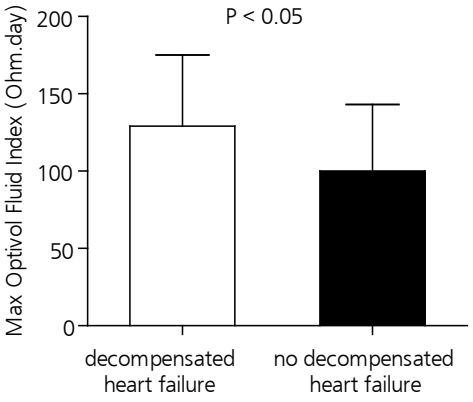
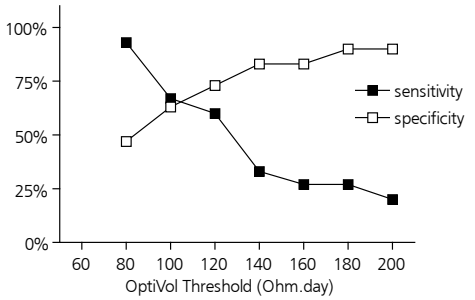


Figure 3. Receiver-operating characteristics curve analysis on the threshold for OptiVol alert (Ω·day) in predicting decompensated heart failure



alert were comparable. The time between implant and OptiVol alert was 238±105 days (range 63 to 512 days). In 5 patients the audible alarm was accidentally disabled, resulting in delay in time between alert and presentation of 6±10 days. Mean maximal OptiVol fluid index was 109±46Ω·day.

True positive vs. false positive alerts

In only 15 alerts clinical signs and symptoms of heart failure requiring medication adjustment were present, whereas in the remaining 30 alerts these clinical signs and symptoms were absent (P<0.05). Only 2 patients with a true positive alert had to be admitted for intravenous therapy. Importantly, no patients were admitted after OptiVol alert for acute decompensation. Of note, the maximum OptiVol index was significantly higher in patients with symptoms of heart failure as compared to patients without symptoms of heart failure (129±46 vs. 100±43 Ω·day, P<0.05, Figure 2). Time between implant and alert, and between alert and presentation respectively, were comparable.

In evaluating the biventricular ICD print-outs no causes for inappropriate elevation of the OptiVol fluid index could be determined.

Prediction of decompensated heart failure

The proposed cut-off value of 60 Ω·day was very sensitive to detect heart failure, but at the cost of a very low specificity. ROC curve analysis (Figure 3) showed that increasing the threshold for OptiVol alert provided a better balance between sensitivity and specificity, with the optimal cut-off value identified at 120 Ω·day, yielding a sensitivity of 60% with a specificity of 73%.

DISCUSSION

The current findings demonstrate that OptiVol intrathoracic impedance measurement may be a useful tool to prevent worsening heart failure symptoms. The proposed threshold for OptiVol fluid alert of 60 Ω·day is very sensitive but at the cost of a low specificity, since more than half of the alerts were false positive. The maximum OptiVol index was significantly higher in patients with symptoms of heart failure as compared to patients without symptoms of heart failure, and consequently, increasing the threshold for OptiVol alert provided a better balance between sensitivity and specificity to predict decompensated heart failure.

Decompensated heart failure is associated with high morbidity, mortality and treatment costs (1). In addition, a considerable delay between onset of symptoms and initiation of therapy exists; for example Evangelista et al reported a mean delay from the onset of worsening symptoms to hospital admission of 3 days, and almost 30% of the patients had a delay exceeding 5 days (5).

Furthermore, decompensated heart failure is often not recognized clinically. Physicians rely on the subjective assessment of clinical examination, exercise tolerance and changes in body weight; however, patients with chronic heart failure may not have marked clinical signs or symptoms at all. Stevenson et al reported a sensitivity of only 58% for the combination of rales, edema and elevated jugular venous pressure to detect a pulmonary capillary wedge pressure ≥22 mmHg in patients with moderate-to-severe heart failure (6).

The ability to monitor pulmonary fluid status may permit early identification of decompensated HF; this may potentially reduce hospitalization rate and improve quality of life. Thoracic fluid status monitoring was first tested in the Medtronic Impedance Diagnostics in Heart Failure Trial (MID-HeFT) (2). The study enrolled 33 patients with NYHA class III or IV, scheduled for implantation of an ICD. Nine patients had 24 hospitalizations for heart failure during a mean follow-up of 20 months. Analysis revealed that the impedance was on average 18±10 days (range 3 to 42 days) below the reference value before admission with decompensated HF occurred. A threshold of 60 Ω·day for impedance was proposed to identify patients who have a high likelihood to develop decompensated heart failure with the need for hospitalization, yielding a sensitivity of 77% (2).

Furthermore, preliminary results in 5 patients demonstrated a good relation between the reduction in pulmonary capillary wedge pressure after treatment for acute decompensated heart failure on the one hand, and the rise in intrathoracic impedance on the other hand ($r=-0.61$, $P<0.001$).

We evaluated the clinical value of the OptiVol fluid monitoring feature in a prospective setting, and with the use of the proposed threshold of 60 Ω·day, we detected 45 alerts during follow-up. However, most alerts occurred in absence of heart failure symptoms. As can be observed from Figure 3, a low detection threshold was very sensitive for prediction, but at the cost of a low specificity. Conversely, when using a higher threshold, a substantial increase in specificity is noted, but with a drop in sensitivity. In conclusion, with the proposed cut-off value for the OptiVol threshold of 120 Ω·day, a reasonable balance between sensitivity and specificity is obtained, although this cut-off value needs further testing in prospective, larger studies. Still, the initial results are promising and are relevant to an increasing number of heart failure patients who are being considered for device therapy.

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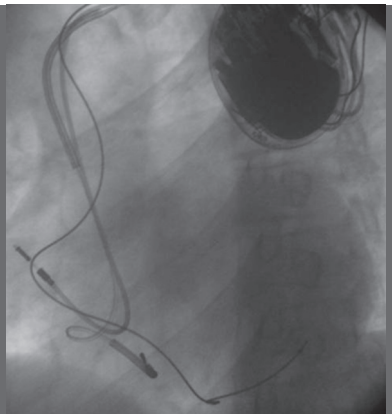
Chapter 17



Non-invasive imaging in cardiac resynchronization therapy – part 2: follow-up and optimization of settings

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ABSTRACT

Cardiac resynchronization therapy has become a therapeutic option for drug-refractory heart failure. Several non-invasive imaging techniques play an increasingly important role before and after device implantation. This review highlights the acute and long-term CRT benefits after implantation as assessed with echocardiography and nuclear imaging. Furthermore, optimization of CRT settings, in particular atrioventricular and interventricular delay, will be discussed using echocardiography and other (device-based) techniques.

INTRODUCTION

Despite the impressive results of cardiac resynchronization therapy (CRT) in the large clinical trials, a consistent percentage of patients failed to benefit when the current selection criteria (New York Heart Association [NYHA] class III or IV, left ventricular ejection fraction [LVEF] <35% and QRS duration >120 ms) were used, the so-called "non-responders". Pre-implantation selection of patients who will respond is still difficult. An extensive review on non-invasive imaging techniques addressing these selection issues before implantation, mainly focusing on the identification of responders, is provided in part 1 of this review (1).
Next to prediction of CRT response, imaging techniques can evaluate the effects of CRT, such as improvement in LV function, and changes in myocardial perfusion and oxidative metabolism. In addition, incorrect pacemaker programming may impair CRT response.
This review discusses short and long-term echocardiographic changes, as well long-term benefit as determined with nuclear imaging. Next, optimization of settings after implantation will be addressed.

A. BENEFICIAL EFFECTS AFTER CRT

Echocardiography to assess immediate effects of CRT

The immediate effects on hemodynamics and systolic function of the LV have been demonstrated by various studies (2,3). Improved LV function is reflected by an immediate reduction in LV end-systolic volume (ESV), whereas LV end-diastolic volume (EDV) remains unchanged (resulting in an increase in LVEF). Importantly, this effect disappeared immediately when the device was turned off again (4).
The acute impact of CRT on diastolic function is not fully understood. Nevertheless, Waggoner et al studied 41 heart failure (HF) patients and demonstrated that besides increased LV function, improved diastolic filling and lower filling pressures were noted; however E/A ratio remained unchanged (5). Interestingly, the benefits in diastolic function were dependant on LV filling characteristics before CRT implantation; patients with a mitral E/A ratio >1 demonstrated improvements in LV diastolic filling and lower filling pressures whereas those with an E/A ratio <1 did not show significant changes in diastolic indices. In addition, Yu et al demonstrated that cessation of biventricular pacing was associated with an immediate loss of benefit in increased LV filling time (6).
In addition, echocardiographic studies demonstrated that some patients exhibit an immediate reduction in mitral regurgitation after CRT (4,7,8). Breithardt et al evaluated 24 HF patients with functional mitral regurgitation and reported that the effective regurgitant orifice area decreased from 25±19 mm^2 to 13±8 mm^2 ($P<0.001$) immediately after CRT initiation and was related with an acute increase in LV dP/dt (4). Another small study by Ypenburg et al evaluated 25 patients after showing an acute reduction in vena contracta width by CRT (from 0.54±0.15 cm to 0.39±0.13 cm, $P<0.001$) (7). The mechanism underlying the reduction was studied with radial strain imaging at the level of the papillary muscles. A significant mechanical delay between the posterolateral and the anterolateral papillary muscles was demonstrated

at baseline (169±69 ms), which was reduced immediately after CRT implantation (25±26 ms, P<0.001), indicating that resynchronization of the papillary muscles acutely restored valvular competency. Moreover, interruption of biventricular pacing after 6 months resulted in desynchronization of the papillary muscles and recurrence of mitral regurgitation.

Echocardiography can also be useful in assessing the extent of resynchronization immediately after implantation (6,9). A recent study by Bleeker et al evaluated 100 HF patients according the current selection criteria including substantial LV dyssynchrony of ≥65 ms as assessed with tissue Doppler imaging (10). Immediately after CRT a reduction in LV dyssynchrony was noted from 114±36 ms to 40±33 ms (P<0.001). However, despite the presence of LV dyssynchrony at baseline, 15 patients showed no evidence of reverse remodeling (>10% reduction in LVESV after 6 months of CRT). Interestingly, the 15 non-responders showed no significant reduction in LV dyssynchrony after CRT initiation. The extent of resynchronization immediately after CRT appeared to be predictive for echocardiographic response after 6 months. The mechanisms underlying failure to resynchronize are not entirely clear, but a suboptimal position of the LV pacing lead (11) or the presence of scar tissue in the area of the LV pacing lead (12) may result in lack of resynchronization and consequently absence of response to CRT. Of note, the precise influence of biventricular pacing on the TDI velocity curves is currently unknown.

Echocardiography to assess late effects of CRT

Large clinical trials have shown that these acute effects are accompanied by an improvement in LV function at mid-term follow-up (13-16). Smaller studies have even proposed that the improvement in LV function will further improve over time. Yu et al evaluated 25 HF patients with NYHA III or IV, LVEF <40%, QRS duration >140 ms and performed serial echocardiographic acquisitions after device implantation. LV function improved gradually from 28±10% to 34±13%, and 40±15% after respectively one day and 3 months (both P<0.05 vs. baseline) Interestingly, cessation of pacing caused an immediate decrease in LVEF to 34±13% with a further reduction to 30±12%, P<0.01 (6) (Figure 1). However, large clinical trials reported a more modest improvement in LVEF; for example, sub-analysis of 228 CRT patients of the MIRACLE showed an improvement in LV function from 24±7% to 29±9% (P<0.05) (17). This improvement persisted up to 12 months after implantation, with a further improvement to 31±11% after 12 months of CRT (P<0.05 vs. 6 months). Interestingly, the authors suggested that this ongoing improvement was partially related to underlying etiology; the ischemic

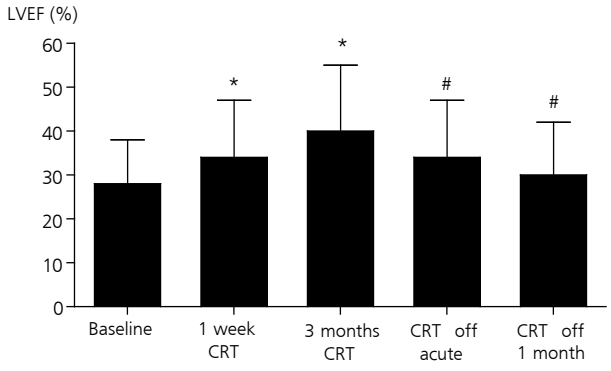


Figure 1. Time course of LV function after CRT

Changes in LV function following CRT in 25 heart failure patients. A gradual increase in LV ejection fraction (LVEF) was noted (* P<0.05 vs. baseline). After cessation of pacing at 3 months follow-up, a gradual decline in LVEF was observed (# P<0.05 vs. baseline). Adapted from Yu et al (6).

