Cardiac resynchronization therapy:

Advances in optimal patient selection

Gabe B. Bleeker

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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Chapter 1

General introduction and outline of the thesis

Chronic heart failure

Chronic (systolic) heart failure is a clinical syndrome which evolves from damage of the myocardium resulting in the inability of the heart to eject blood in line with the needs of the body. As a result of this relative shortage in cardiac output (in particular during exercise) the syndrome of heart failure mainly manifests itself as dyspnea and fatigue, fluid retention and exercise intolerance [1,2]. The severity of heart failure symptoms generally progresses over time and is classified according to the classification of the New York Heart Association (NYHA).

In the majority of heart failure patients the damage to the myocardium is the result of ischemic heart disease, due to a previous myocardial infarction or chronic ischemia. Other reasons for the damage to the myocardium are a persistent overload, such as in hypertension or valvular disease or from loss of functional myocardium as a result of (usually viral) myocarditis or the prolonged presence of tachycardia [1,3] (Table 1). After the initial damage to the myocardium (e.g. after an acute myocardial infarction), the clinical syndrome of heart failure usually takes several years to arise. During these years the heart attempts to restore and/or maintain cardiac output through several adaptational mechanisms. Initially, the main adaptational mechanism is hypertrophy of the (surviving) myocardium, but this mechanism is only able to maintain cardiac function for a limited period of time. If myocardial hypertrophy alone is inadequate the left ventricle starts to dilate in order to maintain stroke volume (this process is referred to as LV remodeling). However, the wall stress induced by LV dilatation and the increased load of the left ventricle results in (further) myocyte death and a consequent stretch of the mitral annulus leading to an increasing mitral regurgitation. This process can be

Table 1: Causes of heart failure

- Myocardial disease
  - o Coronary artery disease
    - Post myocardial infarction
    - Chronic ischemia
  - o Hypertension
  - o Infectious
  - o Auto-immune
  - o Metabolic/infiltrative
  - o Endocrine
  - o Toxic
  - o Idiopathic
- Valvular disease
- Pericardial disease
- Congenital heart disease
- Arrhythmias (brady-or tachycardia)
- High output states
- Volume overload

Adapted from reference #3

considered as a vicious circle leading to continuing LV dilatation which will eventually lead to progressive heart failure symptoms and finally end-stage heart failure [1,3].

Prevalence and Prognosis

Over the past decades chronic heart failure has emerged as a growing health-care problem in the Western World with an almost "epidemic" increase in the number of patients who develops end-stage heart failure, which makes it one of the major challenges in clinical cardiology today [4-6]. This increase is caused largely by the aging of the population in developed countries, and the improved survival following acute cardiac events such as myocardial infarction.

According to a report by the American Heart Association nearly 5 million people suffer from heart failure in the US alone, with an incidence of 10 per 1000 among persons older than 65 years of age [1,4,5]. These numbers are in line with recent European data that reported an incidence of 14.4 per 1000 among persons aged over 55 [6]. The prevalence of heart failure is somewhat higher in men than in women and shows a strong relationship with increasing age ranging from 0.9% in subjects aged 55-64 years to 17.4% in those aged ≥85 years. At the age of 55 the life-time risk for the development of heart failure is 33% in men and 29% for women [6].

Among patients with heart failure, the rates of related morbidity and mortality are alarmingly high and the prognostic importance of heart failure is often underestimated. Despite the introduction of new pharmacologic therapies, such as ACE inhibitors, beta-blockers and spironolactone, mortality is similar or worse than most cancers; after first admission for heart failure, 1-year survival is 63% and the 5-year survival is only approximately 30% [6,7]. Heart failure mortality is closely related to the severity of heart failure symptoms (Figure 1), the severity of LV dysfunction and the extent of LV remodeling (Figure 2) [7-10]. The predominant modes of death in heart failure patients are either death from progressive heart failure or sudden cardiac death due to ventricular arrhythmias [11].

In addition to the high mortality, patients with heart failure suffer from a considerable morbidity. The quality-of-life of heart failure patients (in particular NYHA class III and IV patients) is usually poor, which is mainly caused by a (severely) reduced exercise capacity resulting in severe limitations of patient activities in daily life. Moreover, heart failure patients frequently suffer from episodes of acute heart failure resulting in hospitalizations. Heart failure is the single most important cause for hospitalizations in patients over 65 and the rate of hospitalizations for acute decompensated heart failure has increased by 159 percent over the last decade which makes heart failure a costly disorder. [1].

Therapeutic options for heart failure

The cornerstone of the treatment of every patient with chronic heart failure is an optimal pharmacological regimen [8,9,12-14]. In the last decade several improvements have been

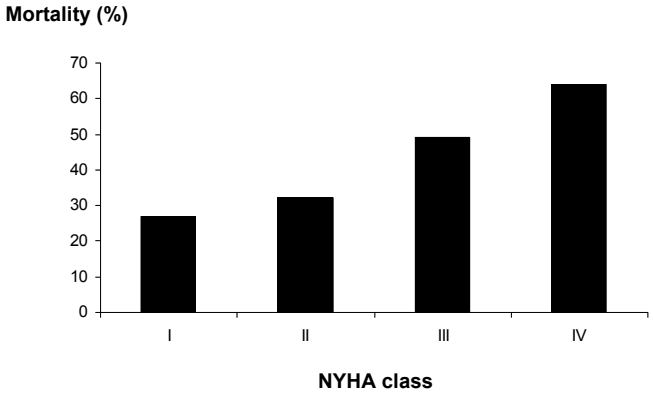

Figure 1: Mortality of heart failure patients according to New York Heart Association (NYHA) functional class after a mean follow-up period of 41.4 months. Data from 2569 heart failure patients included in the SOLVD-trial [8].

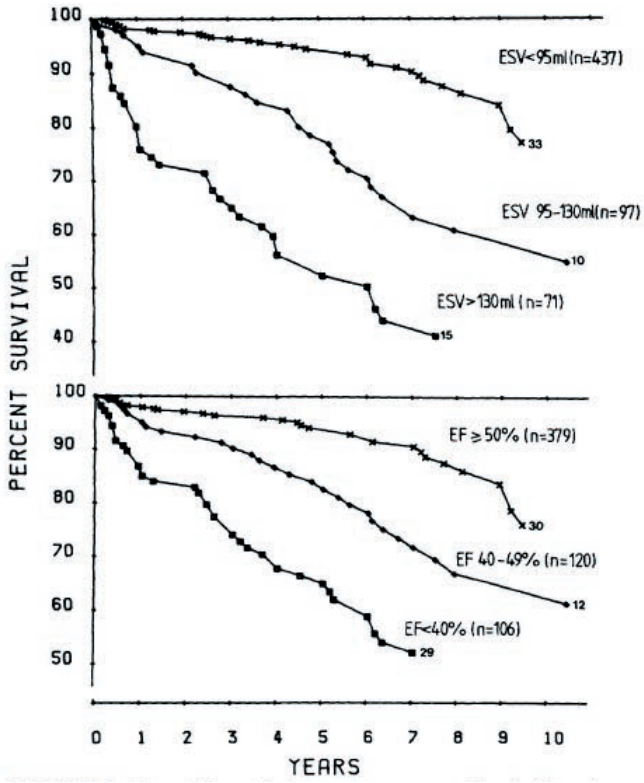

Figure 2: Patient survival according to LV end-systolic volume (ESV) and LV ejection fraction (EF). Survival curves of 605 male patients after myocardial infarction divided into three groups according to their ESVs (top) and EFs (bottom) (reprinted with permission from reference #10)

made in the pharmacological treatment of heart failure with the introduction of ACE inhibitors [8,9,12], beta-blockers [13] and spironolactone [14]. However, despite aggressive medical treatment of heart failure many patients show a progression of heart failure symptoms and their prognosis remains poor.

The presence of patients with drug refractory heart failure has increased great interest in a variety of non-pharmacological treatments for patients with drug-refractory heart failure. Heart transplant probably remains the best solution with a good quality-of-life and a 1-and 5-year survival of 90% and 70%, respectively [15]. However, at present cardiac transplantation is limited to a small minority of patients due to the shortage of donor hearts. In addition, coronary revascularization in the presence of myocardial ischemia is a good option if heart failure is the result of coronary artery disease, however bypass surgery in patients with impaired LV function is associated with a considerable mortality of 10-15% and LV dysfunction frequently persists [16,17]. Other surgical options that are increasingly being used in patients with heart failure include surgical ventricular restoration (Dor plasty) [18,19] or mitral valve surgery [20]. Still, despite these continuous advances, many patients remain in advanced heart failure and/or have a contra-indication for these treatment options.

Thus, the search for other therapies to improve symptoms and survival in patients with chronic heart failure has continued. Now more than a decade ago atrial synchronized biventricular pacing or cardiac resynchronization therapy (CRT) has been introduced for the treatment of heart failure patients [21,22]. CRT has been developed as a novel pacemaker technology that aims at resynchronizing cardiac contractions in order to improve cardiac pumping efficiency. In recent large trials CRT resulted in dramatic improvements in both patient morbidity and mortality and is therefore considered a major revolution in the treatment of patients with drug-refractory heart failure.

CARDIAC RESYNCHRONIZATION THERAPY

CRT has been developed as a novel pacemaker technology that aims at resynchronizing cardiac contractions in patients with drug-refractory heart failure, but without any classic indication for permanent cardiac pacing. The first clinical cases of CRT were described in 1994 by Bakker et al. in the Netherlands [21] and Cazeau et al. in France [22]. After these first promising cases the use of CRT has developed dramatically and is now considered a Class I (level of evidence A) indication in patients with drug refractory heart failure [23,24].

Rationale for CRT

Since many years it has been recognized that in failing hearts, LV function is affected not only by a depressed contractile status of the myocardium, abnormal loading conditions or both, but frequently also by a dyssynchronous activation of the heart, resulting in an inefficient

cardiac pumping function and poor hemodynamics [25-28]. The rationale for CRT is to correct the dyssynchronous activation (and subsequent contraction) of the heart through atrial synchronized biventricular pacemaker stimulation in order to improve LV hemodynamics and cardiac efficiency.

A dyssynchronous activation of the heart is a relatively common problem in heart failure patients and can be divided into three types:

1] atrio-ventricular dyssynchrony,

2] inter-ventricular dyssynchrony (dyssynchrony between the left and the right ventricle)

3] (intra-) LV dyssynchrony (dyssynchrony within the left ventricle).

Atrio-ventricular dyssynchrony

Atrio-ventricular dyssynchrony results from a prolonged atrio-ventricular conduction time. As a consequence the diastolic filling period, in particular the early passive diastolic filling time, is reduced leading to suboptimal ventricular filling. This negatively affects ventricular performance, particularly in patients with already impaired LV function. In addition, a late diastolic mitral regurgitation may occur.

By definition, CRT reduces the AV conduction interval (in patients with intact atrio-ventricular conduction), since the ventricles have to be pre-excited in order to achieve biventricular stimulation. The reduction of the AV-interval by CRT improves diastolic filling time, which has proved to be beneficial in patients undergoing CRT [29].

Inter-ventricular dyssynchrony

In normal hearts, left-and right ventricular contractions occur almost simultaneously. However, heart failure patients frequently exhibit inter-ventricular dyssynchrony (dyssynchrony between the right and the left ventricle), which is usually the result of the delayed activation of the left ventricle. Early activation of the right ventricle may push the inter-ventricular septum into the left ventricle resulting in a dyssynchrony within the left ventricle (LV dyssynchrony) [30].

Left ventricular dyssynchrony

A notable proportion of patients with heart failure has a substantial dyssynchrony within the left ventricle, referred to as LV dyssynchrony [31]. Recent studies have indicated that LV dyssynchrony can heavily affect LV hemodynamics and pumping efficiency [27,32]. The abnormal activation of the left ventricle in the presence of LV dyssynchrony results in a prestretch of the LV region of latest activation (generally the (postero-)lateral wall) during contraction of the early activated segments (usually the inter-ventricular septum). Next, the contraction of the late activated LV region results in a higher stress and systolic stretch of the early activated segments. The LV dyssynchrony reflects a balance of forces, with the early activated region being unable to withstand the stress generated by the late activated LV segments

[25-28,33,34]. The regional wall contractions are not effectively converted to pressure build up in the left ventricle, but rather cause substantial blood volume shifts within the LV cavity. The overall result is a decrease in LV pumping efficiency because LV ejection fraction is reduced despite maintained or even increased energy demand. Other detrimental effects of LV dyssynchrony include mitral valve dysfunction due to a lack of co-ordination of the papillary muscles and an impairment of LV diastolic function related to the late systolic stretch and consequent delayed muscle relaxation [25-28,33,34]. The presence of LV dyssynchrony in patients with heart failure also has clear prognostic implications. Bader et al. [32] studied 104 patients with heart failure and noted that patients with severe LV dyssynchrony were at higher risk of cardiac events than patients without LV dyssynchrony, irrespective of LV ejection fraction [32].

Although still incompletely understood the correction of the LV dyssynchrony is currently believed to be the key beneficial mechanism of CRT. For example Bax et al. evaluated 25 patients undergoing CRT and reported an acute improvement in LV ejection fraction, associated with an immediate reduction in LV dyssynchrony (from 97±35 ms to 28±21 ms, $P<0.05$) [35]. Subsequent studies demonstrated that patients with extensive baseline LV dyssynchrony had a high likelihood of improvement following CRT, whereas patients without LV dyssynchrony did not improve [36-39]. Moreover, all other parameters, including the presence of inter-ventricular dyssynchrony, were unable to predict improvement following CRT [30,36,38].

Technical aspects

To achieve cardiac resynchronization typically three different pacing leads are implanted: one lead will be inserted in the right atrium, one in the right ventricle (usually in the apex) and the other one will be placed on the LV (postero-) lateral wall through the coronary sinus (or in some cases by a minimally invasive surgical technique inserted directly on the LV epicardial region of interest) (Figure 3). These three leads will be connected to a biventricular device and cardiac dyssynchrony is corrected through atrial synchronized biventricular stimulation. The dyssynchrony within the left ventricle is restored by simultaneously stimulating the RV apex (RV pacing lead activates the inter-ventricular septum) and the LV lateral wall (LV pacing lead) [40] (Figure 4). The hemodynamic benefit of CRT can be further enhanced by optimizing the AV pacing interval and (in the latest generation of CRT devices) by adjusting the pacing interval between the right and the LV pacing lead (the VV interval) [41,42].
In addition, ventricular arrhythmias are a frequent observation in patients with impaired LV function. In order to prevent sudden cardiac death in patients undergoing CRT implantation the majority of CRT devices is now combined with a defibrillator backup (ICD) in the same device [40,43,44].

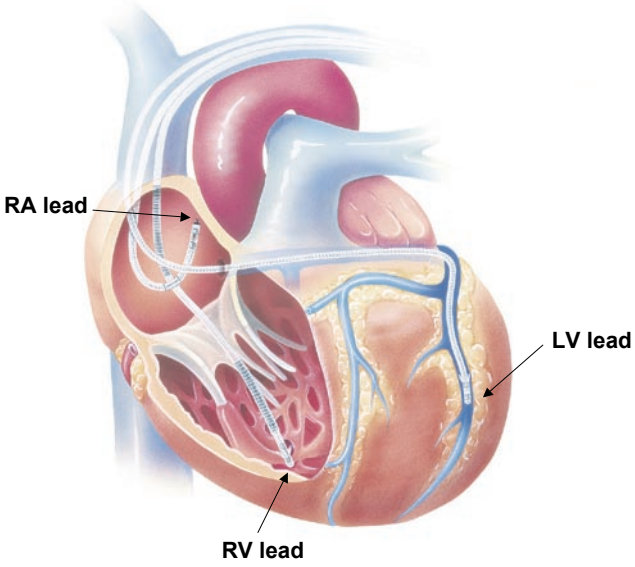

Figure 3: Position of the pacemaker leads in cardiac resynchronization therapy. One lead is positioned in the right atrium (RA lead). One lead is placed in the right ventricle (usually in the apex, RV lead) and the other one will be placed on the LV (postero-) lateral wall through the coronary sinus (LV lead) (or in some cases by a minimally invasive surgical technique inserted directly on the LV epicardial region of interest).

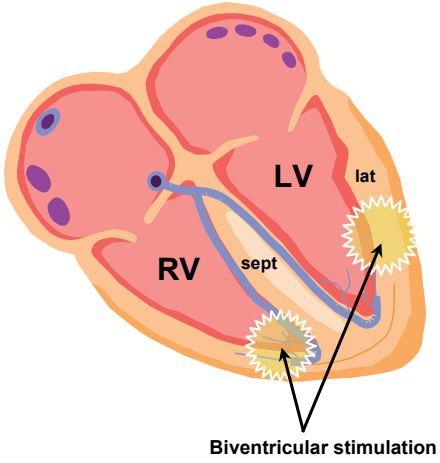

Figure 4: Schematic display of atrial synchronized biventricular stimulation in CRT. After atrial sensing (right atrial lead) both ventricles are stimulated using the right (RV) and left ventricular (LV) pacing leads. LV dyssynchrony generally occurs between the early activated interventricular septum (sept) and the late activated (postero-) lateral LV wall (lat) and is restored through the simultaneous activation of the interventricular septum by the RV pacing lead and the LV (postero-)lateral wall by the LV pacing lead.

Clinical results

After the first cases of CRT reported by Bakker et al. and Cazeau et al. [21,22] the beneficial effects of CRT in patients with drug-refractory heart failure have been widely studied. Several studies have demonstrated the immediate benefit of CRT on hemodynamics and systolic performance of the left ventricle [29,45,46]. Moreover, the immediate benefits of CRT were accompanied by an improvement in heart failure symptoms, exercise capacity, and LV ejection fraction at mid-term follow-up [47-49]. In addition, CRT resulted in a significant LV reverse remodeling and a dramatic reduction in heart failure related hospitalizations. The startling benefits of CRT observed in many smaller studies have now been clearly confirmed in larger randomized controlled multi-center trials which have now included more than 4000 patients [50-61] (Table 2).

The Multicenter InSync Randomized Clinical Evaluation ***(MIRACLE)-trial*** [57] was the first prospective double-blind randomized controlled trial evaluating CRT. In this trial 453 patients (inclusion criteria NYHA class III-IV, QRS duration ≥130 ms and LV ejection fraction ≤35%) underwent successful CRT device implantation. After implantation, patients were randomized to a CRT group (n=228) or a control group (Pacemaker OFF, n=225) for 6 months, while optimal medical therapy for heart failure was maintained. Neither the patients nor the physicians were aware of the treatment assignment. The rate of implantation related complications was very low (1.3%) with 4 patients suffering from refractory hypotension, bradycardia or asystole (2 of whom died) and by perforation of the coronary sinus requiring pericardiocentesis in two others.

Improvements in clinical parameters (NYHA class, quality of life and the distance walked in 6 minutes) at 6 months follow-up were the primary end-points of the MIRACLE-trial. Compared to the control group CRT patients experienced an improvement in the 6 minute walking distance (+39 m versus +10 m, P<0.005), NYHA functional class (Figure 5), quality-of-life (-18.0

Table 2: Major clinical trials on cardiac resynchronization therapy and their main inclusion criteria

	No of patients	NYHA class	QRS duration (ms)	Rhythm
PATH-CHF [50,51]	41	III-IV	≥120	SR
PATH CHF II [52]	86	II-IV	≥120	SR
CONTAK-CD [53]	490	III-IV	≥120	SR
MUSTIC-SR [54,55]	58	III	>150	SR
MUSTIC-AF [55,56]	43	III	>200*	AF
MIRACLE [57]	453	III,IV	≥130	SR
MIRACLE ICD [58]	362	III,IV	≥130	SR
COMPANION [59]	1520	III,IV	≥120	SR
CARE HF [60]	813	III,IV	≥120**	SR

All trials required the presence of an LV ejection fraction ≤35%. * = during right ventricular pacing , ** = when QRS duration was 120-149 patients were required to have echocardiographic evidence of left ventricular dyssynchrony. (NYHA= New York Heart Asssociation, SR = sinus rhythm, AF = atrial fibrillation).

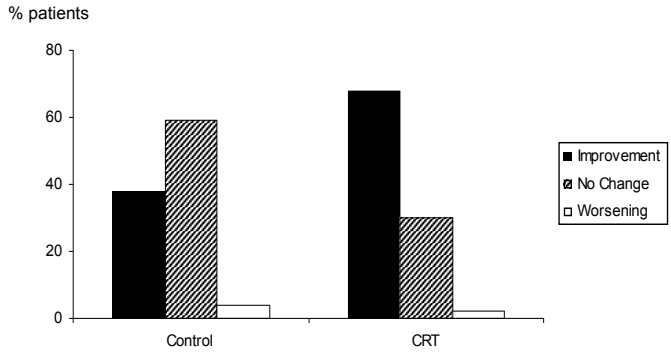

Figure 5: Changes in New York Heart Association functional (NYHA) functional class after 6 months follow-up in the MIRACLE trial [57] for patients in the cardiac resynchronization (CRT) group (n=228) and the control group (n=225). Note that although the level of clinical improvement is higher in the patients undergoing CRT, still 32% of the patients in the CRT group do not improve in NYHA functional class (referred to as clinical non-responders).

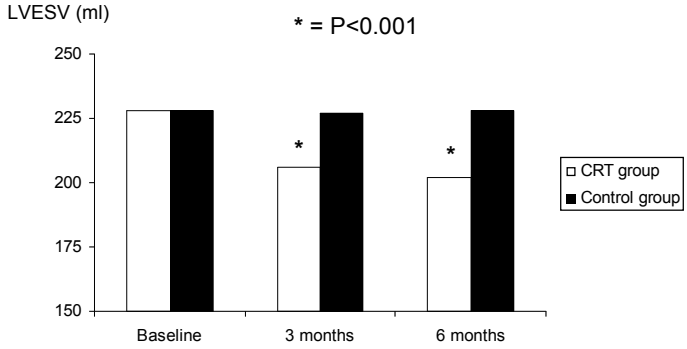

Figure 6 : Changes in left ventricular (LV) end-systolic volume after 3 and 6 months follow-up in the MIRACLE trial [57,61] for patients in the cardiac resynchronization (CRT) group versus the control group (n=225).

versus -9.0 points, P=0.001), time on the treadmill during exercise testing (+81 sec versus +19 sec, P=0.001) and LV ejection fraction (+4.6 % versus -0.2 %). In addition, CRT patients had fewer heart failure hospitalizations than the controls (P=0.02) [57].

In addition, St John Sutton et al. studied the Doppler echocardiograms of the patients in the MIRACLE-trial and revealed the favourable effects of CRT on LV volumes (LV reverse remodeling) (Figure 6) and on the severity of mitral regurgitation. In contrast, the patients in the control group did not experience LV reverse remodeling or improvement in mitral regurgitation [61,62].

Thus, the MIRACLE-trial clearly demonstrated the beneficial effects of CRT on heart failure symptoms, exercise capacity and LV function [57].

The Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure ***(COMPANION)*** trial [59] was the largest prospective multi-center randomized controlled clinical trial to date and was designed to evaluate the effects of CRT on a composite end-point of all-cause mortality and all-cause hospitalization. A total of 1520 patients (inclusion criteria: NYHA class III-IV, LVEF ≤35% and QRS duration ≥120 ms) were randomized in a 1:2:2 ratio to receive optimal pharmacological therapy alone or in combination with a CRT-pacemaker or a combined CRT-defibrillator. This trial confirmed previous findings demonstrating that CRT results in improved clinical symptoms, greater functional capacity and reduced morbidity.

In addition, the risk of death from any cause or hospitalization for heart failure was reduced by 34 % in the CRT-pacemaker group (P<0.002) and by 40% in the CRT-defibrillator group (P<0.001). Also, the CRT-defibrillator reduced the risk of all cause mortality (secondary endpoint) by 36% (P=0.003). Implantation of a CRT-pacemaker however, did not result in a significant decrease in the all-cause mortality of (24% P=0.06). These findings support the use of an ICD backup in patients undergoing CRT implantation [59].

The recently published Cardiac Resynchronization-Heart Failure ***(CARE-HF)-***trial [60] was the first CRT-trial to demonstrate an improvement in all-cause mortality of CRT without an ICD backup compared to patients on optimal medical therapy alone. A total of 813 patients were enrolled (inclusion criteria: NYHA class III-IV, QRS duration ≥120 ms and LV ejection fraction ≤35%). In addition, patients with a QRS duration between 120 of 149 ms were required to meet some (simple) echocardiographic criteria of cardiac dyssynchrony. Patients were randomized in an unblinded fashion to evaluate the effects of CRT without a defibrillator in advanced heart failure. There were 82 deaths in the CRT group, as compared with 120 in the medical-therapy group (20% versus 30%, P<0.002) (Figure 7). Heart failure hospitalizations were reduced by 52% and the positive effects of CRT on LV ejection fraction, mitral regurgitation and LV end-systolic volume were confirmed.

Thus, the CARE-HF trial demonstrated for the first time the beneficial effects of CRT (without an ICD) on survival in patients with drug-refractory heart failure [60].

The vast majority of the randomized CRT-trials trials only included patients in sinus rhythm. At present, the evidence for the use of CRT in patients with atrial fibrillation is less strong. The Multisite Stimulation In Cardiomyopathies and Atrial Fibrillation ***(MUSTIC-AF)*** [56] is the only randomized CRT trial addressing the issue of CRT in patients with atrial fibrillation. In this trial 43 patients were randomized in a crossover study of three months for biventricular pacing versus three months of RV pacing, both in VVIR-mode (ventricular inhibited pacing). In the patients with effective CRT the mean walked distance increased by 9.3% (P=0.05) and peak oxygen uptake increased by 13% (P=0.04). In addition, the number of hospitalizations decreased by 70% and 85% of patients preferred the biventricular pacing period (P<0.001) [56].