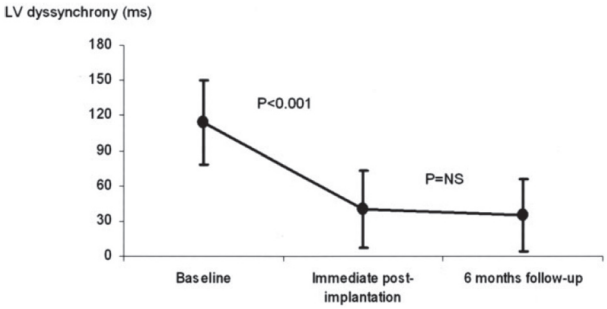


Figure 2. Time course of LV resynchronization after CRT

Immediately after CRT, tissue Doppler imaging demonstrated a reduction in LV dyssynchrony from 114±36 ms to 40±33 ms. After 6 months follow-up, the reduction in LV dyssynchrony was sustained with an LV dyssynchrony of 35±31 ms (P=0.14 vs. immediately after implantation). Adapted from Bleeker et al (10).

patients exhibit a gradually improvement in LV function, whereas the improvement occurs immediately in patients with non-ischemic cardiomyopathy.

LV reverse remodeling can be demonstrated with a reduction in both end-systolic and end-diastolic volumes. For example, the MIRACLE ICD trial showed a median decrease in LVESV of 20 ml and a decrease in LVEDV of 22 ml, which reflects a reduction of ~10% (18). In addition, reverse remodeling is clinically relevant; Yu et al demonstrated in 144 CRT-recipients that a reduction of >10% in LVESV is clinically important as a predictor of event-free survival after 12 months of follow-up (19). This observation underlines the importance of evaluating LV volumes as an outcome measurement for response to CRT.

Reverse remodeling may also lead to a reduction in mitral regurgitation. For instance, the MIRACLE trial reports a reduction in jet area of approximately 30% after 6 months of CRT (16). Porciani et al focused specifically on patients showing improvement in mitral regurgitation after 6 months of CRT (n=19) and related the improvement to a reduction in annular dimensions as well as a more coordinated contraction of the LV (20).

In addition, Bleeker et al demonstrated beneficial effects of CRT on right ventricular (RV) chamber size and tricuspid regurgitation (21). After 6 months of CRT both the RV short-axis and long-axis decreased from 29±11 mm to 26±11 mm and from 89±11 mm to 82±10 mm respectively (both P<0.001). In addition, a reduction in severity of tricuspid regurgitation was noted (from grade 1.8±0.8 to 1.3±0.9, P<0.001) as well as a decrease in pulmonary artery pressure (from 40±12 mmHg to 30±11 mmHg, P<0.001). The precise mechanism underlying the beneficial effects on the RV is not fully understood, but the authors suggest that the sustained improved LV performance may have led to a reduction in pulmonary artery pressure, resulting in an improved RV function (as evidenced also by a reduction in tricuspid regurgitation).

Regarding diastolic function, CRT studies with long-term follow-up also report increases in diastolic filling-time, decreases in E-wave velocity but an unchanged E/A ratio (16,22,23).

Lastly, LV resynchronization remained at long-term follow-up after CRT. The previously mentioned study by Bleeker et al reported an immediate decrease in extent of LV dyssynchrony after CRT initiation (from 114±36 ms to 40±33 ms, P<0.001) that remained at longer follow-up (35±31 ms, NS vs. post-implantation, Figure 2) (10).

Nuclear imaging to evaluate long-term effects of CRT

Positron emission tomography (PET) is currently the only imaging modality that permits absolute quantification of physiologic processes including myocardial blood flow (MBF),

glucose metabolism and oxidative metabolism. Various studies have used this technique to evaluate the effects of CRT on these physiologic processes (Table 1).

Seven PET studies evaluated the effects of CRT on MBF (24-30). Most studies demonstrated an abnormal distribution pattern of MBF at in HF patients at baseline. None of the studies was able to demonstrate an improvement in global MBF after CRT, but several studies demonstrated are more homogeneous distribution of MBF after CRT. For example, Knaapen et al evaluated

Table 1. Positron emission tomography studies evaluating effects of CRT

Authors	No. of patients	Radionuclide	Parameters	Effects with CRT
Neri et al. (24)	8	^{13}N-ammonia ^{18}F-deoxyglucose	MBF at rest Glucose uptake	No effect on MBF Septal glucose uptake increased
Ukkonen et al. (31)	8	^{11}C-acetate	MVO_2 at rest	No effect on global MVO_2, but regional MVO_2 became more homogenous Myocardial efficiency improved
Nielsen et al. (25)	14	^{13}N-ammonia	MBF at rest	No effect on global and regional MBF
Sundell et al. (26)	10	^{15}O-water ^{11}C-acetate	MBF at rest and during adenosine MVO_2 at rest and during dobutamine	No effect on global and regional MBF, No effect on global MVO_2 Myocardial efficiency improved, Stress MVO_2 enhanced
Braunschweig et al. (27)	6	^{11}C-acetate ^{11}C-acetate	MBF at rest and during dobutamine MVO_2 at rest and during dobutamine	No effect on resting MBF No effect on resting MVO_2, Stress MVO_2 enhanced
Nowak et al. (28)	14	^{15}O-water	MBF at rest	No effect on regional and global MBF
Nowak et al. (33)	15	^{18}F-deoxyglucose	Glucose uptake	Septal glucose uptake increased
Knaapen et al. (29)	14	^{15}O-water	MBF at rest and during exercise	No effect on global MBF, but regional MBF became more homogenous
Knuuti et al. (73)	10	^{15}O-water	RV MVO_2 at rest and during dobutamine	No effect on resting RV MVO_2, Stress RV MVO_2 enhanced High RV MVO_2 reflected non-responders
Lindner et al. (32)	16	^{11}C-acetate	MVO_2 at rest	No effect on global MVO_2, but regional MVO_2 became more homogenous; Myocardial efficiency increased
Lindner et al. (30)	42	^{11}C-acetate	MVO_2 at rest MBF at rest	No effect on global MVO_2 and MBF, but regional MVO_2 and MBF became more homogenous

CRT: cardiac resynchronization therapy; MBF: myocardial blood flow; MVO2: myocardial oxygen consumption; RV: right ventricular

14 HF patients and demonstrated higher MBF in the lateral wall as compared with the septum, evidenced by a septal/lateral flow ratio of 0.77±0.27. After 3 months of CRT, blood flow tended to decrease in the lateral wall, with a consequent increase in the septal/lateral flow ratio to 0.97±0.34, indicating almost homogeneous flow distribution. Similar findings were reported by Lindner et al (30).

In addition, five studies used ^{11}C-acetate PET to assess oxidative metabolism. These studies uniformly showed no change in global LV oxidative metabolism, but did show increased myocardial efficiency, indicating improved oxygen cost of forward work by CRT. For instance, Ukkonen et al investigated the effect of CRT on myocardial oxidative metabolism and efficiency in 8 patients with severe HF during atrial pacing (control) and biventricular pacing (31). The authors reported a significant improvement in LV function (stroke volume index increased by 10%, P=0.011) with CRT, without a change in global myocardial oxidative metabolism (MVO_2 index 0.042±0.003 vs. 0.041±0.006, P=0.86). In addition, a more homogenous distribution was noted, as evidenced by a significant increase in septal/lateral wall ratio. Two studies by Linder et al found similar homogenization throughout the LV after CRT (30,32).

Changes in myocardial glucose uptake have been evaluated in two studies (24,33). HF patients with depressed LV function and LBBB exhibit reduced glucose utilization in the septum with a normal blood flow (34). Nowak et al evaluated 15 non-ischemic HF patients at baseline and after 2 weeks of CRT using ^{F18}-fluorodeoxyglucose (FDG) PET. After CRT, glucose utilization decreased in the lateral wall, with an increase in the septum, resulting in homogeneous distribution of FDG uptake (the septal/lateral ratio for FDG uptake was 0.62±0.12 before CRT and increased to 0.91±0.26 after CRT, P<0.01).

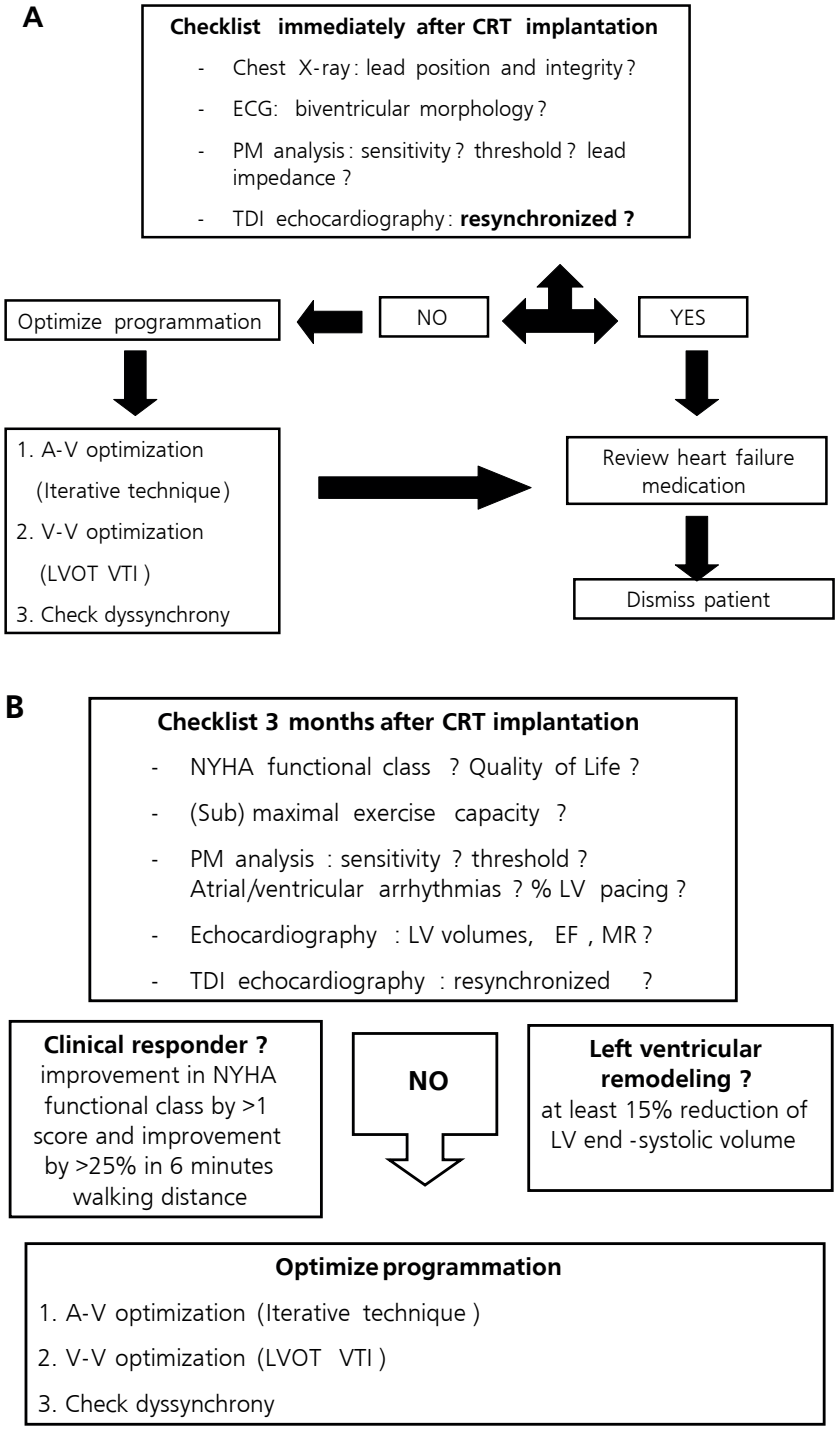
Lastly, single photon emission computed tomography (SPECT) imaging with ^{123}I-metaiodobenzylguanidine (MIBG) can be used to evaluate cardiac innervation and denervation. In patients with chronic HF, hyperactivity of the sympathetic nervous system is observed with an increase in plasma norepinephrine. This hyperactivity is unfavorable and may result in desensitization and down regulation of myocardial ß-adrenoceptors with further impairment of cardiac performance and poor outcome. It has been shown that patients with HF have reduced MIBG uptake as compared to normal individuals. At present, only one small study evaluated the effect of CRT on the neurohormonal system (35). Erol-Yilmaz and colleagues demonstrated increased MIBG uptake after six months of CRT in 13 HF patients, possibly suggesting increased cardiac innervation (36).

B. OPTIMIZATION OF SETTINGS

Biventricular pacing has two primary (electrical) effects on the heart; the first effect is the change in A-V interval, which influences the timing of atrial contraction relative to both preceding and subsequent QRS complexes. The second effect causes a change in coordination of ventricular contraction (V-V intervals). Optimization of both settings can be performed immediately after device implantation as well as during follow-up; Figure 3 provides schematic suggestions of follow-up algorithms. It should be emphasized that it is unknown when, and in which order (A-V versus V-V), optimization should take place.

Figure 3. Follow-up after CRT

Schematic suggestions on follow-up after CRT. A. Immediately after device implant; B. At mid-term follow-up.