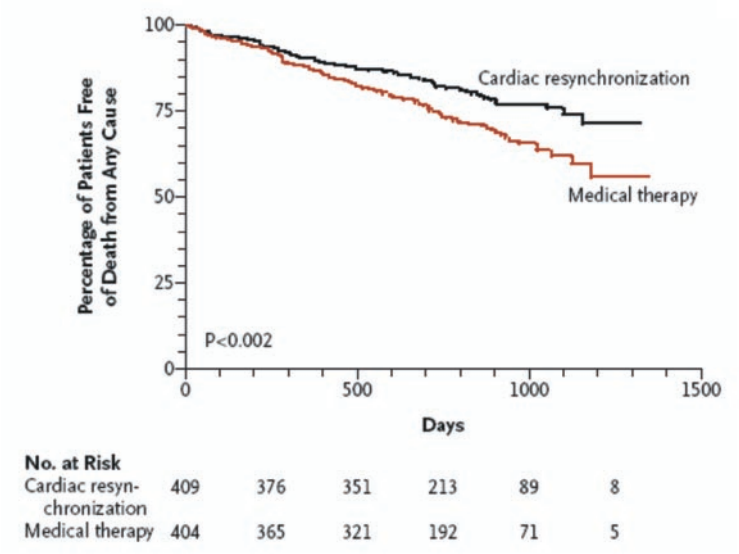

Figure 7 : Kaplan-Meier curves of the time to all-cause mortality (optimal medical therapy versus cardiac resynchronization without ICD) in the CARE-HF trial. (reprinted with permission from reference #60).

CRT selection criteria

(HRS/AHA/ACC guidelines 2005)

- NYHA class III-IV
- LV ejection fraction ≤35%
- QRS duration ≥120 ms
- Sinus rhythm
- Optimal medical therapy

Figure 8 : Current implantation criteria for a cardiac resynchronization (CRT) device according to the 2005 HRS/AHA/ACC guidelines (level of evidence IA, HRS = Heart Rhythm Society, AHA = American Heart Association, ACC = American College of Cardiology) [23].

Based on the results from these large trials (Table 2) CRT is now considered a Class I (level of evidence A) indication in patients drug refractory moderate-to-severe heart failure (NYHA class III/IV), QRS duration ≥120 ms, sinus rhythm and LV ejection fraction ≤35% (Figure 8).

The issue of non-responders to CRT

Despite the impressive results of CRT in recent large randomized trials a consistent number of patients fails to improve following CRT implantation when the established CRT selection criteria (NYHA class III-IV heart failure, LV ejection fraction ≤35% and QRS duration >120 ms)

were applied. For example, close analysis of the data from the MIRACLE trial revealed that 32% of patients did not improve or even worsened in NYHA class after 6 months of CRT [57] (Figure 5). The presence of clinical non-responders to CRT has now been confirmed in several other studies and is usually around 30% [47,59] . In addition, if response to CRT is defined using more objective parameters such absence of LV reverse remodeling or lack of improvement in LV ejection fraction on echocardiography at mid-term follow-up the number of non-responders is usually between 40-50% [39].
In view of the unnecessary procedure risks and health care expenses in patients without response to CRT the percentage of non-responders among patients selected according to the current selection criteria (Figure 8) is unacceptably high and should be reduced.

AIM AND OUTLINE OF THE THESIS

The relatively high number of patients without benefit from CRT (referred to as non-responders) indicates the need for refinement of the current selection criteria in order to 1] better identify those patients with the highest likelihood of response to CRT and 2] avoid device implantations in patients that are unlikely to respond to CRT.
The aim of the current thesis was to improve and refine the current CRT selection criteria through the evaluation of the mechanisms underlying (non-) response to CRT.
In **part I** the clinical and echocardiographic response rates to CRT were studied and compared between different patient subgroups. The effects of age and gender on response to CRT were studied in Chapter 2 and Chapter 3. The precise relationship between clinical and echocardiographic response following CRT was evaluated in Chapter 4 in order to better understand and define response to CRT
In **part II** the pathophysiological mechanisms underlying clinical and echocardiographic benefit to CRT were studied on a ventricular level. The positive effects of CRT on both left and right ventricular size and function were evaluated in Chapters 5 and 6. The mid-term hemodynamic effects of CRT were studied using pressure-volume loop in Chapter 7. Finally, the beneficial effects of CRT were related to the effects of CRT on LV dyssynchrony (Chapter 8).
Next, the information about the mechanisms of (non-)response to CRT derived from parts I and II was used in **part III** to develop improved selection criteria for CRT. The ability of QRS duration to detect LV dyssynchrony was tested in Chapter 9 and in chapter 10 the occurrence of LV dyssynchrony was evaluated in a group of heart failure patients with a narrow QRS complex. The ability of M-mode echocardiography to detect LV dyssynchrony and to predict response to CRT was evaluated in Chapter 11. Next, a novel echocardiographic technique called color-coded tissue Doppler imaging (TDI) was used to quantify LV dyssynchrony and to predict response to CRT (Chapter 12). The relationship between scar tissue in the postero-

lateral LV segments (which is usually the area of the LV pacing tip) and response to CRT was evaluated in chapter 13 using contrast enhanced MRI.

The better understanding of the mechanisms of benefit from CRT in parts I and II and the development of additional selection criteria in part III led to the observation that several patients groups outside the current selection criteria may potentially benefit from CRT. These novel indications for CRT are evaluated in **part IV**. In chapter 14 the effects of CRT are tested in patients with a narrow QRS complex (<120 ms) and LV dyssynchrony and in chapter 15 the effects of CRT were investigated in patients with a mild symptoms of heart failure (NYHA class II).

Part V (Chapter 16) contains an integration of the information described in chapters 2-15 and gives an overview of the optimal use of different non-invasive imaging modalities, in particular echocardiography, in patients undergoing CRT implantation, both before implantation (to optimize patient selection), as well as during follow-up (evaluation of therapy success and optimization of pacemaker settings).

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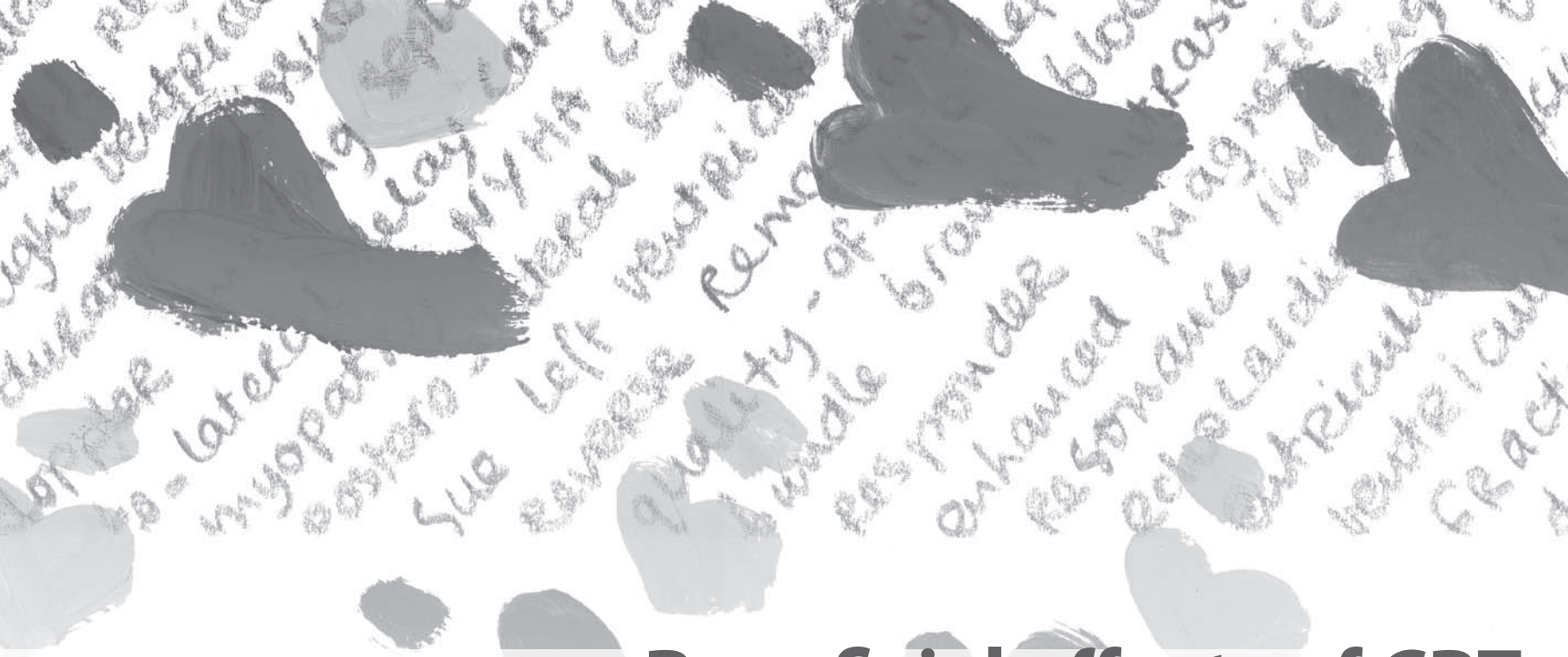

Beneficial effects of CRT

Part I

Chapter 2

Comparison of effectiveness of cardiac resynchronization therapy in patients <70 vs ≥70 years of age

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ABSTRACT

In the present study, the effects of cardiac resynchronization therapy (CRT) in elderly patients were evaluated. The study included 170 consecutive patients whose clinical and echocardiographic improvements were evaluated at 6 months follow-up. Survival was evaluated up to 2 years. The effects of CRT in elderly patients (≥70 years) were compared to results in younger (<70 years) patients.

INTRODUCTION

Cardiac resynchronization therapy (CRT) has been demonstrated to be beneficial in patients with end-stage heart failure despite optimized medical therapy. Various studies have shown improvement in heart failure symptoms, exercise capacity and left ventricular (LV) systolic function [1-4]. However, patient responses to CRT vary significantly. Whether patient age would negatively affect response to CRT is currently unknown; this is an important issue, since the majority of patients with heart failure are of older age. Accordingly the beneficial effects of CRT were evaluated in patients ≥70 years and compared to results obtained in patients <70 years.

METHODS

Patients and study protocol

A total of 170 consecutive patients with heart failure, scheduled for the implantation of a CRT device, were included. The following selection criteria for CRT were applied: moderate-to-severe heart failure (New York Heart Association (NYHA) class III or IV), LV ejection fraction ≤35% and QRS duration >120 ms with left bundle branch block configuration). Patients with a recent myocardial infarction (<3 months) or decompensated heart failure were excluded. Before pacemaker implantation, clinical status was assessed and two-dimensional echocardiography was performed to assess LV volumes and LV ejection fraction. Next, tissue Doppler imaging was performed to evaluate LV dyssynchrony; tissue Doppler imaging was also used to assess resynchronization immediately after implantation. 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. Patients with an improvement of at least 1 NYHA functional class at 6 months follow-up were classified as responders. Data on long-term survival were collected by chart review and telephone contact. Follow-up data were acquired up to 2 years.

Echocardiography

Patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed system FiVe/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). The LV volumes (end-systolic,

end-diastolic) and LV ejection fraction were calculated from the conventional apical 2- and 4-chamber images, using the biplane Simpson's technique [5].

For tissue Doppler imaging, color Doppler frame rates varied between 80 and 115 frames/s depending on the sector width of the range of interest; pulse repetition frequencies were between 500 Hz and 1 KHz, resulting in aliasing velocities between 16 and 32 cm/s. Data were analyzed using commercial software (Echopac 6.1, General Electric - Vingmed). To determine LV dyssynchrony, the sample volume was placed in the basal portions of the septum and the LV lateral wall; peak systolic velocities and time-to-peak systolic velocities were obtained and the septal-to-lateral delay in peak velocity was calculated as an indicator of LV dyssynchrony. Based on previous observations a septal-to-lateral delay >60 ms was considered to represent substantial LV dyssynchrony [6]. Inter- and intra-observer agreement for assessment of septal-to-lateral delay were 90% and 96%, respectively [7]. Echocardiographic data were analyzed by 2 independent observers, blinded to clinical outcome.

Pacemaker implantation

The LV pacing lead was inserted transvenously via the subclavian route. First, 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. When a conventional indication for an internal defibrillator existed, a combined device was implanted. In all patients the implantation of the CRT device (Contak TR or CD, Guidant, Minneapolis, Minnesota, and Insync III or CD, Medtronic Inc., Minneapolis, Minnesota) was successful without major complications. Two types of LV leads were used (Easytrak 4512 to 80, Guidant, or Attain-SD 4189, Medtronic Inc.).

Statistical analysis

Data are presented as mean ±SD, and compared using (un-)paired Student's t-test when appropriate. Univariate analysis for categorical variables was performed using the chi-square test with Yates' correction. Simultaneous comparison of >2 values was performed by using one-way ANOVA with Bonferroni correction. Survival was evaluated by the method of Kaplan-Meier. For all tests, a P-value <0.05 was considered statistically significant.

RESULTS

Study population

A total of 170 consecutive patients were included, the study population comprised 137 men/33 women with a mean age of 66±11 years (range 18-85 years); 102 patients were aged <70 years and 68 patients were ≥70 years. Mean NYHA class was 3.2±0.4, with most patients

in NYHA class III (83%). Severe dilatation of the LV was observed in most patients (LV end-diastolic volume 254±86 ml and LV end-systolic volume 201±79 ml), accompanied by an LV ejection fraction of 21±9%. Tissue Doppler imaging demonstrated severe LV dyssynchrony in this patient group (98±60 ms).

The baseline characteristics of the patients <70 years and the patients ≥70 years are summarized in Table 1. Patients ≥70 years were more likely to have an ischemic origin of the cardiomyopathy (48% vs. 66%, P<0.05). No other differences in baseline characteristics were observed between these patient groups.

Post-implantation

Following CRT implantation, QRS duration decreased from 173±27 ms to 153±24 ms (P<0.001). Tissue Doppler imaging demonstrated a reduction in LV dyssynchrony immediately after implantation from 98±60 ms to 36±33 ms (P<0.001), indicating LV resynchronization. Within 6 months after CRT, 10 patients (6%) died, (6 patients due to refractory heart failure, 3 patients due to sudden cardiac death; in 1 patient the cause of death was unknown). Another 2 patients (1%) underwent cardiac transplantation within 6 months following CRT implantation, both because of ongoing heart failure. Because these patients did not have the 6-month follow-up assessment, they could not be included in the comparison of response to CRT, but they were included in the comparison of survival following CRT. In addition, no differences were observed between the baseline characteristics of patients with (n=158) and without (n=12) 6-month follow-up assessment.

Table 1. Baseline characteristics of patients <70 years (n=102) versus patients ≥70 years (n=68).

	<70 years	≥70 years
Age (years)	59±9	76±4
Male/Female	80/22	57/11
NYHA class		
III	83	58
IV	19	10
Etiology		
Ischemic	49 (48%)*	45 (66%)*
Idiopathic	53 (52%)	23 (44%)
QRS duration (ms)	175±28	171±24
6-minute walking distance (m)	290±142	250±125
Quality-of-life score	42±16	41±14
LV ejection fraction (%)	22±8	21±7
LV end-diastolic volume (ml)	261±84	239±79
LV end-systolic volume (ml)	207±79	191±71
LV dyssynchrony (ms)	100±60	95±59

* = P<0.05

Clinical and echocardiographic improvement following CRT

At 6 months follow-up the clinical status of the patients was re-assessed. NYHA class improved from 3.2±0.4 to 2.2±0.7 (P<0.001). In addition, the Minnesota score decreased from 42±16 to 27±17 (P<0.001) and the 6-minute walking distance increased from 273±138 to 385±148 (P<0.001). Based on lack of improvement in NYHA class at 6 months, 38 patients (24%) were classified as non-responders.

LV ejection fraction improved from 21±8% to 28±9% (P<0.05), associated with a significant reduction in LV volumes (end-systolic volume from 200±76 ml to 163±74 ml and end-diastolic volume from 252±82 ml to 220±79 ml, both P<0.05).

Patients <70 years versus patients ≥70years

The extent of immediate resynchronization was similar between the patients <70 years and ≥70 years (from 100±60 ms to 36±32 ms (P<0.001) vs. from 95±59 ms to 35±34 ms (P<0.001), respectively, ns). In addition, both patient groups showed a significant improvement in clinical symptoms at 6 months follow-up. Improvements in NYHA class, Minnesota- score and 6-minute walking distance were similar in both groups (Table 2). The number of non-responders was equal in the patients <70 years and ≥70 years (response rate 75% vs. 78%, respectively, ns). Furthermore, improvement in LV ejection fraction and the extent of LV remodeling were

Table 2. Six months follow-up results in patients <70 years (n=102) versus patients ≥70 years (n=68).

	<70 years (n=102)	≥70 years (n=68)
NYHA class		
Baseline	3.2±0.4	3.1±0.4
Follow-up	2.2±0.7*	2.2±0.6*
6- minute walking distance (m)		
Baseline	290±142	250±125
Follow-up	399±154*	363±139*
Quality-of-life score		
Baseline	42±16	41±14
Follow-up	28±17*	27±16*
LV end-systolic volume (ml)		
Baseline	207±79	191±71
Follow-up	173±78*	150±65*
LV end-diastolic volume (ml)		
Baseline	261±84	239±79
Follow-up	230±83*	206±72*
LV ejection fraction (%)		
Baseline	22±8	21±7
Follow-up	28±10*	28±9*
Died within 6 months	5 (5%)	5 (7%)
Heart transplantation within 6 months	2 (2%)	0

*:P<0.05 follow-up vs. baseline value.

not statistically different between the two groups (Table 2). Survival at 1 year after implantation was comparable in the patients <70 years (90%;95% confidence interval 84-96%) and patients ≥70 years (83%;95% confidence interval 73-93%, ns, Figure 1).

DISCUSSION

Despite the encouraging results from CRT in recent trials, the individual responses to CRT vary significantly. It is currently unclear whether elderly patients respond less favorably to CRT as compared to younger patients. If age would have an influence on clinical outcome, this may be an argument to restrict the use of CRT according to age. Therefore, in the present study, the beneficial effects of CRT were compared between patients <70 years versus patients ≥70years. Elderly patients were more likely to have an ischemic etiology of cardiomyopathy as compared to patients <70 years. Other baseline clinical and echocardiographic characteristics were similar; in particular, the extent of LV dyssynchrony (assessed by tissue Doppler imaging) was comparable. Immediately after implantation of the CRT device, tissue Doppler imaging showed a substantial decrease in LV dyssynchrony, which was similar in patients <70 years and patients ≥70 years; this observation indicates that resynchronization following CRT occurs also in elderly patients.

At 6 months follow-up, CRT proved beneficial in both groups, as reflected by an improvement in clinical and echocardiographic parameters. Moreover, the magnitude of improvement was comparable between the two groups, both in clinical (NYHA class, quality-of-life score and 6-minute walking distance), as well as in echocardiographic parameters (improvement in LV

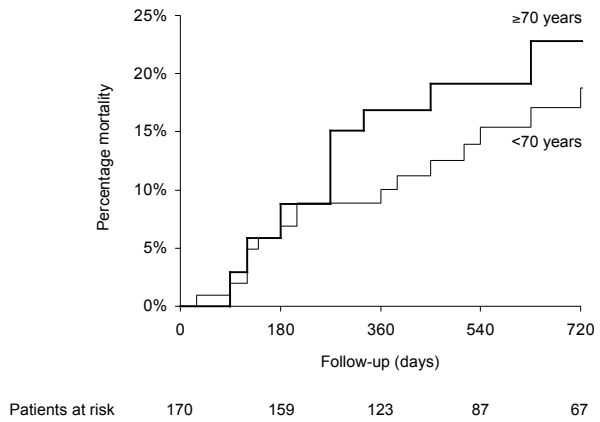

Figure 1: One-year survival was similar in patients <70 years (n=102) and patients ≥70 years (n=68), (90% vs. 83%, ns).

ejection fraction and the extent of LV reverse remodeling). In addition, the number of non-responders was comparable between the patients <70 years (25%) and the patients ≥70 years (22%). Although the definition of a clinical responder by an improvement of ≥1 NYHA class is widely used, this remains a somewhat subjective parameter, which may be considered as a limitation. Finally, patient survival was not different between the patients groups.

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Chapter 3

Does a gender difference in response to cardiac resynchronization therapy exist?

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ABSTRACT

Background

Cardiac resynchronization therapy (CRT) has a beneficial effect on clinical symptoms, exercise capacity and systolic left ventricular (LV) performance in patients with heart failure. The aim of the current study was to evaluate whether a gender difference exists in the response to CRT.

Methods

Consecutive patients with end-stage heart failure (NYHA class III-IV), LV ejection fraction ≤35%, QRS duration >120 ms, and left bundle branch block configuration underwent CRT. At baseline and 6 months post-CRT, clinical and echocardiographic parameters were evaluated; follow-up was obtained up to 5 years. The effects of CRT were compared between women and men.

Results

The study population comprised 137 men and 36 women (mean age 66±11 years). No differences in baseline characteristics were observed except that non-ischemic cardiomyopathy was more frequent in women than men (67% vs. 38%, P<0.05).

In all patients, clinical and echocardiographic parameters improved significantly at 6 months follow-up. The magnitude of improvement in different parameters was similar between women and men; e.g. the improvement in NYHA class was 0.9±0.6 in women and 1.0±0.7 in men (NS) and the increase in LV ejection fraction was 8±8% in women as compared to 7±9% in men (NS). The percentage of individual responders was not different between women and men (76% vs. 80%, NS) and 2-year survival was comparable for women and men (84% vs. 80%, NS).

Conclusion

No gender differences were observed in response to CRT and long-term survival after CRT.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is currently considered a major breakthrough in the treatment of patients with drug-refractory heart failure. In recent years, several major randomized trials have shown the beneficial effects of CRT on clinical symptoms, exercise capacity and left ventricular (LV) systolic function [1-4]. More recently, it was demonstrated in the CARE-HF trial that CRT also increased survival as compared to optimized medical therapy, and this was associated with a significant reduction in the number of re-hospitalizations for heart failure [4].

Despite these impressive results, it is known that individual response to CRT varies significantly. Whether a gender-related difference in response to CRT exists is unknown. This is an important issue, since various studies pointed out the gender differences in presentation of coronary artery disease and differences in response to therapy [5-7]. Accordingly, the objective of the present study was to evaluate whether a gender difference exists in response to CRT. To address this issue, the effects of CRT on clinical symptoms, LV function and survival were evaluated in a consecutive cohort of patients undergoing CRT and the responses between women and men were compared.

METHODS

Study Population

A total of 173 consecutive patients with heart failure, scheduled for the implantation of a CRT device, were included. The following selection criteria for CRT were applied: moderate-to-severe heart failure (New York Heart Association (NYHA) class III or IV), LV ejection fraction (EF) ≤35% and QRS duration >120 ms with left bundle branch block configuration. Patients with a recent myocardial infarction (<3 months) or decompensated heart failure were excluded.

Before pacemaker implantation, clinical status was assessed and 2D echocardiography was performed to assess LV volumes and LVEF. Next, tissue Doppler imaging (TDI) was performed to evaluate LV dyssynchrony. LV dyssynchrony was re-assessed immediately after implantation. Clinical status, LVEF 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. Patients with an improvement of at least 1 NYHA functional class at 6 months follow-up were classified as responders.

In addition, long-term follow-up was performed by chart review, telephone contact and outpatient clinical visits. Events were classified as death or heart transplantation. Follow-up data were acquired up to 5 years.

Echocardiography and Tissue Doppler Imaging

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 and 2- and 4-chamber images). Standard 2D and color Doppler data, triggered to the QRS complex, were saved in cine-loop format. The LV volumes (end-systolic, end-diastolic) and LVEF were calculated from the conventional apical 2- and 4-chamber images, using the biplane Simpson's technique [8].

For TDI, color Doppler frame rates varied between 80 and 115 frames/s depending on the sector width of the range of interest; 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 images of 3 consecutive heart beats by offline analysis. Data were analyzed using commercial software (Echopac 6.1, General Electric - Vingmed).

To determine LV dyssynchrony, the sample volume was placed in the basal portions of the septum and the LV lateral wall; peak systolic velocities and time-to-peak systolic velocities were obtained and the septal-to-lateral delay in peak velocity was calculated as an indicator of LV dyssynchrony [9,10]. Based on previous observations a septal-to-lateral ≥65 ms was considered to represent substantial LV dyssynchrony [9]. Inter- and intra-observer agreement for assessment of septal-to-lateral delay were 90% and 96%, respectively [11]. Echocardiographic data were analyzed by 2 independent observers, blinded to clinical outcome.

Pacemaker Implantation

The LV pacing lead was inserted transvenously via the subclavian route. First 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. When a conventional indication for an internal defibrillator existed, a combined device was implanted. In all patients the implantation of the CRT-device (Contak TR or CD, Guidant, Minneapolis, Minnesota, USA and Insync III or CD, Medtronic Inc., Minneapolis, Minnesota, USA) was successful without major complications. Two types of LV leads were used (Easytrak 4512 to 80, Guidant, or Attain-SD 4189, Medtronic Inc.).

Statistical Analysis

Data are presented as mean ±SD, and compared using (un-)paired Student's t-test when appropriate. Univariate analysis for categorical variables was performed using the chi-square test with Yates' correction. Survival was evaluated by the method of Kaplan-Meier. For all tests a P-value <0.05 was considered statistically significant.