A-V optimization

The A-V interval during A-V sequential pacing influences LV systolic performance by modulating the preload (Figure 4). Programming of the A-LV delay remains important because if programmed poorly, it has the potential of curtailing the beneficial effects of CRT. In acute studies, A-V optimization significantly improved LV dP/dt max and stroke volume. A-V optimization will not convert a non-responder to a responder, but may convert an under-responder to improved status. The optimal A-V delay in CRT patients exhibits great patient to patient variability (2,37). The long-term consequences of programming the A-V delay to promote fusion of intrinsic conduction over the right bundle branch with the LV paced complex are unknown. Furthermore, several studies suggested that the optimal A-V delay changes with time (38-41). How to program the A-V delay on exercise (technically difficult and inconvenient) remains unclear. There is preliminary evidence in an acute study suggesting that the short sensed A-V delay at rest should be prolonged during exercise to achieve optimal LV systolic performance (42). Although A-V delay optimization improves the acute hemodynamic response after CRT (43), and may improve long-term clinical outcomes (2,37), to date, only one randomized trial compared the outcome in patients with an echocardiographic optimized A-V delay to patients with an empiric delay of 120 ms (44). Optimal A-V delay was defined as the A-V delay associated with the largest average aortic Doppler VTI (see below). The optimal A-V delay varied widely from 60 to 200 ms, with a mean of 119 ms, practically identical to the empiric delay of 120 ms.

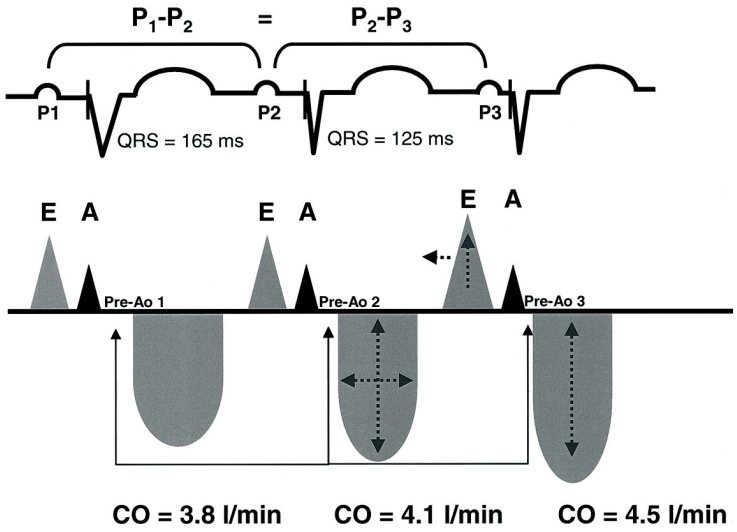


Figure 4. A-V delay

Consequences of optimization of A-V delay during biventricular pacing at stable heart rate. The QRS complex resulting from P1 is wide due to apical right ventricular pacing (165 ms). The aortic pre-ejection time interval (Pre-Ao1) is long; the aortic systolic phase is also long due to the wide QRS complex. The second QRS complex resulting from P2 is narrowed due to biventricular pacing leading to a shorter aortic pre-ejection time interval (Pre-Ao2) compared with Pre-Ao1. Consequently, time duration of the aortic systolic phase is reduced, and the E-wave corresponding to P3 occurs earlier (compared to P1 and P2) with a greater amplitude, indicating a better LV filling phase. Pre-Ao3 is even shorter than Pre-Ao2 due to the addition of an A-V delay optimization during P3, resulting in a greater cardiac output (CO) during P3 compared with the one obtained during P2, in which biventricular pacing was delivered without A-V delay optimization. Adapted from Bax et al (42).

Patients with optimized A-V delay showed greater immediate improvement in LVEF (7.8±6.2% vs. 3.4±4.4%, P<0.02) and more improvement in NYHA class after 3 months of CRT (1.0±0.5 vs. 0.4±0.6, P<0.01). However, no differences in echocardiographic outcome or clinical events as hospitalization or death were noticed at 3 months.

Optimized A-V synchrony is achieved by finding the A-V delay setting that provides the best left atrial contribution to LV filling, the maximum stroke volume, shortening of the isovolemic contraction time, and the longest diastolic filling time in absence of diastolic mitral regurgitation (in patients with a long PR interval) (42). Traditionally, Doppler echocardiography has been used for A-V optimization in DDD(R) pacemakers and still is widely used in CRT patients for acute and long-term assessment. Non-echocardiographic techniques include device-based automated algorithms as well as impedance cardiography and plethysmography and are discussed below (45-47).

Echocardiography to optimize A-V delay

Doppler echocardiographic methods for A-V optimization in CRT patients vary substantially in performance. They include analysis of mitral, LV outflow tract and aortic blood flow velocity profiles using conventional pulsed and continuous wave Doppler techniques and determination of the maximal rate of LV systolic pressure increase (LV dP/dt max) derived from the continuous wave Doppler profile of mitral regurgitation. At a minimum, one has to ensure the absence of E and A wave fusion or A wave truncation in Doppler transmitral flow recordings.

1. Ritter's technique. The Ritter mitral inflow technique was originally described for patients with A-V block and has often been used for A-V optimization in CRT patients (48,49). The method is based on the premise that LV diastolic filling is optimized when mitral valve closure due to LV systole, coincides with the end of the Doppler A wave. This approach provides the longest diastolic filling time and allows completion of atrial systole prior to ventricular contraction. It must be used cautiously in CRT patients; in patients with a normal or short PR interval (<150 ms), the second part of the Ritter protocol cannot ensure biventricular pacing with a long A-V delay due to intact intrinsic conduction. Other limitations include difficult interpretation in high heart rates and limited visualization of the truncated A wave in patients with increased LV end-diastolic pressure due to A wave attenuation or abbreviation. Importantly, there is mounting evidence that it may not represent the maximum achievable hemodynamic benefit (50).

2. Iterative technique. This method uses pulsed-wave Doppler imaging of the mitral inflow. The iterative method is performed as follows: 1) programming a "long" A-V delay, slightly shorter than the intrinsic A-V interval; 2) shortening the A-V delay by 20 ms increments until the A-wave is truncated, and 3) prolonging the A-V delay in 10 ms increments until A-wave truncation is eliminated (51). The iterative method provides maximal separation of the E and A waves and the longest diastolic filling time.

3. Doppler-derived velocity-time integral of the LV outflow tract. This widely used method uses 2D echocardiography (in the parasternal long-axis view) to measure the diameter of the LV outflow tract together with pulsed-wave Doppler interrogation of the LV outflow tract (in apical long-axis view) to obtain its blood flow velocity profile. This yields the velocity-time integral (VTI) of blood flow which is a surrogate of stroke volume. Measuring the diameter of the LV outflow tract allows calculation of its cross-sectional area by assuming it is circular. The product of the cross-sectional area and the VTI determines the Doppler derived stroke volume

(42-44,50,52-57). A-V delay optimization with Doppler echocardiography is often done by assessing the VTI without measuring the stroke volume and cardiac output. The optimal A-V delay is associated with the largest average LV outflow tract VTI is directly proportional to stroke volume and correlates well with invasive hemodynamic data. Obtaining LV outflow tract VTI measures under different A-V delays requires a skilled operator, maintenance of constant position of the transducer and Doppler interrogation site, a cooperative patient for a long study, and quantification of the Doppler VTI by tracing numerous blood flow velocity envelopes. Small changes in the angle of incidence between the outflow jet and the ultrasound

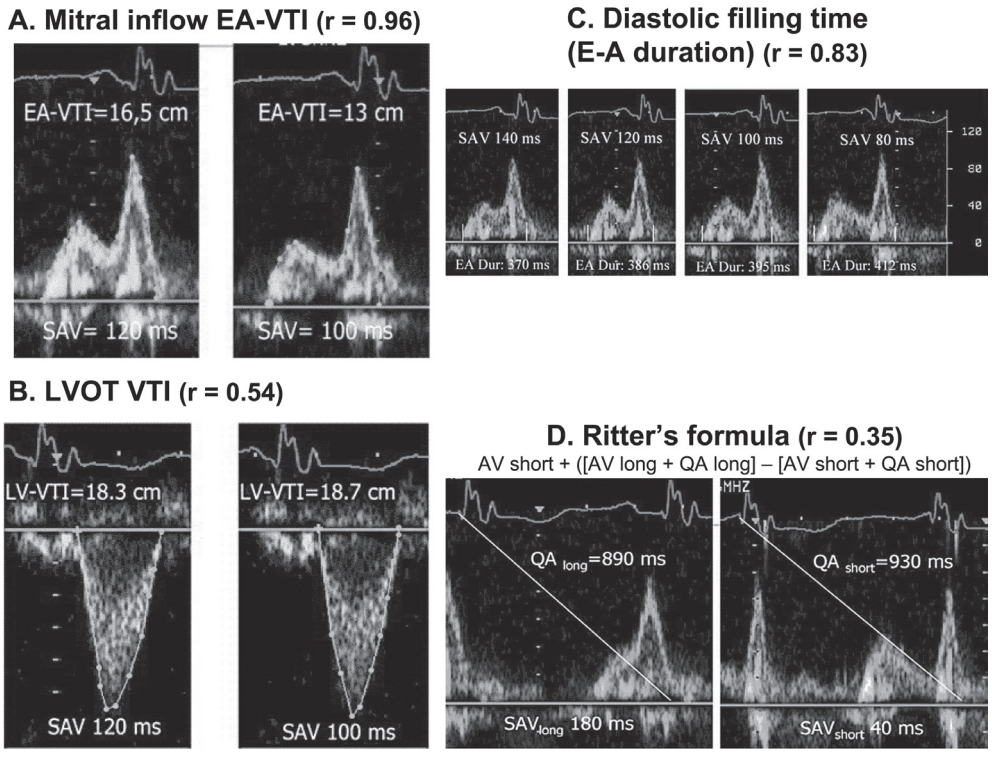
Figure 5. Comparison of several echocardiographic techniques for A-V delay optimization

A. Velocity-time integral (VTI) of transmitral flow (EA VTI) at 2 consecutive sensed A-V delays (SAV). The values are the average of 4 heart beats. Note the clear difference in EA VTI value with change in the sensed A-V delay.

B. EA duration of 4 different sensed A-V delays (SAV). Shortening of the sensed A-V delay increased the EA duration by progressively separating the E and A waves. At 80 ms, the A wave is abbreviated, therefore the optimal A-V delay by EA duration is 100 ms. This example illustrates the difficulty in judging A wave abbreviation.

C. Example of the VTI of the left ventricular outflow tract (LV VTI) at 2 adjacent sensed A-V delays (SAV). The LV VTI is averaged from 4 beats. Note panel and right panels represent, respectively, long and short sensed A-V delays (SAV). The corresponding QA time (time from the onset of electrical activation until the end of the A wave) is measured and the small difference in outcome.

D. Ritter's formula for optimizing A-V delay. The left optimal A-V delay calculated as A-V short + ([A-V long + QA long] – [A-V short + QA short]). In this example, the derived optimal A-V delay is 140 ms. Adapted from Jansen et al (50).



transducer or a small miscalculation of the outflow tract dimension can introduce significant error into the calculation of LV stroke volume. Even if VTIs are measured with great care and optimal equipment settings, interobserver variability is at least 10% (58). Accordingly, it could be suggested that VTI changes should be at least 10% before reprogramming the device.

4. Doppler-derived velocity-time integral of the diastolic transmitral flow. Jansen et al recently investigated the most hemodynamically appropriate A-V delay in 30 HF patients <24 hours after CRT device implantation (50). Doppler optimization of A-V delay was correlated with the optimal sensed A-V delay determined by LV dP/dt max measured invasively. The Doppler methods included the VTI of the diastolic transmitral flow (E-A VTI), diastolic filling time (E-A duration), the VTI of the LV outflow tract or aorta and Ritter's formula (Figure 5). Measurement of the maximal VTI of mitral inflow was found to be the most accurate method compared with the invasive LV dP/dt max index. The optimal A-V delay with the E-A VTI method was concordant with LV dP/dt max in 29 of 30 patients (r = 0.96), with E-A duration in 20 of 30 patients (r= 0.83), with LV VTI in 13 patients (r = 0.54), and with Ritter's formula in none of the patients (r = 0.35).

5. LV dP/dt max determination. LV dP/dt max can be measured non-invasively from continuous-wave spectral Doppler recordings of mitral regurgitation (59). This methodology involves measuring the time for the mitral regurgitant velocity to increase from 1 m/s to 3 m/s (Figure 6). The dP/dt max index is equal to 32 divided by this time difference. Of note, this method is feasible only when substantial mitral regurgitation is present.