RESULTS

Study Population

The study population comprised 173 patients (137 men, mean age 66±11 years) with a wide QRS complex (mean QRS duration 173±27 ms) and left bundle branch block configuration. Most patients were in NYHA class III (87%). The majority of the patients (88%) were in sinus rhythm. Severe dilatation of the LV was present in most patients (LV end-diastolic volume 254±81 ml and LV end-systolic volume 202±75 ml), with a mean LV ejection fraction of 21±9%. TDI showed the presence of severe baseline LV dyssynchrony (98±59 ms).

In Table 1, the baseline characteristics of men and women are compared. Male patients more frequently had ischemic cardiomyopathy (62% vs. 33%, P<0.05), whereas female patients more frequently had non-ischemic cardiomyopathy. No other differences in baseline characteristics were observed between the groups.

Table 1. Baseline characteristics of the study population (n=173).

	Men (n=137)	Women (n=36)	P-value
Age (yrs)	66±11	65±11	NS
NYHA class			
III	117 (85%)	33 (92%)	NS
IV	20 (15%)	3 (8%)	
Etiology			
Ischemic	85 (62%)	12 (33%)	P<0.05
Idiopathic	52 (38%)	24 (67%)	
QRS (ms)	173±28	168±35	NS
6-MWT (m)	248±113	225±135	NS
LVEF (%)	21±8	21±7	NS
LVEDV (ml)	257±82	242±78	NS
LVESV (ml)	204±76	193±72	NS
LV dyssynchrony (ms)	101±61	86±47	NS

LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; 6-MWT: 6-minute walk test; NYHA: New York Heart Association; QoL: quality of life score.

Following CRT implantation, QRS duration decreased from 173±27 ms to 153±23 ms (P<0.001). TDI demonstrated a reduction in LV dyssynchrony immediately after implantation from 98±59 ms to 36±33 ms (P<0.001), indicating LV resynchronization. Within 6 months after CRT, 8 patients (5%) died, (5 patients due to worsening heart failure, 2 patients due to sudden cardiac death and in 1 patient the cause of death was unknown). Another 2 patients (1%) underwent cardiac transplantation within 6 months following CRT implantation because of worsening heart failure. These patients did not have the 6-month clinical and echocardiographic follow-up assessment; they were included in the comparison of survival following CRT, but could not be included in the comparison of 6-months response to CRT. Of note, no differences were observed between the baseline characteristics of patients with (n=163) and without (n=10) the 6-month follow-up assessment.

Clinical and Echocardiographic Changes After 6-months of CRT

At 6 months follow-up, the clinical status of the patients was re-assessed. NYHA class improved from 3.1±0.3 to 2.1±0.7 (P<0.001). In addition, the Minnesota score decreased from 41±15 to 26±16 (P<0.001) and the 6-minute walking distance increased from 243±110 m to 358±136 m (P<0.001). Based on lack of improvement in NYHA class at 6-month follow-up, 35 patients (20%) were classified as non-responders.

Long-term Follow-up

The mean follow-up was 21±14 months (range 1-60 months). During follow-up, 33 (19%) patients died: 4 patients died of sudden cardiac death, 21 due to end-stage heart failure, 1 due to acute myocardial infarction, 3 of non-cardiac origin (1 septic shock, 1 prostate cancer and 1 cerebral hemorrhage) and in 4 patients the cause of death was unknown. Three patients (2%) underwent cardiac transplantation for progressive heart failure. The event-free survival at 1- and 2-year follow-up was 87% and 81% respectively.

Gender versus Response to CRT

The effects of CRT in men versus women are shown in Table 2. The mean reduction in QRS duration was not different in men and women (19±29 ms vs. 25±21 ms, NS). Also, the extent of immediate LV resynchronization was similar between men and women (64±61 ms vs. 54±45 ms, NS).

Both men and women showed a significant improvement in clinical criteria at 6-months follow-up. The reduction in NYHA class was comparable between men and women: 1.0±0.7 in men vs. 0.9±0.6 in women (NS). Also, the improvement in symptoms was not different: the reduction in Minnesota quality-of-life score was 15±14 in men as compared to 16±13 in women (NS). Moreover, the improvement in exercise capacity was similar: the 6-minute walking distance improved on average 114±98 m in men and 121±111 m in women (NS). The absolute number of clinical responders was also not different between men and women (80% vs. 76%, see Figure 1). The

Table 2. Men versus women, clinical variables at 6 months follow-up.

	Men (n=137)	Women (n=36)	P-value
NYHA class			
baseline	3.1±0.4	3.1±0.3	NS
follow-up	2.1±0.7*	2.2±0.6*	NS
6-MWT (m)			
baseline	248±113	225±135	NS
follow-up	362±142*	345±142*	NS
QoL score			
baseline	40±15	45±14	NS
follow-up	25±16*	29±16*	NS
LVESV (ml)			
baseline	204±76	193±72	NS
follow-up	167±71*	156±90*	NS
LVEDV (ml)			
baseline	257±82	242±78	NS
follow-up	226±77*	206±93*	NS
LVEF (%)			
baseline	21±8	21±7	NS
follow-up	28±9*	29±11*	NS
Died within 6 months	8 (6%)	0	NS
HTX within 6 months	1 (1%)	1 (3%)	NS

EDV: End-systolic volume; ESV: End-systolic volume; HTX: heart transplantation; LVEF: Left ventricular ejection fraction; 6-MWT: 6-minute walk test; NYHA: New York Heart Association; QoL: quality of life score.

*: $P<0.05$ follow-up vs. baseline value.

increase in LV ejection fraction was comparable (on average 7±9% in men and 8±8% in women, NS) and the extent of LV reverse remodeling was similar between men and women (see Table 2). Finally, no differences were observed in long-term survival between men and women. The 1-year survival was 86% in men vs. 93% in women (NS), whereas the 2-year survival was 80% in men and 84% in women (NS, see Figure 2).

DISCUSSION

Over the past few years, the beneficial effect of CRT in patients with end-stage heart failure has been demonstrated in various studies. These studies have reported improvements in heart failure symptoms, quality of life, exercise capacity and systolic LV function, associated with a reduction in LV volumes (reverse LV remodeling) following CRT [1-4,12]. These beneficial effects were also observed in the current study. More recently, a superior long-term survival after CRT as compared to optimized medical therapy was shown [4]. The 2-year survival in the current study was comparable to that in the previously reported studies [3,4].

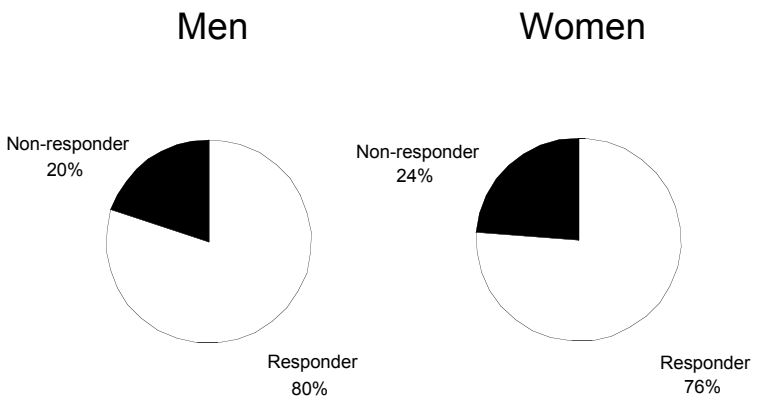

Figure 1. No significant difference was observed in the percentage of responders and non-responders to CRT in men (n=137) and women (n=36), (80% vs. 76%, NS).

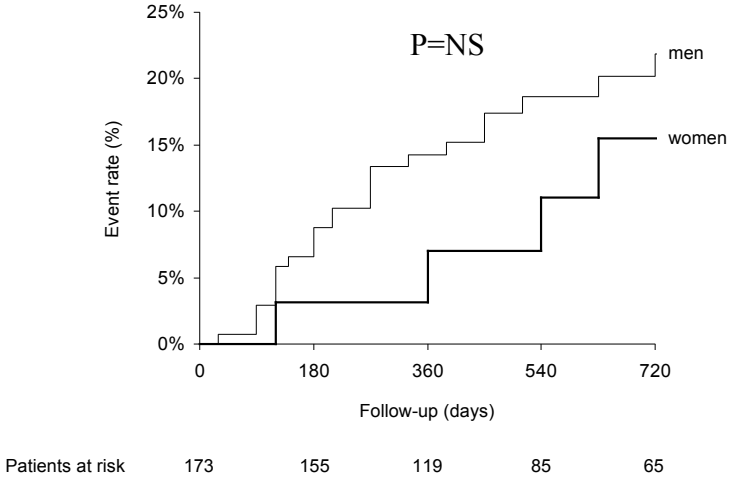

Figure 2. Kaplan-Meier curves of the event rates (death or heart transplantation) in men (n=137) and women (n=36) over a 2-year follow-up period, demonstrating no significant difference in event-free survival between men and women.

However, despite the impressive results from CRT in major trials, individual response to CRT still varies substantially. Careful analysis of the data from the MIRACLE trial revealed that 20-30% of patients did benefit from CRT [1]. Similar percentages of non-responders were reported in other studies [9,10,13,14]. In the current study, 20% of patients did not respond to CRT.

At present, only limited data are available regarding differences in benefit from CRT among different patient subgroups. For example, it is unknown whether gender influences response

to CRT. This is a relevant issue, since previous studies concerning women and heart disease have reported epidemiologic, diagnostic and prognostic differences between women and men [5-7, 15-17]. This may be of particular importance in heart failure. For example, data from the SOLVD trial revealed that women experienced a lesser reduction in mortality and re-hospitalizations after treatment with enalapril as compared to men [18,19].

In the present study the potential effect of gender on response to CRT was evaluated in a large cohort of consecutive patients with heart failure referred for CRT according to established selection criteria [20]. The percentage of women included in the current study was 21%, which is comparable to the percentage of women included in the large, randomized CRT trials (ranging from 27% to 32%) [1-4]. Moreover, the percentage of women included in large, randomized drug trials in heart failure usually varies between 15% to 30% [18,21,22], although it has been suggested that the percentage of women with moderate-to-severe heart failure in the general population may be higher [15,23,24]. Thus, the relatively low percentage of women included in CRT trials may indicate a referral bias, as already suggested in previous studies reporting a lower referral rate in women for diagnostic and therapeutic procedures [16,25].

In the current study, no differences were observed in baseline characteristics between men and women, except for the significantly higher percentage of women with non-ischemic cardiomyopathy (67% vs. 38%, $P<0.05$). Immediately after implantation of the CRT device, TDI showed a substantial decrease in LV dyssynchrony in men and women, indicating no gender difference in resynchronization after onset of CRT.

The immediate LV resynchronization was followed by a significant improvement in clinical and echocardiographic parameters at mid-term follow-up in both groups. Moreover, the magnitude of improvement in clinical parameters (NYHA class, quality-of-life score and 6-minute walking distance), as well echocardiographic parameters (LV ejection fraction, LV volumes) was comparable between men and women. Importantly, the percentage of non-responders to CRT was also not different between men (20%) and women (24%). Finally, patient survival at 1-year (86% for men and 93% for women) and 2-year follow-up (80% and 84%, respectively) were not different.

Conclusion

The percentage of women referred for CRT is lower than man. However, no gender differences were observed in individual response rate to CRT. Men and women experienced a comparable benefit from CRT in terms of improvement in clinical and echocardiographic parameters. Also, 2-year survival after CRT was not different between men and women.

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Chapter 4

Clinical versus echocardiographic parameters to assess response to cardiac resynchronization therapy

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ABSTRACT

Currently, a clear definition of response to cardiac resynchronization therapy (CRT) is still lacking and both clinical and echocardiographic end-points are used. It is also unclear whether patients with clinical response also improve in echocardiographic end-points (and vice versa). To better understand and define response to CRT, the relation between improvement in clinical and echocardiographic parameters was evaluated in 144 patients.

INTRODUCTION

Cardiac resynchronization therapy (CRT) has been demonstrated beneficial in patients with end-stage heart failure [1]. However, patient responses to CRT vary significantly [2,3]. It is currently unclear what the precise relation is between response (or non-response) following CRT defined by clinical parameters as compared to echocardiographic parameters. It is unknown whether patients with a clinical response to CRT also improve in echocardiographic parameters (and vice versa). Accordingly, the correlation between clinical and echocardiographic response to CRT was evaluated in 144 consecutive patients.

METHODS

Patients and study protocol

Consecutive patients with severe heart failure, scheduled for implantation of a CRT device were prospectively included in the study. Patients were selected according to established selection criteria for CRT: 1) severe heart failure (New York Heart Association (NYHA) class III or IV); 2) left ventricular (LV) ejection fraction (EF) ≤35% and 3) QRS duration ≥120 ms with left bundle branch block configuration.