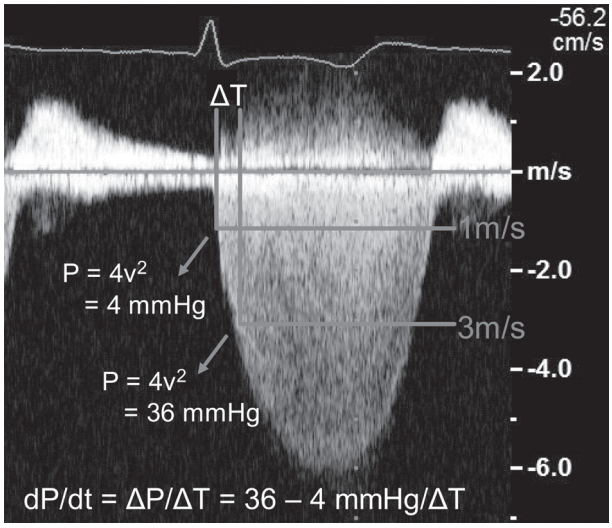


Figure 6. Doppler dP/dt measurement

Doppler-derived dP/dt determined by measuring the time difference (ΔT) between two points on the continuous-wave mitral regurgitation spectral signal corresponding as indicated to 1 m/s and 3 m/s. These points correspond to pressure gradients between the left ventricle and left atrium of 4 mmHg and 36 mmHg according to the modified Bernoulli equation (ΔP=4v2). dP/dt is determined by this change in pressure (32 mmHg) divided by the time difference. P: pressure, T: time, v: velocity.

Non-echocardiographic techniques for A-V optimization

1. ExpertEase (Boston Scientific, St. Paul, Minnesota, USA) uses intracardiac electrograms (IEGM). The IEGM method is based on the measurement of electrical conduction delays (i.e., A-V interval and QRS duration) to determine the optimal A-V delay that provides maximum hemodynamic response. The rationale of the algorithm is that ventricular resynchronization is maximally achieved when there is optimal fusion between intrinsic activation through the

septum (typically from the right bundle branch) and the paced activation of the late-activated region. Optimal fusion maximizes the contribution of intrinsic activation with resynchronization, increases the rate of LV contraction and improves LV synchrony compared with intrinsic activation alone or free wall only initial activation. The ExpertEase IEGM method provides a fast, simple, less expensive, yet accurate determination of A-V timing that may obviate the need for more costly and time-consuming echocardiographic studies. A device-based IEGM optimization method can also be used to monitor and readjust the A-V delay continuously and/or automatically. This method is currently applicable for patients with QRS ≥120 ms, sinus rhythm, a functional A-V node, and an intrinsic A-V interval ranging from 100 to 400 ms (60).

2. Aucoustic cardiography (Audicor, Inovise Medical, Inc., Portland, Oregon, USA) uses a different approach and measures systolic time intervals by recording abnormal diastolic heart sounds using a simultaneously recorded ECG and cardiac acoustical data. A specific systolic time interval, the electromechanical activation time (EMAT), is measured as the time from the onset of the Q wave to the mitral component of the S1. The S1 heart sound consists of acoustic energy from closure of both the mitral and tricuspid valves; the mitral valve component of S1 can be identified through its higher frequency component profile, so Audicor uses the first, most prominent high frequency component of the S1 as the marker for mitral valve closure. The EMAT interval reflects the time required in ms for the LV to generate sufficient force to close the mitral valve. EMAT has been used successfully to optimize A-V delays (61,62). Since EMAT is a measure of contractility, the delay exhibiting the shortest EMAT is considered optimal. Until now only small studies have been published using this technique. Zuber et al tested this method in 20 patients (58). Acoustic cardiography may offer some advantages compared to echocardiography. First, the advantage of analysing and averaging data obtained during 10 sec (usually around 12 heart beats) and not just one heart beat. Second, the time required to perform an optimization using acoustic cardiography is shorter than that required for echocardiography which may become even more important if more delay combinations are tested.

3. Pulse pressure strategies (Finapress, Finapress Medical Systems, Arnhem, The Netherlands) use non-invasive continuous blood pressure measurement during device optimization by choosing the setting producing the highest blood pressure. Whinnett et al applied this continuous finger photoplethysmography technique, to detect direct hemodynamic responses during adjustment of the A-V delay, at different heart rates (45). They found that that even small changes in A-V delay have a significant effect on blood pressure. The peak value varies between individuals, is highly reproducible, and is more pronounced at higher heart rates than resting rates. The same non-invasive finger photoplethysmography technique can also be used to measure aortic pulse pressure changes. The magnitude of finger photoplethysmography changes were strongly correlated with positive aortic pulse pressure changes (46). Photoplethysmography changes selected 78% of the patients having positive aortic pulse pressure changes to CRT and identified the A-V delay giving maximum aortic pulse pressure change in all selected patients.

Interventricular (V-V) interval optimization

Contemporary CRT devices permit programming of the interventricular (V-V) interval usually in steps from +80 ms (LV first) to -80 ms (RV first) to further optimize LV hemodynamics, such as LV dP/dt or aortic VTI. Programming the V-V interval is guided by the same techniques as A-V

delay optimization, and one must avoid right ventricular anodal stimulation which effectively eliminates the V-V delay.

Determination of the extent of residual LV dyssynchrony after V-V programming requires more sophisticated techniques such as tissue Doppler imaging and strain (rate) imaging. V-V programming is additive to A-V delay optimization. V-V programmability may partially compensate for less than optimal LV lead position by tailoring ventricular timing and may also correct for individual heterogeneous ventricular activation patterns commonly found in patients with LV dysfunction and HF.

As with A-V optimization, V-V programmability shows a heterogeneous response with great patient to patient variability of the optimal V-V delay (63,64). The optimal V-V delay also changes over time necessitating frequent readjustments (38,40). A recent study comparing the optimal V-V interval at rest and exercise demonstrated differences in >50% of patients (65).

Although V-V programmability produces a rather limited improvement in LV function or stroke volume, a positive response is important in patients with a less than desirable response to CRT (Figure 7). The optimal V-V delay was recently shown to decrease LV dyssynchrony in some patients (Figure 8) (66) with the potential of improving LV function, and also reduce mitral regurgitation (65), but overall improvement appeared only moderate. In the large InSync III trial, optimization of the V-V interval produced a modest increase (median 7.3%) of stroke

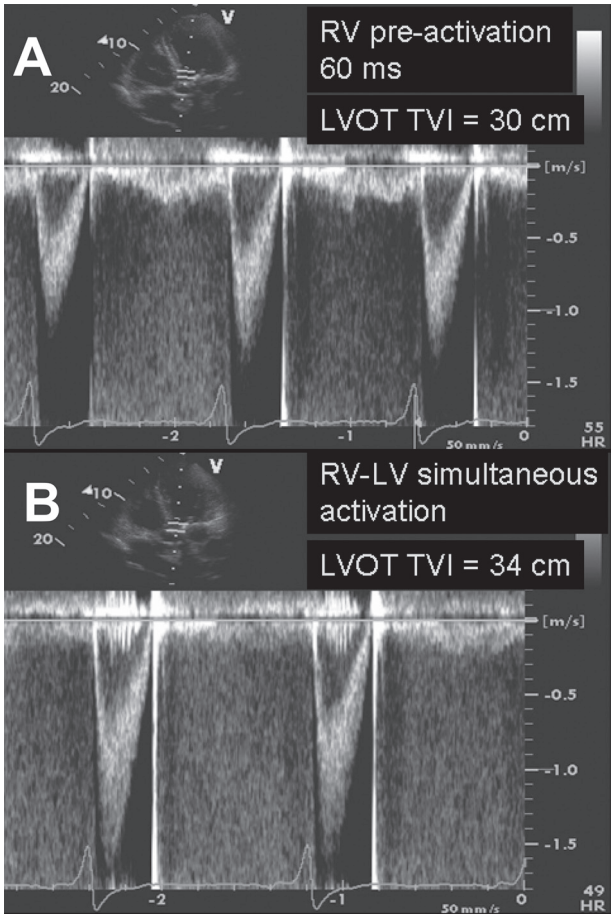


Figure 7. V-V optimization and velocity-time integral

LVOT TVI is substantially lower with RV pre-activation by 60 ms (A) compared to simultaneous RV-LV activation (B).

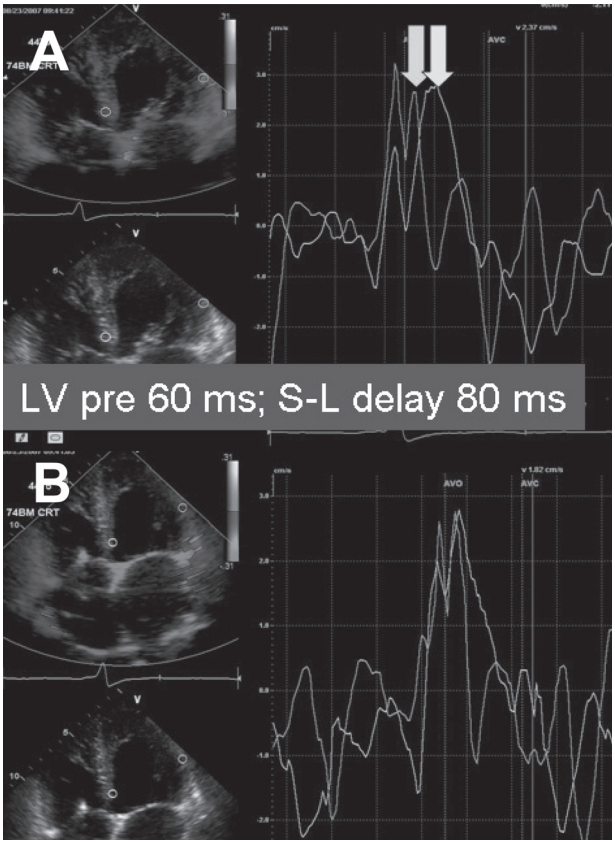


Figure 8. V-V optimization and LV dyssynchrony

Septal-to-lateral delay as marker for LV dyssynchrony assessed by tissue Doppler imaging (S-L delay) was 80 ms with LV pre-activation of 60 ms (A) but shortened to 10 ms after VV setting was changed to simultaneous V-V activation (B).

volume above that achieved during simultaneous CRT in 77% of patients (67). There was no additional improvement in NYHA class or quality of life compared to the simultaneous CRT group. However, patients receiving sequential CRT demonstrated greater exercise capacity. The DECREASE-HF trial is the first randomized, double-blind study comparing simultaneous and sequential CRT (as well as left ventricular pacing only). Preliminary results of the trial in 306 patients did not show any advantage of optimized sequential pacing over simultaneous pacing as concerns improvement in ventricular volumes and systolic function after 6 months (68). However, the V-V interval was not optimized according to hemodynamic response as it was programmed on the basis of baseline intrinsic conduction.

The range of optimal V-V delays is relatively narrow and most commonly involves LV pre-excitation by 20 ms. RV pre-excitation should be used cautiously because advancing RV activation may cause a decline of LV function (63). Consequently RV pre-excitation should be reserved for patients with LV dyssynchrony in the septal and inferior segments provided there is hemodynamic proof of benefit (63). Patients with ischemic cardiomyopathy (with slower conducting scars) may require more pre-excitation than those with idiopathic dilated cardiomyopathy (69), and V-V programming appears of particular benefit in patients with a previous myocardial infarction (67).

Non-echocardiographic optimization of V-V-intervals

1. QuickOpt (St. Jude Medical, St. Paul, Minnesota, USA) also uses IEGM measurements for optimization of the V-V interval. Furthermore, it measures the duration of atrial activation on the IEGM to determine inter-atrial delay. The goal of this algorithm is to set the A-V delay based on the LA-LV time in order to optimize the preload. Advantages of a device integrated optimization algorithm compared to echocardiographic optimization are that it may be time saving, and cost-effective, that it maintains optimal synchronization during follow-up and that it offers the opportunity to evaluate optimization in different circumstances. However, the disadvantages include the limited value in patients without an intrinsic R wave and in patients with atrial fibrillation. More importantly, the largest disadvantage is that in at least 1 study, optimizing the V-V interval using the IEGM method does not yield better hemodynamic results than simultaneous biventricular pacing (70). Although a good correlation between LV contractility determined with Quick Opt and invasive measurements of contractility can be constructed, there is no correlation with the optimal settings of V-V interval in the individual patient.

2. Peak endocardial acceleration was recently introduced in the new CRT device (NewLiving, Sorin Biomedica, Saluggia, Italy). This is an integrated sensor which continuously monitors contractility. According to the manufacturer this will automatically optimize timing and activation sequence of the ventricles to deliver maximum hemodynamic benefit to the patient. Basically, endocardial acceleration, in its systolic and diastolic components, allows estimation of cardiac timings. Ritter et al correlated echocardiographic and endocardial acceleration measurements of aortic pre-ejection interval and ejection time (71). The advantages could be a simplification of patient follow-up and a reduction of the need for time-consuming echocardiographic assessment. Published data on this technique are however still lacking.

3. Thoracic fluid status monitoring via **intrathoracic impedance** is a recently introduced device-based diagnostic capability. Assessment of intrathoracic impedance can be achieved by measuring impedance between the pulse generator and the lead in the right ventricle. This vector encompasses much of the left thoracic cavity. As the patient has worsening heart failure with increasing left atrial filling pressure, more fluid is retained in the pulmonary circulation and a reduction in impedance is expected (72). In addition, impedance cardiography is an established technique for haemodynamic assessment and is capable of calculating cardiac output on a beat-to-beat basis. Heinroth et al used impedance cardiography-based cardiac output measurements to guide the optimization of A-V- and V-V-interval timing of CRT devices (61). Modification of both A-V and V-V intervals in patients with a CRT device significantly improved cardiac output compared with standard simultaneous biventricular pacing and no pacing. The authors found impedance cardiography a useful non-invasive technique for guiding this modification.

CONCLUSIONS AND FUTURE PERSPECTIVES

Effects of CRT include an acute improvement in LV dP/dt, reduction in LV end-systolic volume, improvement in LV function and reduction in mitral regurgitation. There is also evidence of improved myocardial work at similar or lower oxygen consumption resulting in improved cardiac

efficiency, as shown in PET studies. Many of these changes can be demonstrated acutely and are sustained or even further improved during longer follow-up. The impact of CRT on diastolic function is somewhat unclear. Importantly, an acute reduction in dyssynchrony seems to be maintained during longer follow-up and is predictive of positive response to CRT.

Furthermore, echocardiography remains the most frequently used technique for A-V and V-V interval optimization. However, there are still a number of questions concerning device optimization in CRT, and particularly the benefit of V-V optimization remains highly controversial. What echo derived parameters are most useful for A-V and V-V optimization? When is the optimal timing to perform optimization after CRT implantation and is repetition during follow-up necessary? Should A-V optimization precede V-V optimization or vice versa? Do short-term adjustments of the A-V or V-V interval translate into long-term clinical improvement? In addition, what is the effect of optimization in patients with sub-optimal lead position, severe mitral regurgitation or with large extent of scar tissue? Moreover, optimization of settings is time-consuming and sensitive to intra- and inter- observer variability. With the exponential growth in CRT implantations, it will be impossible to optimize devices echocardiographically in all patients. Early experience with device-based algorithms are promising, but need further study.

In conclusion, echocardiography is useful to evaluate a variety of beneficial effects of CRT, both acute and late after implantation. Echocardiography also is the technique of choice for optimization of pacemaker settings after implantation and during follow-up.

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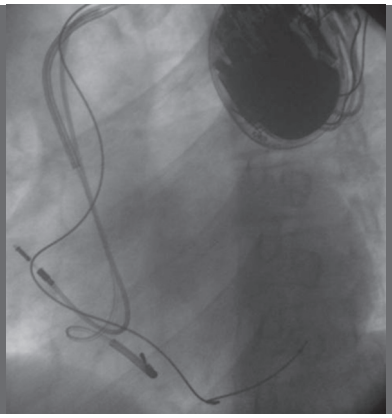


Summary, Conclusions and Future perspectives

SUMMARY, CONCLUSIONS AND FUTURE PERSPECTIVES

Summary

Even with the remarkable results of cardiac resynchronization therapy (CRT) in the large randomized trials, a steady percentage of patients failed to improve after CRT when the established selection criteria (New York Heart Association [NYHA] class III or IV, left ventricular ejection fraction [LVEF] <35% and QRS duration >120 ms) are applied. Many studies addressed the issue of non-response to CRT and have indicated that none of the baseline characteristics (including the current selection criteria) are able to predict a positive response after CRT, thereby highlighting the need for improvement or extension of the current criteria.

Part I aimed to improve the current selection criteria in order to reduce the number of non-responders. Besides the presence of LV dyssynchrony other factors may be important such as scar tissue and lead position. **Part II** describes several issues after device implant such as acute and long-term benefit (LV function, strain, mitral regurgitation, myocardial blood flow, oxidative metabolism), prognosis, interruption of CRT and optimization of device settings (atrioventicular and interventricular optimization). In addition, the number of ICD therapies in CRT-ICD recipients and value of intrathoracic impedance was evaluated.

Part I

In **Chapter 2** a new echocardiographic imaging tool was used to determine LV dyssynchrony. 2D speckle tracking strain analysis can depict three types of deformation within the LV; radial, circumferential and longitudinal deformation. For each type of strain 2 parameters for dyssynchrony were obtained; maximal time delay between peak systolic strain of the (antero) septal and (postero)lateral wall, as well an asynchrony index calculated by the standard deviation of time delays of all segments. Echocardiographic acquisitions were performed in 161 CRT recipients (NYHA class 3.0±0.5, EF 23±7%, QRS 164±34 ms) at baseline and at 6 months after device implantation. After 6 months 88 patients (55%) showed evidence of LV reverse remodeling (reduction in LVESV of ≥15%). Only the baseline values for radial dyssynchrony were different between responders en non-responders. A cut-off value of ≥130 ms for the delay between the anterospetal en posterior segment by radial strain was able to predict reverse remodeling after 6 months of CRT (sensitivity 83%, specificity 80%). Conventional color-coded tissue Doppler imaging (TDI) analysis for septal to lateral delay ≥65 ms applied in this population showed a comparable predictive value (sensitivity 81%, specificity 63%). In addition, dyssynchrony parameters were assessed after 6 months of CRT; only radial strain parameters showed a significant decrease in extent of dyssynchrony in responder patients. This study demonstrated that speckle tracking radial strain analysis is feasible and comparable with conventional TDI. In addition it helps us to understand the mechanism of resynchronization after CRT.

Patient selection based on presence of pre-implantation LV dyssynchrony resulted in a higher response rate as compared to patient selection based on QRS duration alone. Nevertheless, not all patients with LV dyssynchrony at baseline show a positive response after CRT. This issue was addressed in **Chapter 3**, evaluating the time course and extent of LV resynchronization after CRT in 100 CRT patients (NYHA class III-IV, EF <35% and QRS >120 ms) with evidence

of pre-implantation dyssynchrony (≥65 ms with color-coded TDI, see Chapter 2). Immediately after CRT LV dyssynchrony was reduced from 114±36 ms to 40±33 ms (P<0.001). This reduction persisted at 6 months follow-up (35±31 ms, P<0.001 vs. baseline and NS vs. immediate post-implantation). When dividing the patients into responders and non-responders (according to extent of LV reverse remodeling, see Chapter 2), the 85 responders showed a significant reduction in LV dyssynchrony (115±37 ms vs. 32±23 ms, P<0.001), whereas the 15 non-responders failed to show a reduction in dyssynchrony (106±29 ms vs. 79±44 ms, NS). If the extent of LV resynchronization was <20%, response to CRT was never observed. Conversely, 93% of patients with LV resynchronization ≥20% responded to CRT. This study demonstrated that the presence of pre-implantation dyssynchrony results in high response rates (85%). Furthermore, LV resynchronization following CRT is an acute phenomenon and predicts response to CRT at 6 months follow-up.

Ischemic patients show less reverse remodeling after CRT as compared to non-ischemic patients, suggesting the importance of viability and scar tissue. One can imagine that a certain amount of viable myocardium is needed to obtain an improvement in LV function after CRT. In **Chapter 4** viability was assessed using single photon emission computed tomography (SPECT) with ^{18}F-fluorodeoxyglucose in 61 ischemic heart failure patients (EF 23±6%, QRS 165±36 ms, LV dyssynchrony 88±41 ms) before device implantation. Tracer uptake was scored using a 4-point scale (the higher score, the less tracer uptake, the less viable tissue) and applied on a 17-segment model of the LV. The number of normal viable segments (extent of viability) in each patient ranged from 2 to 17 (mean 10±4 segments). Interestingly, the extent of viability was related to the absolute increase in EF after 6 months of CRT (r=0.56, P<0.05); suggesting the more viability at baseline the more improvement in LV function after CRT.

Chapter 5 further addressed this issue by adding the location of the scar tissue, in particular in the region of the LV pacing lead. Fifty-one patients with ischemic heart failure underwent SPECT imaging with ^{99m}Tc-tetrofosmin. The same 17-segment model was applied and segments with a tracer uptake <50% were considered having extensive scar tissue (transmural infarction). Fifteen patients (29%) had transmural scar tissue in the region of the LV pacing lead (as determined by X-ray after implant). These patients showed no clinical or echocardiographic improvements 6 months after device implantation whereas patients without scar tissue in the LV pacing lead region improved significantly.

Contrast-enhanced magnetic resonance imaging (MRI) is the “gold standard” for assessment of location and transmurality of scar tissue. In **Chapter 6**, total scar burden (summed scores divided by 17), the spatial extent (number of affected segments) and transmurality (number of segments with hyperenhancement >50%, reflecting severely damaged segments) were assessed in 34 ischemic patients. All three parameters showed strong inverse correlations with reduction in ESV after CRT; the less scar tissue at baseline, the more reverse remodeling after 6 months of CRT. Furthermore, echocardiographic non-responders had significantly more scar tissue than responders (1.5±0.3 vs. 0.6±0.4, P<0.05). Of note, none of the patients with a total scar burden >1.20 responded to CRT.

In **Chapter 7** presence myocardial contractile response was tested as a predictor of response to CRT in both ischemic (n=20) and non-ischemic patients (n=11). Global and local contractile reserve were determined during infusion of low-dose dobutamine and defined respectively as the increase in EF and the increase in peak strain (with 2D speckle tracking radial strain analysis) at the site were the LV lead was positioned. After 6 months, 17 patients (55%) were considered responders based on presence of LV reverse remodeling. Baseline differences between responders and non-responders consisted of less LV dyssynchrony, les gain in EF during dobutamine infusion (ΔEF 3±4% vs. 13±8%, P<0.001) and less gain in strain of the target LV wall (Δstrain -1±4% vs. 6±5%, P=0.002) in non-responder patients. A cut-off value of 7.5% improvement in EF with dobutamine infusion was calculated to predict CRT response (sensitivity 76%, specificity 86%). Lastly, multivariate analysis revealed that both LV dyssynchrony and myocardial contractile response are independent predictors of response.
These studies show the importance of the extent and location of viability and scar tissue in order to obtain an improvement in LV function after CRT.

Chapter 8 addresses the issue of lead position in 244 CRT recipients (LVEF 24±7%, 58% ischemics). Patients with the LV pacing lead positioned at the site of latest activation (concordant lead position) were compared with patients with a discordant LV lead position. The site of latest mechanical activation was determined by 2D speckle tracking radial strain before device implantation (postero-lateral segments in 69%) and related to the LV lead position on chest X-ray the day after device implantation (lateral 45%, posterior 49% and anterior 5%). Interestingly, one-third of the patients showed a discordant LV lead position. During follow-up, a concordant LV lead position resulted in significant better clinical and echocardiographic improvements at 6 months as well as better outcome during long-term follow-up (32±16 months). Moreover, a concordant LV lead position appeared to be an independent predictor of long-term hospitalization-free survival (hazard ratio 0.22, P=0.004).

In **Chapter 9**, an extensive overview is given of all various non-invasive imaging techniques for the assessment of LV dyssynchrony. Most experience has been obtained with echocardiography, especially color-coded TDI. Color-coded TDI has proven highly predictive for CRT response and event-free survival at follow-up (Chapter 2, 3). Other techniques such as tissue synchronization imaging, TDI-derived strain, 2D speckle tracking (Chapter 2) and 3D echocardiography need more investigation, but initial results are promising. Available evidence is limited on the value of magnetic resonance imaging (MRI) and nuclear imaging to asses LV dyssynchrony. However, the techniques can provide other information, for instance the presence and location of scar tissue and viable myocardium (Chapter 4-6) as well as coronary venous anatomy (with multi-slice computed tomography [MSCT]), potentially important for the selection of CRT candidates.

Part II

As demonstrated in the large clinical trials, individual response to CRT varies significantly. In **Chapter 10** the extent of LV reverse remodeling after 6 months of CRT was related to long-term outcome in 302 heart failure patients. The change in LVESV ranged from an increase in LVESV of 38% to a decrease in LVESV of 78%, with a mean reduction of 18±22%. Based on different extents of LV reverse remodeling, 22% of patients were classified as super-responders (decrease in LVESV ≥30%), 35% as responders (decrease in LVESV 15-29%), 21% as non-

responders (decrease in LVESV 0-14%) and 22% negative-responders (increase in LVESV). More LV reverse remodeling resulted in less heart failure hospitalizations and lower mortality during long-term follow-up (22±11 months); 1- and 2-year hospitalization-free survival rates were 90% and 70% in the negative-responder group, as compared to 98% and 96% in the super-responder group (log-rank P<0.001).

Chapter 11 addressed the question whether LV reverse remodeling influences interruption of CRT; and more practically, whether long-term continuous pacing is necessary in patients with LV reverse remodeling. Therefore, biventricular pacing was interrupted at 6 months follow-up in 135 patients with evidence of LV reverse remodeling (reduction in LVESV ≥15%, n=135) and in 100 non-reverse remodeled patients. During interruption, an acute deterioration in LV function, mitral regurgitation and LV desynchronization were noted in the patients with evidence of LV reverse remodeling. Of note, worsening of these echocardiographic parameters was observed but they did not return to baseline values. In contrast, the patients with no evidence of LV reverse remodeling showed no significant echocardiographic changes during interruption of pacing. These results imply that continuous long-term pacing is warranted to maintain the beneficial effects.