Patients with a recent myocardial infarction (<3 months) or decompensated heart failure were excluded. The study protocol was as follows: before CRT implantation, clinical status was assessed. Two-dimensional echocardiography at rest was performed to determine LV volumes and LVEF. Next, tissue Doppler imaging (TDI) was performed to evaluate LV dyssynchrony. The day after CRT implantation, LV dyssynchrony was re-assessed to evaluate resynchronization. Clinical status, LV volumes and LVEF were re-assessed at 3-6 months follow-up.

Clinical evaluation

Evaluation of clinical status included assessment of NYHA functional class, quality-of-life score (using the Minnesota quality-of-life questionnaire) and 6-minute hall-walk test. In all patients, QRS duration was measured from the surface electrocardiogram using the widest QRS complex from the leads II, V1 and V6. The electrocardiograms 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. Patients with an improvement of at least 1 NYHA functional class at 6 months follow-up were classified as clinical responders.

Echocardiographic evaluation

Resting echocardiography and TDI were performed at baseline, the day after CRT implantation and at 3-6 months follow-up. 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 and 2- and 4-chamber images). Standard two-dimensional and color Doppler data, triggered to the QRS complex were saved in cine-loop format. LV volumes (end-systolic, end-diastolic) were derived from the conventional apical two- and four-chamber images, and LVEF was calculated using the biplane Simpson's technique [4].

Based on previous studies, patients with a decrease >15% in LV end-systolic volume at 6 months follow-up were classified as echocardiographic responders [2,5,6]. Similarly, a decrease >15% in LV end-diastolic volume at 6 months follow-up was considered significant. In addition, an (absolute) improvement in LVEF >5% was considered significant [7,8].

Tissue Doppler imaging to assess LV dyssynchrony In addition to the conventional echocardiographic examination, TDI was performed to assess LV dyssynchrony. For TDI, color Doppler frame rates varied between 80 and 115 frames/s depending on the sector width of the region of interest; 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 from 3 consecutive heart beats by offline analysis. Data were analyzed using commercially available software (Echopac 6.1, General Electric - Vingmed).

To determine LV dyssynchrony, the sample volume was placed in the basal portions of the septum and the LV lateral wall; peak systolic velocities and time-to-peak systolic velocities were obtained and the delay in peak velocity between the septum and the LV lateral wall was calculated as an indicator of LV dyssynchrony (referred to as the septal-to-lateral delay) [2,9]. Inter- and intra-observer agreement for assessment of the septal-to-lateral delay were 90% and 96%, respectively [10].

Pacemaker implantation

The LV pacing lead was inserted transvenously via the subclavian route. First, a coronary sinus venogram was obtained during occlusion of the coronary sinus using a balloon catheter. Next, the LV pacing lead was inserted in the coronary sinus with the help of an 8Fr-guiding catheter, and positioned as far as possible in the venous system, preferably in the (postero-) lateral vein. The right atrial and right ventricular leads were positioned conventionally. When a conventional indication for an internal defibrillator existed, a combined device was implanted. For each patient the atrio-ventricular interval was adjusted to maximize the mitral inflow duration using pulsed-wave Doppler echocardiography.

CRT-device (Contak TR or CD, Guidant, Minneapolis, Minnesota, USA and Insync III or CD, Medtronic Inc., Minneapolis, Minnesota, USA) and lead implantation was successful in all patients without major complications. Two types of LV leads were used (Easytrack 4512 to 80, Guidant, or Attain-SD 4189, Medtronic Inc.).

Statistical analysis

Data are presented as mean ± SD, and compared using the (un-)paired Student's t-test when appropriate. Univariate analysis for categorical variables was performed using the chi-square test with Yates' correction. For all tests, a P-value <0.05 was considered statistically significant.

RESULTS

A total of 144 consecutive patients were included in the study (108 men, mean age 66±11 years). Baseline characteristics of the study population are summarized in Table 1.

Outcome Post-implantation

Following CRT implantation, QRS duration decreased from 165±26 ms to 149±23 ms (P<0.001). TDI demonstrated a reduction in LV dyssynchrony immediately after implantation from 76±58 ms to 37±34 ms (P<0.001), indicating LV resynchronization.

Table 1. Patient characteristics (n=144).

Age (years)	66±11
Male/female	108/36
NYHA class	
III	126 (87%)
IV	18 (13%)
QRS duration (ms)	165±26
Sinus rhythm	128 (89%)
Atrial fibrillation	16 (11%)
Etiology	
Ischemic	77 (53%)
Non-ischemic	67 (47%)
Medication	
Diuretics	130 (90%)
ACE inhibitors	123 (85%)
Beta-blockers	83 (58%)
LV ejection fraction (%)	21±8
LV end-diastolic volume (ml)	227±84
LV end-systolic volume (ml)	180±77
LV dyssynchrony (ms)	76±58

LV: left ventricular; NYHA: New York Heart Association.

Outcome after 3-6 Months of CRT

At 3-6 months follow-up a significant improvement in clinical status was observed. NYHA class improved significantly from 3.1±0.4 to 2.3±0.6 (P<0.001), the Minnesota quality-of-life score decreased from 39±20 to 24±18 (P<0.001) and the 6-minute walking distance improved from 285±135 m to 365±141 m (P<0.001).

Significant LV reverse remodeling was observed at 3-6 months follow-up. LV end-diastolic volume decreased from 227±84 ml to 196±84 ml (P<0.001), whereas LV end-systolic volume decreased from 180±77 ml to 144±74 ml (P<0.001). This resulted in an increase of the LVEF from 21±8% to 28±10% (P<0.001).

Agreement between Clinical and Echocardiographic Response

An improvement of at least 1 NYHA class at 3-6 months follow-up was observed in 101 (70%) patients, indicating clinical response to CRT. These patients also showed a significant improvement in 6-minute walking distance (from 289±132 m to 404±116 m, P<0.001) and quality-of-life score (from 39±19 to 20±15, P<0.001). In contrast, the 43 patients (30%) without an improvement in NYHA class (clinical non-responders) also failed to improve in 6-minute walking distance (from 278±143 m to 278±153 m, ns) and quality-of-life score (from 39±20 to 36±19, ns).

Echocardiographic response (defined as >15% reduction in LV end-systolic volume) was observed in 81 (56%) patients. A reduction >15% in LV end-diastolic volume occurred in 66 (46%) patients and an (absolute) improvement in LVEF >5% was detected in 77 (54%) patients.

The agreement between clinical response (reduction in ≥1 NYHA class) after 3-6 months of CRT and echocardiographic response (defined as a decrease >15% in LV end-systolic volume) is shown in Figure 1. The agreement between clinical and echocardiographic response was 76% (74 patients (51%) exhibited both a reduction in NYHA class and a reduction in LV end-systolic volume, and 36 patients (25%) had no reduction in either NYHA class or LV end-systolic volume). Clinical improvement without >15% reduction in LV end-systolic volume was observed in 27 (19%) patients, whereas 7 (5%) patients failed to show clinical response although a reduction in LV end-systolic volume >15% was observed. Thus, in 34 (24%) patients disagreement between clinical and echocardiographic response was noted; the disagreement was mainly due to patients with clinical response without echocardiographic response. Of note, in the presence of more extensive LV reverse remodeling, the percentage of clinical responders increased gradually (Figure 2). When a cut-off value of >15% reduction in LV end-diastolic volume was applied, disagreement was present in 47 (32%) patients. The disagreement was mainly caused by patients with clinical response and without improvement in LV end-diastolic volume (n=41, 28%). Finally, in 36 (25%) patients, there was a disagreement between clinical response and an (absolute) improvement >5% in LVEF. Again, the disagreement was mainly caused by patients who showed a clinical response without an echocardiographic response (Figure 3).

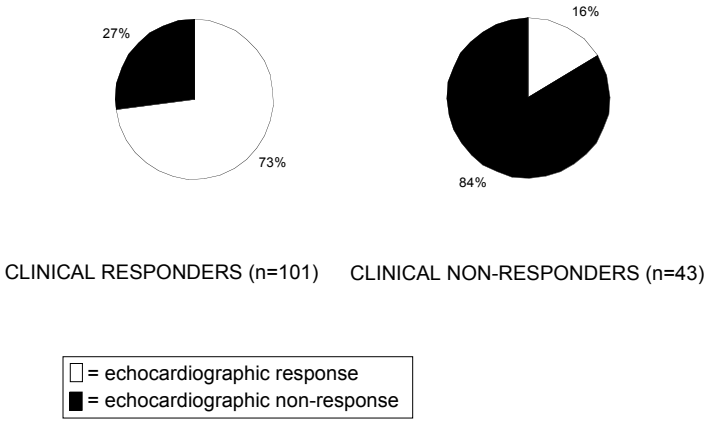

Figure 1. Percentage of echocardiographic responders (defined as a reduction >15% in LV end-systolic volume) in the patients with (n=101) and without (n=43) clinical response (defined as an improvement in NYHA class).

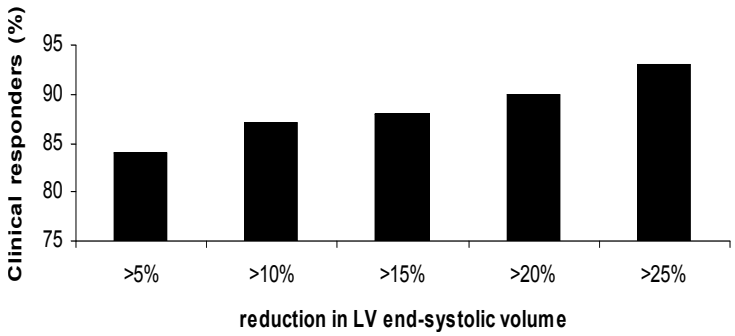

Figure 2. Number of clinical responders (defined as an improvement ≥1 NYHA class) according to the extent of reduction in LV end-systolic volume.

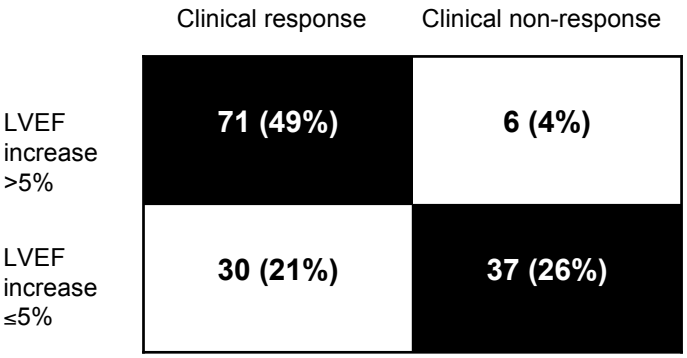

Figure 3. Agreement between clinical (non-) response and an (absolute) increase in LV ejection fraction (LVEF) >5%.

DISCUSSION

In the present study, potential end-points of CRT were evaluated and it was particularly studied to which extent patients respond both clinically and echocardiographically. The definition for clinical response in the current study was improvement in NYHA class by 1 grade or more. Using this definition, the percentage of clinical responders was 70%, which is in line with previous studies. For example, in the MIRACLE-trial 32% of patients did not improve in NYHA class [1]. Also, in other studies the number of clinical non-responders is 20-30% [2,11,12]. Moreover, in the present study, the patients with a reduction in NYHA class demonstrated a significant improvement in other clinical end-points including the quality-of-life score and the 6-minute walking distance. Conversely, the patients without an improvement in NYHA class did not show an improvement in quality-of-life score or 6-minute walking distance.

Besides clinical end-points, echocardiographic end-points have been used in heart failure trials [13]. In particular, a reduction in LV end-systolic volume has been used in CRT trials as an end-point. Yu et al. [14] studied 56 patients undergoing CRT and demonstrated a reduction >15% in LV end-systolic volume in 54% of patients after 3 months of CRT. Moreover, Stellbrink et al. found 64% of patients with reduction >15% in LV end-systolic volume at mid-term follow-up [15].

In the current study, 56% of patients demonstrated a reduction >15% in LV end-systolic volume after 3-6 months of CRT, which is well in line with these previous studies.

Next, the agreement between the clinical response and echocardiographic response was evaluated on an individual basis. The agreement between the 2 parameters was good; in 76% of patients there was an agreement between clinical and echocardiographic (non-) response. Disagreement existed in 34 patients (24% of the entire group), with 27 (19%) showing an improvement in NYHA class without a reduction in LV end-systolic volume, and 7 (5%) showing a reduction in LV end-systolic volume without an improvement in NYHA class. Accordingly, the disagreement between the 2 end-points was mainly related to patients who responded clinically without showing LV reverse remodeling. This observation may be explained by the presence of a placebo effect with respect to improvement in clinical symptoms following CRT, as already reported in double-blind randomized trials [1]. In a previous study by Yu et al. [3], 30 patients underwent CRT and 80% improved in NYHA class whereas only 57% showed LV reverse remodeling. The precise relation between the 2 end-points however was not evaluated in that study.

It is of interest though that the likelihood of improvement in NYHA class increased in parallel to the extent of LV reverse remodeling (Figure 2), indicating some relation between the 2 parameters.