The acute and late effects of CRT on global strain were evaluated in **Chapter 12** using a 2D strain echocardiographic technique, automated function imaging (AFI). Global strain was assessed in 141 heart failure patients (LVEF 25±7%, ischemics 60%) at baseline, immediate after device implantation, after 3-6 months follow-up and during interruption of pacing. During follow-up 57% of the patients were classified as responders (based on a reduction of >15% in LVESV) and 43% as non-responders. Notably, responders and non-responders showed similar value for global strain at baseline. Still, responder patients showed an improvement in global strain during follow-up, combined with significant LV reverse remodeling and improvement in LV function, whereas in no-responders no changes were noted. Importantly, no significant changes were noted immediately after device implantation or during interruption of pacing. Thus, improvement in strain after CRT appears to be a long-term effect and may be related to the extent of LV reverse remodeling.

Mitral regurgitation may improve after CRT, but the precise mechanism is not yet fully understood. **Chapter 13** evaluates 25 selected CRT recipients who showed an immediate reduction in severity of mitral regurgitation immediately after implant. All patients underwent echocardiography including 2D speckle tracking radial strain analysis at baseline, immediate after implant, at 6 months follow-up and during interruption, to study the relationship between dyssynchrony between the papillary muscles and the severity of mitral regurgitation. Mean vena contracta width was 0.54±0.15 cm at baseline with substantial dyssynchrony between the papillary muscles 169±69 ms. Both parameters showed significant reductions immediately after implant. Importantly, these effects were maintained at 6 months follow-up, but acute loss of resynchronization was observed after interruption of CRT, with an acute recurrence of mitral regurgitation. These results imply that CRT can acutely reduce mitral regurgitation in patients with dyssynchrony involving the papillary muscles.

Chapter 14 further extended this finding by evaluating 68 consecutive CRT recipients with at least moderate mitral regurgitation at baseline. Similarly, speckle tracking radial strain echocardiography was performed to asses the extent of LV dyssynchrony as well as the site of latest activation at baseline. The majority of patients improved after CRT, with 43% improving immediately after CRT, and 20% improving late after (6 months) CRT. Early and late improvers had similar extent of LV dyssynchrony at baseline (209±115 ms vs. 190±118 ms, NS); however, the site of latest activation in early improvers was mostly inferior or posterior (adjacent to the posterior papillary muscle), whereas the lateral wall was the latest activated segment in late improvers. These observations indicate that the reduction in mitral regurgitation after CRT is related to the presence of LV dyssynchrony; if the dyssynchrony involves the posterior papillary muscle an acute reduction can be expected after CRT (secondary to resynchronization of the papillary muscles), whereas in patients with LV dyssynchrony not involving the papillary muscles late improvement in mitral regurgitation can be expected (due to LV reverse remodeling with restoration of the mitral valve apparatus).

In **Chapter 15** the number of ICD therapies in patients eligible for CRT (who received a combined device) was evaluated. Of 191 heart failure patients (NYHA class 2.9±0.5, LVEF 21±7%, QRS 163±30 ms), 71 patients experienced previous ventricular arrhythmias (secondary prevention; 11 inducible arrhythmias, 38 spontaneous arrhythmias, 22 out-of-hospital cardiac arrest survivors), whereas 120 patients never experienced ventricular arrhythmias (primary prevention). During follow-up, similar clinical (NYHA class, quality of life and exercise distance) and echocardiographic improvement was noted for the two groups. Nonetheless, primary prevention patients experienced significantly less appropriate ICD therapies as compared to secondary prevention patients (21% vs. 35%, $P<0.05$). Multivariate analysis revealed however no predictors of ICD therapy. Furthermore, mortality rate was higher in the secondary prevention group (18% vs. 3%, $P<0.05$). Thus, since a substantial amount of primary and secondary prevention patients experience ICD therapies within 2 years after CRT, and no predictors of ICD therapy could be identified, implantation of a combined CRT-ICD device should be considered in all patients.

The new generation CRT devices are equipped with novel features to monitor the heart failure status. In **Chapter 16** intrathoracic impedance measurement was analyzed 115 CRT recipients. This measurement may permit early identification of pulmonary fluid accumulation secondary to left-sided heart failure. An audible alert can be triggered when the impedance index precedes the predefined level of 60 Ω·day. During follow-up (9±5 months) there were 45 presentations with an alert in 30 patients. Clinical signs and symptoms of heart failure were present only in 15 patients (33%). Receiver operating characteristic curve analysis showed that increasing the threshold provided a substantial increase in specificity for the detection of heart failure. These findings imply that intrathoracic impedance measurement may be a useful tool to prevent worsening heart failure symptoms, however specificity of the current threshold of 60 Ω·day is too low in daily practice.

Chapter 17 provides a review on non-invasive imaging after CRT. The effects of CRT include an acute improvement in LV dP/dt, reduction in LVESV, improvement in LV function, and a reduction in mitral regurgitation (as determined with echocardiography). There is also evidence

of improved myocardial work at similar or lower oxygen consumption resulting in improved cardiac efficiency, as shown in nuclear studies. Many of these changes are demonstrated acutely and are sustained or even further improved during longer follow-up. Furthermore, echocardiography remains the most frequently used technique for atrioventricular and interventricular optimization. However, optimization is time-consuming and echocardiographic end-points and long-term follow-up are unknown; particularly the benefit of interventricular optimization remains highly controversial. Early experience with device based diagnostics is promising but needs further study.

Conclusions and future perspectives

Even with the remarkable results of CRT in the large randomized trials, a steady percentage of patients failed to improve after CRT when the established selection criteria (NYHA class III or IV, LVEF <35% and QRS duration >120 ms) are applied. Many studies addressed the issue of non-response to CRT and have indicated that none of the baseline characteristics (including the current selection criteria) are able to predict a positive response after CRT, thereby highlighting the need for improvement or extension of the current criteria.

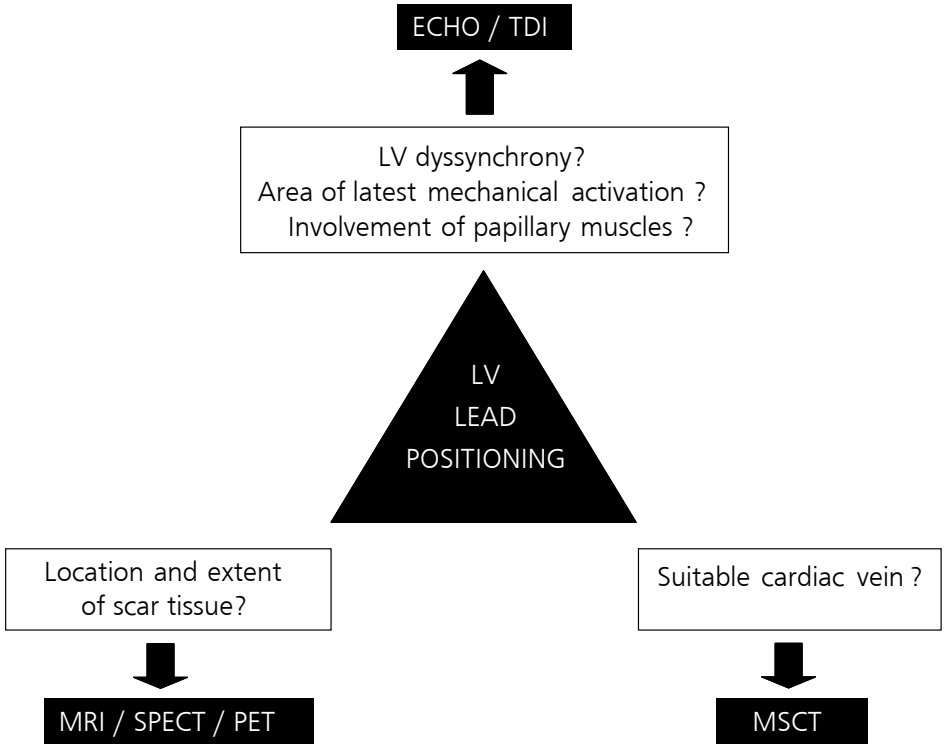
In the search for better selection criteria, the current thesis suggests the following algorithm for each patient referred for CRT (Figure 1). Before a patient is referred for CRT a few questions need to be addressed. First, is substantial LV dyssynchrony present? Traditionally, QRS duration was used as an (indirect) marker for dyssynchrony. However, echocardiographic assessment of LV dyssynchrony showed a superior response rate as compared to selection based on QRS duration. Most evidence has been obtained with TDI. Still, the 'gold standard' for the assessment of LV dyssynchrony is not yet available. Second, where is the area of latest activation for optimal positioning of the LV pacing lead? Pacing in the area of latest activation results in the best clinical response as compared to patients with the LV pacing lead beyond the site of latest activation. Furthermore, does the site of latest activation contain scar tissue? Scar tissue in the region of the LV pacing lead may prohibit LV resynchronization and result in CRT non-response.

Also, in patients with substantial mitral regurgitation, does the site of latest activation involve the posterior papillary muscle? Resynchronization of the papillary muscles may result in an acute reduction in severity of mitral regurgitation. Third, is venous access present to the preferred location? MSCT can provide this information non-invasively before device implantation. A surgical approach is preferred in case of absence of suitable veins. Finally, does the LV contain enough viable myocardium to obtain a substantial improvement in LV function after CRT? The less scar tissue, the more improvement in LV function and LV reverse remodeling.

In conclusion, non-invasive imaging techniques, especially echocardiography, plays an exciting and evolving role in the care of the patient with CRT, from quantifying dyssynchrony and scar tissue before implant as well as improvements in ventricular function and mitral regurgitation and optimizing the device after implantation. Although a great deal of work has been done to quantify mechanical dyssynchrony in hopes of refining patient selection and guiding lead placement, this is a complex and challenging field with future work needed and several promising studies ongoing. Also, advances in our understanding of the pathophysiology of dyssynchrony and CRT have great potential to impact future clinical practice and improve patient outcome.

Figure 1. Patient selection

Information that is needed before CRT implantation: presence of LV dyssynchrony as well as site of latest activation can be assessed with echocardiography such as tissue Doppler imaging (TDI). For evaluation of extent and location of scar tissue and viable myocardium nuclear imaging (single photon emission computed tomography [SPECT] and positron emission tomography [PET]) and magnetic resonance imaging (MRI) can be used, whereas multi-slice computed tomography (MSCT) can be of value for evaluating venous anatomy before LV lead implantation.



SAMENVATTING, CONCLUSIE EN TOEKOMSTPERSPECTIEVEN

Samenvatting

Ondanks de indrukwekkende resultaten van cardiale resynchronizatie therapie (CRT) in de grote gerandomiseerde studies, blijkt een constant percentage patiënten niet te verbeteren wanneer zij volgens de huidige selectie criteria (NYHA functionele klasse III of IV, verminderde linker ventrikel ejectie fractie [LVEF] <35% en QRS duur op het electrocardiogram >120 ms) worden geselecteerd. Veel studies hebben dit fenomeen bestudeerd en komen allen tot de conclusie dat geen van de patiënt karakteristieken (inclusief de huidige selectie criteria) een goede voorspeller is voor een verbetering (response) na CRT. Hierbij wordt de noodzaak tot het verbeteren of uitbreiden van de huidige criteria benadrukt.
Het doel van **Deel I** was dan ook de huidige selectie criteria te verbeteren om zo het aantal 'non-responders' te verminderen. Naast de aanwezigheid van LV dyssynchronie, kunnen ook andere factoren als litteken weefsel in de LV of de plaatsing van de LV pacing lead van invloed zijn op response na CRT. **Deel II** beschrijft verschillende zaken die van belang zijn na CRT implantatie zoals acute en lange termijn resultaten (LV functie, strain, mitralisklep insufficiëntie, myocardiale bloedstroom en oxidatieve metabolisme), prognose, het onderbreken van CRT en de optimalisatie van verschillende pacemaker instellingen (zoals optimalisatie van atrioventriculaire en interventriculaire tijdsverschil). Hiernaast, wordt het aantal ICD therapieën bekeken in een cohort met CRT-ICD patiënten en wordt de waarde van intrathoracale impedantie meting geëvalueerd.

Deel I

In **Hoofdstuk 2** wordt een nieuwe echocardiografische techniek gebruikt om LV dyssynchronie te bepalen. 2-Dimensionale speckle tracking strain analyse kan 3 typen deformatie van de LV weergeven; radiale, longitudinale and circumferentiële verandering (of strain). Voor elk type deformatie werden 2 parameters voor dyssynchronie berekend; een locale parameter (maximale tijdsverschil tussen 2 LV segmenten) en een globale parameter (standaard deviatie van alle individuele tijdsverschillen). Honderd-een-en-zestig patiënten (NYHA class 3.0±0.5, EF 23±7%, QRS 134±34 ms) ondergingen echocardiografisch onderzoek voor CRT implantatie en na 6 maanden follow-up. Na 6 maanden lieten 88 patiënten (55%) reverse remodeling van de LV zien, gedefinieerd als een reductie in LV eind-systolisch volume (ESV) ≥15%. Bij het vergelijken van de dyssynchronie parameters tussen de twee groepen, waren alleen de dyssynchronie parameters van de radiale strain significant verschillend. Een afkapwaarde van ≥130 ms voor het tijdsverschil tussen het anteroseptale en posterior segment (anteroseptal-to-posterior delay) met radiale strain bleek een goede voorspeller van LV reverse remodeling na 6 maanden CRT (sensitiviteit 83%, specificiteit 80%). De conventionele color-coded tissue Doppler imaging (TDI) analyse voor het tijdsverschil tussen het septum en de lateral wand (septal-to-lateral delay) ≥65 ms liet in deze populatie een vergelijkbare voorspellende waarde zien (sensitiviteit 81%, specificiteit 63%). Deze studie laat zien dat deze nieuwe techniek uitvoerbaar is en vergelijkbaar aan conventionele TDI. Hiernaast helpt het ons het mechanisme achter LV dyssynchronie beter te begrijpen.

Selectie van patiënten gebaseerd op de aanwezigheid van LV dyssynchronie voor de implantatie hebben hogere CRT response getallen laten zien dan wanneer de selectie van patiënten is

gebaseerd op de duur van het QRS complex. Desondanks, tonen niet alle patiënten met LV dyssynchronie een verbetering na CRT. Dit onderwerp werd besproken in **Hoofdstuk 3**, waarin het tijdsbeloop en de hoeveelheid LV dyssynchronie na CRT werd bekeken in 100 patiënten (NYHA fucntionele klasse III en IV, EF <35% en QRS >120 ms) met echocardiografisch bewijs van LV dyssynchronie (≥65 ms met color-coded TDI, zie Hoofdstuk 2). Meteen na CRT implantatie was er een afname van LV dyssynchronie van 114±36 ms naar 40±33 ms (P<0.001). Deze reductie bleef onveranderd na 6 maanden follow-up (35±31 ms, P<0.001 vs. voor implantatie en P=NS vs. meteen na implantatie). Wanneer de patiënten werden verdeeld in responders en non-responders (volgens de aanwezigheid van LV reverse remodeling na 6 maanden), lieten de 85 responders een significante afname zien in LV dyssynchronie (115±37 ms vs. 32±23 ms, P<0.001) en de 15 non-responders niet (106±29 ms vs. 79±44, NS). Onder de patiënten met <20% acute reductie in LV dyssynchronie werd geen echocardiografische response gezien; patiënten met een reductie ≥20% daarentegen hadden een 93% response percentage. Concluderend laat deze studie zien dat de aanwezigheid van LV dyssynchronie voor implantatie een hoge response laat zien (85%). Hiernaast is LV resynchronizatie een acuut fenomeen, en de aan-/afwezigeid hiervan is een voorspeller van response na CRT.

De hoeveelheid LV reverse remodeling na CRT blijkt verschillend te zijn in patiënten met een ischemische en een non-ischemische cardiomyopathie. Dit suggereert dat de aan-/afwezigheid van litteken weefsel en vitaal myocard een rol kunnen spelen. Men kan zich voorstellen dat een bepaalde hoeveelheid vitaal weefsel nodig is om een verbetering in pompfuctie na CRT te verkijgen. In **Hoofdstuk 4** wordt de hoeveelheid vitaal weefsel in de LV voor implantatie bepaald middels single photon emission computed tomography (SPECT) met ^{18}F-fluordeoxyglucose in 61 patiënten met ischemisch hartfalen (EF 23±6%, QRS 165±36 ms, LV dyssynchronie 88±41 ms). Een 4-punts schaal werd gebruikt om te hoeveelheid tracer opname te scoren (hoe hoger de score, hoe minder de hoeveelheid tracer opname, hoe minder vitaal het myocard) voor elk van de 17 segmenten van de LV. Het gemiddelde aantal vitale segmenten was 10±4 per patiënt, uiteenlopend van 2 tot 17 segmenten per patiënt. Bovendien bleek de hoeveelheid vitale segmenten gecorreleerd te zijn met de hoeveelheid verbetering in pompfunctie na 6 maanden CRT (r=0.56, P<0.05). Samenvattend geeft meer vitaal weefsel in LV voor CRT implantatie een grotere verbetering in LV functie gedurende follow-up.

Hoofdstuk 5 gaat door op dit onderwerp door de locatie van het littekenweefsel toe te voegen, met name op de plek waar de LV pacing lead wordt geplaatst. Een-en-vijftig patiënten met ischemische cardiomyopathie ondergingen SPECT met ^{99m}Tc-tertrofosmin. Hetzelfde 17-segmenten model werd gehanteerd en segmenten met <50% tracer opname werden geclassificeerd als hebbende uitgebreid littekenweefsel (transmurale infarcering). Transmurale infarcering op de plek van de LV pacing lead (beoordeeld met röntgendiagnostiek na implantatie) werd gezien in 15 patiënten (29%). Deze patiënten lieten geen klinische of echocardiografische verbeteringen na 6 maanden CRT in tegenstelling tot de patiënten zonder littekenweefsel op de plek van de LV pacing lead.

Contrast-enhanced magnetic resonance imaging (MRI) is de 'gouden standaard' voor de bepaling van de lokalisatie and transmuraliteit van litteken weefsel in de LV. In **Hoofdstuk 6** worden de totale litteken burden (totale score van alle segmenten gedeeld door 17), het aantal

aangedane segmenten en de transmuraliteit (het aantal segmenten met >50% oplichting, ofwel het aantal segmenten met uitgebreide verlittekening) bepaald voor implantatie in 34 patiënten met ischemisch hartfalen. Alle drie de parameters lieten een sterke relatie zien met de reductie in ESV na CRT; hoe minder littekenweefsel voor implantatie, hoe meer reverse remodeling na 6 maanden CRT. Tevens hadden non-responders significant meer littekenweefsel dan responders (litteken burden 1.5±0.3 vs. 0.6±0.4, P<0.05). Ook, liet geen van de patiënten met een totale litteken burden van ≥1.20 CRT response zien.

In **Hoofdstuk 7** werd de aanwezigheid van contractiele reserve getest als voorspeller van response na CRT in ischemische (n=20) en non-ischemische patiënten (n=11). Globale en locale contractiele reserve werden bepaald tijdens infusie van lage dosering dobutamine en werden respectievelijk gekwantificeerd als de toename in EF en de toename in strain (met 2D speckle tracking radiale strain analyse) op de locatie van de LV pacing lead. Na 6 maanden follow-up werden 17 patiënten (55%) geclassificeerd als responders gebaseerd op de aanwezigheid van LV reverse remodeling. De pre-implantatie patiënt karakteristieken toonden significant minder LV dyssynchronie, minder toename in EF tijdens dobutamine infusie (ΔEF 3±4% vs. 13±8%, P<0.001) en minder toename in strain in het gepacede segment (Δstrain -1±4% vs. 6±5%, P=0.002) in non-responders. Een afkapwaarde van 7.5% toename in EF met dobutamine infusie werd berekend om response na CRT te voorspellen (sensitiviteit 76%, specificiteit 86%). Hiernaast liet multivariate analyse zien dat LV dyssynchronie en myocardiale contractiele reserve beide onafhankelijke voorspellers zijn van response na CRT.
Samenvattend laten deze 4 studies de belangrijke rol zien van de uitgebreidheid en lokalisatie van littekenweefsel voor implantatie en de relatie met response na CRT.

Normaliter, wordt de LV pacing lead bij voorkeur geplaatst in een postero-laterale tak van de coronaire sinus. **Hoofdstuk 8** bekijkt de waarde van de positie van de LV pacing lead in 244 CRT patiënten (LVEF 24±7%, 58% ischemisch). Patiënten waarbij de LV lead was geplaatst op het laatst contraherende LV segment (concordante positie) werden vergeleken met patiënten met een discordante LV lead positie. Het laatst contraherende segment werd bepaald met 2D speckle tracking radiale strain analyse voor CRT implantatie (het postero-laterale segment in 69%) en gerelateerd aan de positie van de LV pacing lead middels röntgenonderzoek na implantatie (lateraal 45%, posterior 45%, anterior 5%). Een-derde van de patiënten bleek een discordante lead positie te hebben. Bij 6 maanden follow-up toonden patiënten met een concordante lead positie significant betere klinische en echocardiografische veranderingen als ook een betere prognose bij lange termijn follow-up (32±16 maanden). Hiernaast bleek een concordante lead positie een goede voorspeller voor lange termijn overleving vrij van opnames voor hartfalen (risico 0.22, P=0.004).

In **hoofdstuk 9** wordt een uitgebreid overzicht gegeven van alle niet-invasieve beeldvormings-technieken om LV dyssynchronie te bepalen. De meeste ervaring is opgedaan met echocardiografie, voornamelijk met color-coded TDI (Hoofdstuk 2 en 3). Color-coded TDI bleek van hoge voorspellende waarde voor CRT response en overleving na CRT. Andere technieken zoals tissue synchronization imaging, TDI-afgeleide strain, 2D speckle tracking (Hoofdstuk 2, 9) en 3D echocardiografie moeten verder onderzocht worden, maar de eerste resultaten in kleine studies zijn veelbelovend. Er is weinig bekend over de waarde van MRI en nucleaire

beeldvorming voor het bepalen van LV dyssynchrony. Echter, deze technieken kunnen andere informatie bieden zoals de aanwezigheid en lokalisatie van litteken weefsel en vitaal weefsel (Hoofdstuk 4-6) alsook informatie over de coronaire veneuze anatomie (met multislice CT) welke van belang kunnen zijn bij de selectie van patiënten.

Zoals de grote gerandomiseerde studies hebben laten zien, is er grote individuele variatie in response na CRT. In **Hoofdstuk 10** wordt de mate van LV reverse remodeling na 6 maanden CRT gerelateerd aan de lange termijn prognose in 302 hartfalen patiënten. De mate van reverse remodeling liep sterk uiteen van een toename in LVESV van 38% tot een vermindering in LVESV van 78%, met een gemiddelde vermindering van 18±22%.Twee-en-twintig % van de patiënten werden geclassificeerd als super-responders (vermindering in LVESV ≥30%), 35% als responders (vermindering in LVESV 15-29%), 21% als non-responders (vermindering in LVESV 0-14%) en 22% als negatieve responders (toename in LVESV). Meer LV reverse remodeling na 6 maanden resulteerde in minder opnames voor hartfalen en een lagere mortaliteit tijdens follow-up (22±11 maanden); 1- en 2-jaars overleving vrij van opnames voor hartfalen waren respectievelijk 90% en 70% in de negatieve responders groep, en 98% en 96% in de super-responder groep (log-rank P<0.001).

Hoofdstuk 11 behandelt de vraag of LV reverse remodeling van invloed is op het onderbreken van biventriculair pacen; en meer praktisch, of oneindig biventriculair pacen nodig is in patiënten met een 'reverse remodel-de LV'. Zodoende werd biventriculair pacen onderbroken na 6 maanden CRT in 135 patiënten met tekenen van LV reverse remodeling (reductie in LVESV ≥15%) en in 100 patiënten zonder reverse remodeling. Tijdens deze onderbreking werd een acute verslechtering gezien in LV functie, mitralisklep insufficiëntie en desynchronisatie van de LV in de patiënten met LV reverse remodeling. Echter deze verslechteringen keerden niet volledig terug tot het niveau van voor de implantatie. In tegenstelling, de patiënten zonder reverse remodeling lieten geen significante veranderingen tijdens de onderbreking. Deze resultaten impliceren dat continu biventriculair pacen noodzakelijk is om de positieve effecten te handhaven.

De acute en lange termijn effecten van CRT op globale strain in de LV werden geëvalueerd in **Hoofdstuk 12** met behulp van 2D strain echocardiografie, genaamd automated functional imaging (AFI). De hoeveelheid strain werd bepaald in 141 hartfalen patiënten (LVEF 25%, 60% ischemisch) op 4 verschillende tijdstippen; voor implantatie, meteen na implantatie, na 6 maanden follow-up en tijdens onderbreking van biventriculair pacen. Tijdens follow-up werd 57% van de patiënten geclassificeerd als responder (gedefinieerd als reductie ≥15% in LVESV). Voor CRT implantatie hadden responders en non-responders dezelfde waarde voor globale strain. Echter, responders toonden tijdens follow-up een verbetering in globale strain, evenals LV reverse remodeling en verbetering in LV functie, terwijl in non-responders geen verandering werd geobjectiveerd. Er werden geen significante veranderingen in strain gezien meteen na de implantatie of tijdens onderbreking van pacing. Dus, de verbetering in strain na CRT lijkt een lange termijn effect en kan gerelateerd zijn aan de mate van LV reverse remodeling.

Mitralisklep insufficiëntie kan verbeteren na behandeling met CRT, echter het precieze mechanisme is nog niet bekend. In **Hoofdstuk 13** werden 25 geselecteerde patiënten die een acute verbetering hebben laten zien in de ernst van de mitralisklep insufficiëntie meteen na CRT implantatie geanalyseerd. Alle patiënten kregen een uitgebreide echocardiografie inclusief 2D speckle tracking radiale strain analyse voor de implantatie, meteen na, na 6 maanden follow-up en tijdens onderbreking van biventricular pacen. Middels echocardiografie werd de relatie bestudeerd tussen de ernst van de mitralisklep insufficiëntie en dyssynchronie tussen de beide papillair spieren. De gemiddelde vena contracta wijdte was 0.54±0.15 cm voor implantatie met tekenen van aanzienlijke dyssynchronie tussen de papillair spieren van 169±69 ms. Beide parameters vertoonden een acute reductie direct na implantatie. Deze reducties werden behouden na 6 maanden follow-up maar toonden een acute terugval tijdens onderbreking van pacing. Deze resultaten impliceren dat in patiënten met mitralisklep insufficiëntie en dyssynchronie tussen de papillair spieren CRT de ernst van de kleplekkage direct kan verminderen.