When other echocardiographic end-points were used in the current study, i.e. a reduction in LV end-diastolic volume or an increase in LVEF, a similar discrepancy was observed between clinical response and echocardiographic response. Only 59% of patients with an improve-

ment in NYHA class showed a reduction >15% in LV end-diastolic volume, whereas 70% showed an improvement in LVEF. Again, the disagreement was mainly related to patients with a clinical response not showing an echocardiographic response.

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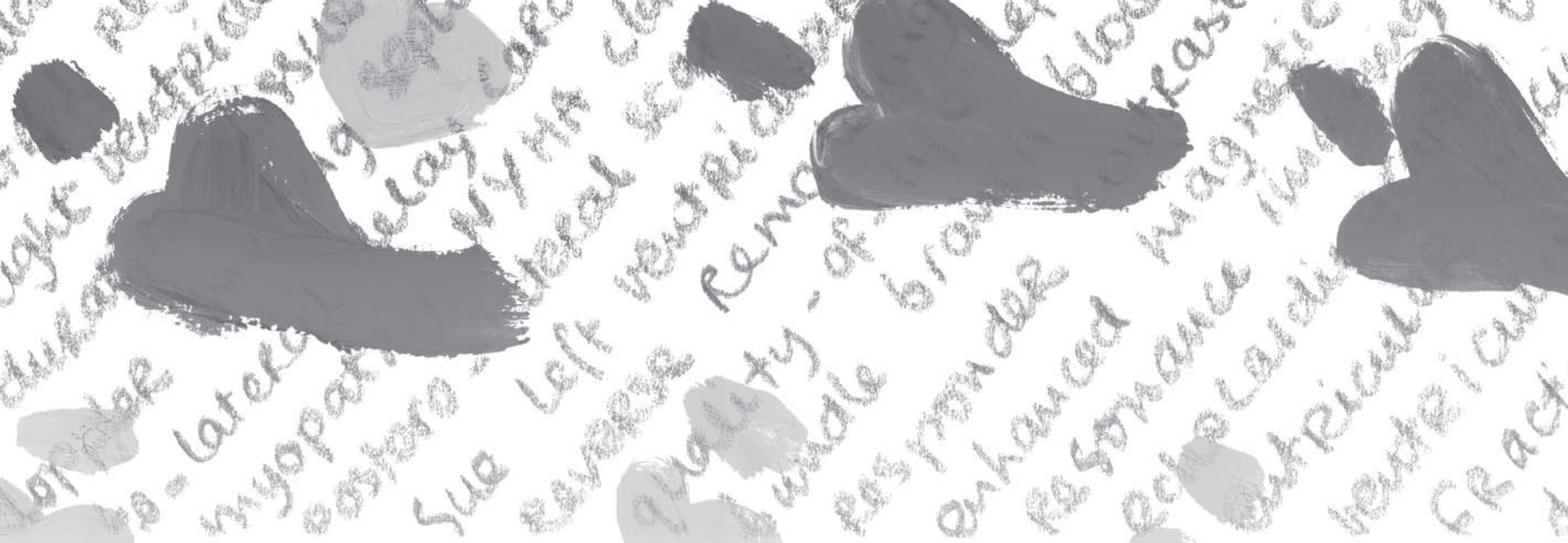

Mechanism of benefit from CRT

Part II

Chapter 5

Left ventricular dyssynchrony predicts right ventricular remodeling after cardiac resynchronization therapy

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ABSTRACT

Objective To evaluate right ventricular (RV) remodeling after 6 months of cardiac resynchronization therapy (CRT).

Background CRT is beneficial in patients with end-stage heart failure. The effect of CRT on RV size is currently unknown. Accordingly, the effects of CRT on RV size, severity of tricuspid regurgitation and pulmonary artery pressure were evaluated.

Methods Fifty-six consecutive patients with end-stage heart failure (52% ischemic cardiomyopathy), left ventricular (LV) ejection fraction (EF) ≤35%, QRS duration >120 ms and left bundle branch block were included. Clinical parameters, LV volumes, LVEF, LV dyssynchrony and RV chamber size were assessed at baseline and after 6 months of CRT. LV dyssynchrony was assessed using tissue Doppler imaging.

Results Clinical parameters improved significantly. LV dyssynchrony was acutely reduced after CRT and remained unchanged at 6 months follow-up. LVEF improved significantly from 19±6% to 26±8% (P<0.001) and LV end-diastolic volume decreased from 257±98 ml to 227±86 ml (P<0.001). RV annulus decreased significantly from 37±9 mm to 32±10 mm, RV short-axis from 29±11 mm to 26±7 mm, and RV long-axis from 89±11 mm to 82±10 mm (all P<0.001). LV and RV reverse remodeling were only observed in patients with substantial LV dyssynchrony at baseline. Finally, significant reductions in severity of tricuspid regurgitation and pulmonary artery pressure were observed.

Conclusion CRT results in significant reverse LV and RV remodeling after 6 months of CRT in patients with LV dyssynchrony. Moreover, CRT leads to a reduction of the severity of tricuspid regurgitation and a decrease in pulmonary artery pressure.

INTRODUCTION

Congestive heart failure is one of the leading causes of morbidity and mortality in the Western world [1,2]. A relatively new treatment modality in patients with end-stage heart failure and a wide QRS complex is cardiac resynchronization therapy (CRT). Several large randomized trials have shown sustained clinical benefit from CRT [3-7]. Patients experienced an improvement in heart failure symptoms, quality-of-life and exercise capacity. Moreover CRT results in a significant reduction of the number of hospitalisations for decompensated heart failure and recent trials indicate a positive effect of CRT on mortality [3-8].

Echocardiographic evaluation of patients undergoing CRT indicated that clinical improvement is caused by resynchronization of dyssynchronous left ventricular (LV) contraction [9-12]. CRT induced LV resynchronization results in improved LV systolic function, a decrease in mitral regurgitation and reverse LV remodeling [9-13]. Currently, no data are available regarding the effects of CRT on right ventricular (RV) chamber size and the severity of tricuspid regurgitation. Beneficial effects of CRT on the size of the RV and on the severity of tricuspid regurgitation may further explain the mechanism of symptomatic benefit from CRT [14,15].

Accordingly, the objective of this study was to evaluate RV remodeling after 6 months of CRT using echocardiography. The effects of CRT on the severity of tricuspid regurgitation and pulmonary artery pressure were also evaluated. Finally, the relation between LV dyssynchrony and the effects of CRT on the RV was explored.

METHODS

Patients and Study Protocol

Fifty-six consecutive patients with severe heart failure, scheduled for implantation of a biventricular pacemaker were prospectively included in this study. Patients were selected according to traditional selection criteria for CRT: LV ejection fraction (EF) ≤35%, severe heart failure (New York Heart Association (NYHA) class III or IV) and a QRS duration >120 ms with left bundle branch block configuration. Patients with a recent myocardial infarction (<3 months) or decompensated heart failure were excluded.

Before pacemaker implantation, clinical status and QRS duration were assessed.

Two-dimensional echocardiography at rest was performed to calculate LV volumes and LVEF, and to assess RV chamber size. Next, tissue Doppler imaging (TDI) was performed to evaluate LV dyssynchrony. LV dyssynchrony and QRS duration were re-assessed on the day after implantation and at 6 months follow-up. Clinical status, LV volumes, LVEF, and RV chamber size were also 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 quality-of-life questionnaire) and 6-minute hall-walk test. 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.

Echocardiography

Resting echocardiography and TDI were performed at baseline, the day after implantation and at 6 months follow-up. 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 and two- and four-chamber images). Standard two-dimensional and colour Doppler data, triggered to the QRS complex were saved in cine loop format. LV volumes (end-systolic, end-diastolic) and LVEF were calculated from the conventional apical two- and four-chamber images, using the biplane Simpson's technique [16].

Assessment of RV chamber size. RV end-diastolic chamber size was assessed using three parameters which were described previously by Foale et al. [17,18]. These parameters were assessed from the apical four-chamber view, as schematically displayed in Figure 1. The first parameter is the diameter of the annulus of the tricuspid valve (TV ANN), defined as the point of attachment of the septal and posterior leaflets to the atrioventricular junction. The second measurement is the maximum dimension of the middle third of the RV, parallel to the tricuspid annulus (RV SAX). The last measurement included the major axis of the RV (RV LAX) and is defined as the distance between the RV apex to the mid-point of the tricuspid annulus.
Inter- and intra-observer agreement for assessment of RV chamber size were 98% and 96% for TV ANN, 90 and 92% for RV SAX, and 94% and 95% for RV LAX respectively.

Tissue Doppler imaging to assess LV dyssynchrony. In addition to the conventional echocardiographic examination, TDI was performed to assess LV dyssynchrony. For TDI, color Doppler frame rates varied between 80 and 115 frames/s depending on the sector width of the range of interest; 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 images of three consecutive heart beats by offline analysis. Data were analyzed using commercial software (Echopac 6.1, General Electric - Vingmed).
To determine LV dyssynchrony, the sample volume was placed in the basal portions of the septum and the LV lateral wall; peak systolic velocities and time-to-peak systolic velocities were obtained and the delay in peak velocity between the septum and the LV lateral wall

was calculated as an indicator of LV dyssynchrony (referred to as the septal-to-lateral delay) [9,19,20]. Interventricular dyssynchrony was assessed by comparing the delay between peak systolic velocity of the RV free wall and the LV lateral wall [11].
Based on previous observations, a septal-to-lateral delay >60 ms was considered to represent severe LV dyssynchrony [9]. Inter- and intra-observer agreement for assessment of the septal-to-lateral delay were 90% and 96%, respectively [21].

Assessment of mitral and tricuspid regurgitation. The severity of mitral and tricuspid regurgitation was graded semi-quantitatively from color-flow Doppler images. For quantification of mitral and tricuspid regurgitation, the apical 4-chamber images were used. Mitral and tricuspid regurgitation were classified as: mild=1+ (jet area/atrial area <10%), moderate=2+ (jet area/atrial area 10-20%), moderately severe =3+ (jet area/atrial area 20-45%), and severe=4+ (jet area/atrial area >45%) [22,23].
Continuous-wave Doppler examination was also performed to estimate pulmonary artery systolic pressure from the trans-tricuspid maximal regurgitant flow velocity.
All echocardiographic measurements were obtained by two independent observers without knowledge of the clinical status of the patient.

Pacemaker Implantation

The LV pacing lead was inserted transvenously via the subclavian route. First, a coronary sinus venogram was obtained during occlusion of the coronary sinus using a balloon catheter. Next, the LV pacing lead was inserted in the coronary sinus with the help of an 8Fr-guiding catheter, and positioned as far as possible in the venous system, preferably in the (postero-) lateral vein. The right atrial and RV leads were positioned conventionally. When a conventional indication for an internal defibrillator existed, a combined device was implanted. For each patient the atrio-ventricular interval was adjusted to maximize the mitral inflow duration using pulsed-wave Doppler echocardiography. No adjustments were made to the V-V interval during the first 6 months of CRT.
CRT-device and lead implantation was successful in all patients without major complications (Contak TR or CD, Guidant, Minneapolis, Minnesota, USA and Insync III or CD, Medtronic Inc., Minneapolis, Minnesota, USA). Two types of LV leads were used (Easytrack 4512 to 80, Guidant, or Attain-SD 4189, Medtronic Inc.).

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. Univariate analysis for categorical variables was performed using the chi-square test with Yates' correction. For all tests a P-value <0.05 was considered statistically significant.

RESULTS

Fifty-six consecutive patients were included in this study (44 male, age 64±11 years). Baseline patient characteristics are summarized in Table 1.

Follow-up after CRT

Clinical parameters and left ventricular remodeling. QRS duration at baseline was 176±30 ms (range 122-240 ms) and shortened to 149±23 ms (P<0.001, range 92-198 ms) immediately post-implantation, which remained unchanged (153±22 ms, range 86-202 ms) at 6 months after CRT.

At 6 months follow-up a significant improvement in clinical status was observed, in combination with an improvement in LVEF and a significant LV reverse remodeling (Table 2).

Left ventricular dyssynchrony. The day after implantation of the pacemaker, TDI demonstrated a significant reduction in septal-to-lateral delay from 114±57 ms to 37±32 ms (P<0.001), indicating LV resynchronization. Resynchronization was maintained after 6 months of CRT, as evidenced by a septal-to-lateral delay of 40±36 ms (P<0.001 vs baseline, ns vs immediately

Table 1. Baseline characteristics

	Patient characteristics (n=56)
Age (yrs, range)	64±11 (18-81)
Gender (M/F)	44/12
NYHA	
class III	50 (89%)
class IV	6 (11%)
Etiology	
ischemic	29 (52%)
nonischemic	27 (48%)
QRS duration (ms)	176±30
Rhythm	
sinus rhythm	49 (87%)
atrial fibrillation	7 (13%)
LVEF (%)	19±6
LVEDV (ml)	258±98
LVESV (ml)	213±91
Medication:	
diuretics	46 (82%)
ACE-inhibitors	52 (93%)
beta-blockers	28 (50%)
anticoagulants/aspirin	52 (93%)

LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; NYHA: New York Heart Association

Table 2. Clinical and echocardiographic variables before and after 6 months of CRT.