Hoofdstuk 14 vervolgt deze bevinding door 68 patiënten met een tenminste gemiddelde mitralisklep insufficiëntie te evalueren. Ook in deze studie werd 2D speckle tracking radiale strain analyse gebruikt om de hoeveelheid dyssynchronie evenals het laatst contraherende segment te bepalen. De meerderheid van de patiënten toonden een verbetering in de ernst van de kleplekkage na CRT; 43% liet deze verbetering meteen (vroeg) na implantatie zien en 20% liet deze verbetering na 6 maanden follow-up (laat) zien. Vooraf aan de implantatie werd dezelfde hoeveelheid dyssynchronie gezien in 'vroege' en 'late' responders (209±115 ms vs. 190±118 ms, NS); echter, het laatst contraherende segment verschilde tussen beide groepen, in vroege responders was dit het inferior en posterior segment (aangrenzend aan de posterior papillair spier) en in late responders het laterale segment. Deze bevindingen impliceren dat reductie in de ernst van mitralisklep insufficiëntie is gerelateerd aan de aanwezigheid van LV dyssynchronie; als de dysysnchronie zich in de posterior papillair spier bevindt kan een acute verbetering in kleplekkage worden gezien (dankzij de resynchonizatie van de papillair spieren, Hoofdstuk 13) en als de dyssynchrony zich buiten de papillair spier in de laterale wand bevindt kan een late verbetering in mitralisklep insufficiëntie verwacht worden (dankzij LV reverse remodeling met herstel van het mitralisklep apparaat).

In **Hoofdstuk 15** wordt het aantal ICD therapieën in patiënten met een gecombineerd CRT-ICD apparaat geëvalueerd. Vooraf aan de CRT implantatie in 191 hartfalen patiënten (NYHA functionele klasse 29.±0.5, LVEF 21±7%, QRS 163±30 ms) hadden 71 patiënten reeds ventriculaire arritmieën ervaren (secundaire preventie; 11 patiënten met een induceerbare ventrikeltachycardie, 38 spontane ventriculaire arritmieën en 22 plotse hartstilstand overlevers) en 120 patiënten niet (primaire preventie). Tijdens follow-up werd een gelijke klinische (NYHA functionele klasse, kwaliteit van leven en inspanningstolerantie) en echocardiografische verbetering gezien in beide groepen. Desondanks toonde primaire preventie patiënten significant minder correcte ICD therapieën dan secundaire preventie patiënten (21% vs. 35%, $P<0.05$). Multivariate analyse resulteerde echter niet in een voorspeller voor ICD therapieën. Verder was ook de mortaliteit hoger in de secundaire preventie groep (18% vs. 3%, $P<0.05$). Dus, gezien een substantieel deel van de patiënten correcte ICD therapieën ervaart binnen 2 jaar na implantatie en er geen voorspellers zijn, moet een gecombineerd CRT-ICD apparaat worden overwogen in alle patiënten die in aanmerking komen voor CRT.

De nieuwe generatie CRT en ICD apparaten zijn uitgerust met het vermogen de hartfalen 'status' te monitoren. In **Hoofdstuk 16** wordt de intrathoracale impedantie meting geëvalueerd in 115 CRT patiënten. Deze meting kan tekenen van vroege pulmonale congestie als uiting van linkszijdig hartfalen detecteren. Een hoorbaar alarm kan ingeschakeld worden wanneer de impedantie index boven een bepaalde gedefinieerde drempel van 60 Ω·dag komt. Tijdens follow-up (9±5 maanden) waren er 45 presentaties met een alarm in 30 CRT patiënten. Klinische tekenen en symptomen van hartfalen binnen 2 weken na het optreden van het alarm werden slechts in 15 patiënten (33%) gezien. Receiver operating characteristic curve analyse toonde dat het verhogen van de drempel een verhoging van de specifiteit hartfalen te detecteren tot gevolg had. De bevindingen van deze studie laten zien dat intrathoracale impendatie meting zoals geïntegreerd in de nieuwe CRT apparaten een nuttige toevoeging kan zijn om episoden van gedecompenseerd hartfalen te voorkomen. Echter, de specificiteit van de huidige drempel van 60 Ω·dag is te laag voor in de dagelijkse praktijk.

Hoofdstuk 17 is een review over niet-invasieve beeldvorming na CRT implantatie. De effecten na CRT omvatten een acute verbetering in LV dP/dt, reductie in LVESV, verbetering in LV functie en een vermindering in de ernst van mitralisklep insufficiëntie (zoals vastgesteld met ehocardiografie). Er is ook bewijs van een verbeterde 'myocardial work' met gelijke of verminderde zuurstof consumptie resulterend in verbeterde cardiale efficiëntie, zoals getoond in nucleaire studies. Veel van deze veranderingen worden meteen na CRT implantatie gezien en blijven bestaan of tonen nog meer verbetering gedurende follow-up. Hiernaast is echocardiografie de meest frequent gebruikte techniek om atrioventriculaire en interventriculaire optimalisatie te verrichten. Echter, het optimaliseren is erg arbeids-intensief en echocardiografische eindpunten en lange termijn uitkomsten zijn (nog) onbekend; vooral het profijt van interventriculaire optimalisatie is nog steeds uiterst controversieel. Eerste ervaringen met device-based diagnostics zijn veelbelovend, maar behoeven nog verdere studie.

Conclusies en toekomstperspectieven

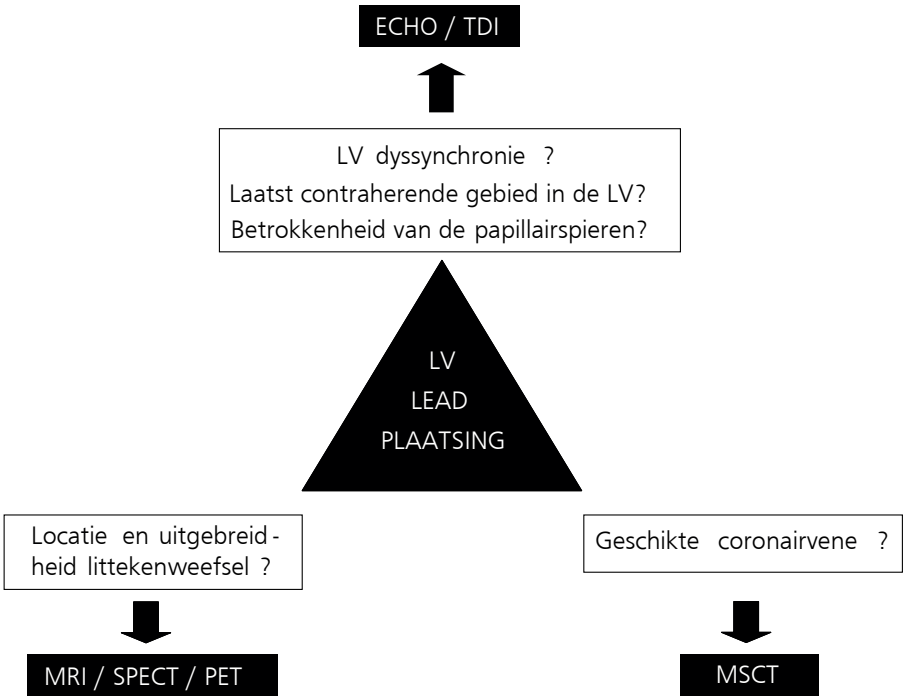
In de zoektocht naar betere selectie criteria, stelt dit proefschrift het volgende selectie algoritme voor voor elke patiënt die in aanmerking komt voor CRT (Figuur 1). Voordat een patiënt wordt verwezen voor CRT moeten een aantal zaken bekeken worden. Als eerste, is er een substantiële hoeveelheid dyssynchronie in de LV? Van oudsher werd QRS duur gebruikt als een (indirecte) marker voor LV dyssynchronie. Echter, de echocardiografische bepaling van LV dyssynchronie toonde een betere CRT response dan wanneer de QRS duur werd gehanteerd. De meeste ervaring is opgedaan met color-coded TDI. Toch is er momenteel nog geen 'gouden standaard' voor de bepaling van LV dyssynchronie. Ten tweede, wat is het laatst contraherende gebied om de meest optimale LV lead positie te bepalen? Pacen in het laatst contraherende gebied resulteert in betere klinische en echocardiografische response in vergelijking met patiënten waarvan de pacing lead niet gepositioneerd is in het laatst contraherende gebied. Verder, bevat dit laatst contraherende gebied littekenweefsel? Transmurale infarcering in het gebied waar de LV pacing lead is geplaatst kan LV resynchronizatie verhinderen en zo leiden tot non-response. Tevens, voor patiënten met substantiële mitralisklep insufficiëntie, valt het laatst contraherende gebied samen met de posterior papillair spier? Resynchronizatie van de papillair spieren kan resulteren in een acute reductie in kleplekkage. Ten derde, is er een veneuze toegang tot de voorkeurslokalisatie van de LV pacing lead? Met MSCT kan deze informatie niet-invasief

verkregen worden vooraf aan de implantatie. Een minimale chirurgische ingreep kan nodig zijn wanneer er geen beschikbare coronair venen zijn. Tot slot, bevat de LV genoeg vitaal myocard om een beduidende verbetering in pompfuctie te bewerkstelligen? In patiënten met een ischemische cardiomyopathie leidt een grotere hoeveelheid littekenweefsel tot minder of geen verbetering in LV functie of LV reverse remodeling.

Concluderend spelen niet-invasieve beeldvormingstechnieken, en voornamelijk echocardiografie, een belangrijke en evoluerende rol in de zorg voor patiënten met CRT; van het kwantificeren van dyssynchronie en litteken weefsel vooraf aan de implantatie, tot het kwantificeren van de verbeteringen in ventrikel functie en mitralisklep insufficiëntie, alsook het optimaliseren van de device na implantatie. Hoewel veel onderzoek verricht is naar de kwantificatie van dyssynchronie in de hoop de huidige patiënt selectie te verbeteren en de lead positie te begeleiden, is dit een complex en uitdagend terrein waarbij toekomstige studies nodig zijn. Hiernaast zullen verbeteringen in ons begrip van de pathosfysiologie van CRT en dyssynchronie leiden tot gunstige beïnvloeding van de toekomstige klinische praktijk en de uitkomst van patiënten met CRT.

Figuur 1. Patient selectie

Informatie die nodig is voor CRT implantatie: aanwezigheid van dyssynchronie alsook het detectie van het laatst contraherende gebied kan worden bepaald met echocardiografie, zoals met color-coded tissue Doppler imaging (TDI). Voor de evaluatie van de uitgebreidheid en lokalisatie van litteken weefsel en vitaal myocard kunnen magnetic resonance imaging (MRI) en nucleaire beeldvorming (single photon emission computed tomography [SPECT] en positron emission tomography [PET]) gebruikt worden. Multi-slice CT (MSCT) kan van waarde zijn om de coronaire veneuze anatomie vooraf in beeld te brengen.



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Claudia

CURRICULUM VITAE

De auteur van dit proefschrift werd geboren op 31 augustus 1979 in Amstelveen. In 1997 behaalde zij haar eindexamen Gymnasium aan het Hermann Wesselink College te Amstelveen. Van 1997 tot en met 2004 studeerde zij Geneeskunde aan de Vrije Universiteit van Amsterdam. Tijdens de doctoraalfase was zij werkzaam als student-assistent bij de vakgroep Celbiologie. Tevens was zij betrokken bij wetenschappelijk onderzoek naar trombose op de afdeling Vasculaire Geneeskunde in het Academisch Medisch Centrum in Amsterdam (Prof. M.M. Levi). In de periode 2002-2004 liep zij haar co-assistentschappen in de regio Noord-Holland. Aansluitend werd het artsexamen in 2004 cum laude afgelegd. Nadien werkte zij gedurende 8 maanden als AGNIO cardiologie in het Medisch Centrum Alkmaar (Dr. J.H. Ruiter). In 2005 begon zij met promotieonderzoek op de afdeling cardiologie van het Leids Universitair Medisch Centrum onder begeleiding van Prof. J.J. Bax en Prof. M.J. Schalij. De resultaten hiervan staan beschreven in dit proefschrift. Hiernaast heeft zij deel uitgemaakt van het opzetten en draaien van een hartfalen polikliniek voornamelijk gericht op cardiale interventies binnen deze populatie (Dr. H.F. Verwey). In april 2008 startte zij met de opleiding tot cardioloog vanuit het Leids Universitair Medisch Centrum (Prof. E.E. van der Wall). Momenteel volgt zij de vooropleiding interne geneeskunde in het Spaarne Ziekenhuis in Hoofddorp (Dr. A.B. Arntzenius). Vervolgens zal zij werkzaam op de afdeling cardiologie van het Rijnland ziekenhuis te Leiderdorp (Dr. C.J.H.J. Kirchhof) en het Leids Universitair Medisch Centrum.