	Baseline data (n=56)	6 months follow-up (n=56)	P-value
NYHA class	3.1±0.3	1.9±0.5	<0.001
QOL-score	41±15	24±13	<0.001
6-MWT (m)	277±143	409±140	<0.001
LVEF (%)	19±6	26±8	<0.001
LVEDV (ml)	257±98	227±86	<0.001
LVESV (ml)	213±91	172±80	<0.001
RV chamber size:			
TV ANN (mm)	37±9	32±10	<0.001
RV SAX (mm)	29±11	26±7	<0.001
RV LAX (mm)	89±11	82±10	<0.001
Mitral Regurgitation (grade)	2.1±0.9	1.3±0.9	<0.001
Tricuspid regurgitation (grade)	1.8±0.8	1.3±1.0	<0.001
Pulmonary artery pressure (mmHg)	40±12	30±11	<0.001

6-MWT: 6 minute walk test; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; NYHA: New York Heart Association; QOL: Quality-of-life; RV: right ventricle; RV SAX: right ventricular short axis; RV LAX: right ventricular long axis; TV ANN: tricuspid valve annulus

after implantation). Mean inter-ventricular (RV-LV) dyssynchrony at baseline was 51±36 ms, which decreased significantly after 6 months of CRT to 37±27 ms (P<0.05).

Right ventricular remodeling. In line with the reverse remodeling of the LV, CRT also resulted in a significant reverse remodeling of the RV at 6 months follow-up (Table 2). All three parameters reflecting RV chamber size showed a significant decrease after 6 months of CRT. The TV ANN showed a significant decrease from 37±9 mm to 32±10 mm (P<0.01), RV SAX decreased from 29±11 mm to 26±7 mm (P<0.001) and RV LAX showed a reduction from 89±11 mm to 82±10 mm (P<0.001). Of note, RV reverse remodeling did not occur immediately after CRT (e.g. the RV SAX was 29±11 mm before CRT and 30±10 mm immediately after CRT, NS).
Patients were subsequently divided into quartiles according to the baseline values for each RV size parameter. RV reverse remodeling was most outspoken in patients with the largest RV dilatation at baseline (Figures 2A-C). A significant reduction in TV ANN was demonstrated in the third and fourth quartiles, whereas the patients with smaller TV ANN at baseline (first and second quartiles) showed no significant reduction in size (Figure 2A). Similarly, RV SAX and RV LAX showed a significant reduction after 6 months CRT in patients with larger baseline values (Figure 2B and 2C). Of note, 6 of 14 patients in the fourth quartile had signs of right-sided heart failure.
RV reverse remodeling was associated with a significant reduction in tricuspid regurgitation from 1.8±0.8 to 1.3±1.0 (P<0.001, Table 2). Moreover, CRT also resulted in a significant reduction of pulmonary artery pressure from 40±12 mmHg to 30±11 mmHg (P<0.001).

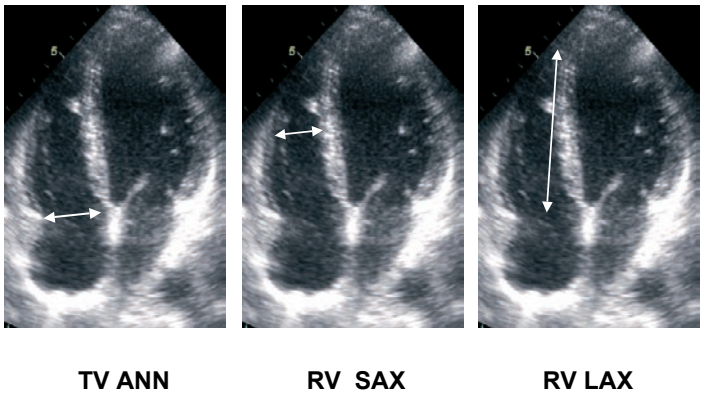

Figure 1. Apical four-chamber two-dimensional echocardiogram. Schematic display of parameters reflecting RV end-diastolic chamber size. (RV LAX = right ventricular long-axis, RV SAX = right ventricular short-axis, TV ANN = tricuspid valve annulus).

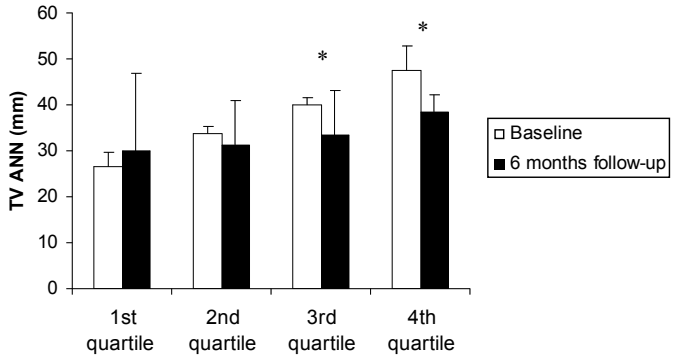

Figure 2a. TV ANN at baseline and after 6 months of CRT. Patients are divided into quartiles according to baseline TV ANN. (* = P<0.05)

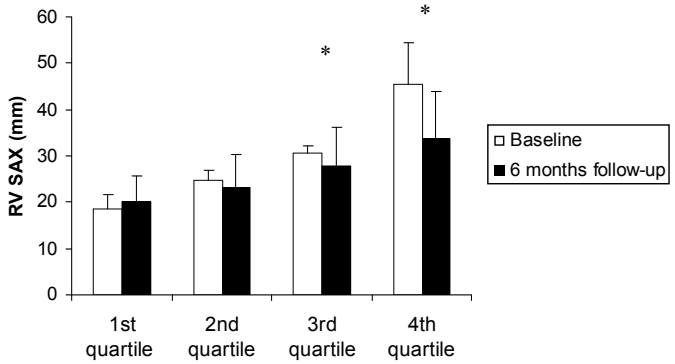

Figure 2b. RV SAX at baseline and after 6 months of CRT. Patients are divided into quartiles according to baseline RV SAX. (* = P<0.05)

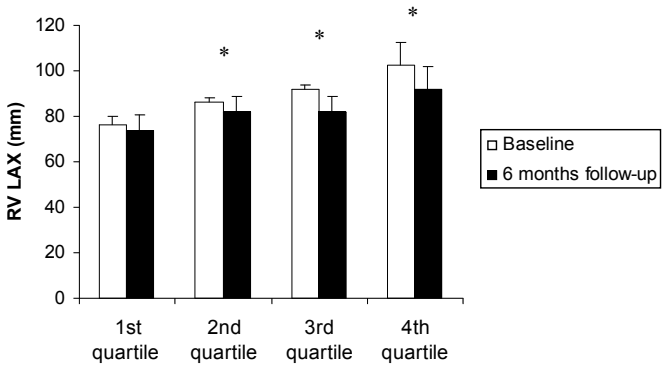

Figure 2c. RV LAX at baseline and after 6 months of CRT. Patients are divided into quartiles according to baseline RV LAX. (* = P<0.05)

Reverse Remodeling versus LV Dyssynchrony

Patients with severe baseline LV dyssynchrony were defined as having a septal-to-lateral delay >60 ms on TDI before implantation of the pacemaker. Accordingly, 44 (79%) patients had significant LV dyssynchrony (mean septal-to-lateral delay 137±41 ms, with an immediate decrease to 40±40 ms after CRT, P<0.001), and 12 (19%) patients did not have substantial dyssynchrony on TDI (mean septal-to-lateral delay 41±27 ms, which remained unchanged following CRT, 38±25 ms, NS). Baseline characteristics were not statistically different between the two groups (Table 3).

The changes in LV volumes, LVEF and RV diameters in patients with and without LV dyssynchrony are summarized in Table 4. Patients with severe LV dyssynchrony before implantation showed reverse LV remodeling, whereas LV volumes did not decrease significantly after 6 months of CRT in patients without LV dyssynchrony at baseline. Moreover, LVEF increased significantly after 6 months of CRT in the patients with LV dyssynchrony only. Similarly, a significant reduction in RV dimensions was only observed in the patients with LV dyssynchrony at baseline.

Of note, in the patients with significant LV dyssynchrony at baseline, 86% showed an improvement of at least 1 NYHA class after 6 months of CRT.

DISCUSSION

The main findings can be summarized as follows. In patients with LV dyssynchrony, CRT induces not only LV reverse remodeling, but also a significant reverse remodeling of the RV. This effect was most outspoken in patients with severe RV dilatation at baseline.

Table 3. baseline characteristics in patients with (n=44) and without LV dyssynchrony (n=12) at baseline.

	LV dyssynchrony (n=44)	No LV dyssynchrony (n=12)	P-value
Age (yrs)	64±12	65±8	NS
Gender (M/F)	34/10	10/2	NS
NYHA			
class III	38	12	NS
class IV	6	0	
Etiology			
ischemic	23	6	NS
non-ischemic	21	6	
QRS duration (ms)	178±31	169±27	NS
6-MWT (m)	270±126	303±139	NS
QOL-score	42±15	37±16	NS
Septal-to-lateral delay (ms)	137±41	41±27	-

6-MWT: 6 minute walk test; NYHA: New York Heart Association; QOL: Quality-of-life

At present, CRT is considered a major breakthrough in the treatment of patients with moderate-to-severe heart failure and has been demonstrated to result in a sustained improvement in symptoms and LV systolic function [5,13]. Similar benefits were demonstrated in the current study. Despite the reproducible positive clinical results, the exact mechanism underlying the benefit of CRT is still not entirely clear but may be related to 1). an improvement of LV systolic function, 2). reduction of mitral regurgitation, and 3). reverse remodeling of the LV. The presence of LV dyssynchrony appears mandatory for these effects to occur as demonstrated in previous studies [9-11,13]. In the present study, LV dyssynchrony (assessed by TDI prior to CRT) was significant with a septal-to-lateral delay of 114±57 ms. In particular, 79 % of patients exhibited significant LV dyssynchrony (defined as a septal-to-lateral delay >60 ms) and 21% of patients did not show LV dyssynchrony. In the patients with LV dyssynchrony, resynchronization was obtained immediately after CRT, which persisted during 6 months follow-up. A significant improvement in LVEF was observed in the dyssynchronous patients with significant reverse LV remodeling, in line with previous studies [9,11,12]. However, these beneficial effects were not observed in the absence of dyssynchrony at baseline (Table 4), confirming previous observations [9,11].

No data were yet available regarding the effects of CRT on RV function. Since CRT causes an improvement in LV function, reduces mitral regurgitation and normalizes neurohormonal status, it seems plausible that CRT may also have beneficial effects on pulmonary artery pressure, RV function and RV dilatation. In the current study, the effects of CRT on RV size, tricuspid regurgitation and pulmonary artery pressure were evaluated. RV chamber size was evaluated using 3 echocardiographic measurements that were introduced previously by Foale et al [17,18]. This standardized echocardiographic approach for the assessment of RV dimensions

Table 4. LV volumes, LV ejection fraction and RV dimensions at baseline and after 6 months of CRT in patients with (n=44) and without LV dyssynchrony (n=12) at baseline.

	Baseline	6 months follow-up	P-value
LVESV (ml)			
LV dyssynchrony present	220±93	170±83	P<0.05
LV dyssynchrony absent	189±82	176±77	NS
LVEDV (ml)			
LV dyssynchrony present	265±100	229±88	P<0.05
LV dyssynchrony absent	232±90	223±82	NS
LVEF (%)			
LV dyssynchrony present	18±6	27±8	P<0.05
LV dyssynchrony absent	20±7	22±8	NS
TV ANN (mm)			
LV dyssynchrony present	37±8	32±6	P<0.05
LV dyssynchrony absent	38±9	34±8	NS
RV SAX (mm)			
LV dyssynchrony present	30±11	25±7	P<0.05
LV dyssynchrony absent	29±10	29±8	NS
RV LAX (mm)			
LV dyssynchrony present	90±10	82±9	P<0.05
LV dyssynchrony absent	86±9	82±6	NS

LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; RV LAX: right ventricular long axis. RV SAX: right ventricular short axis; TV ANN: tricuspid valve annulus

has been demonstrated to adequately reflect RV size. The current results illustrate that CRT not only induced LV reverse remodeling, but also resulted in a significant reverse remodeling of the RV. Of interest, the effect was most outspoken in patients with more severe RV dilatation at baseline. Moreover, RV reverse remodeling was associated with a reduction in the severity of tricuspid regurgitation and a significant decrease in pulmonary artery pressure. The precise mechanism underlying the beneficial effects on the right ventricle is unclear. Similar to LV reverse remodeling, RV reverse remodeling was related to the presence of LV dyssynchrony at baseline. Patients without baseline LV dyssynchrony did not exhibit RV reverse remodeling after 6 months of CRT (Table 4). Still, the reduction in RV dimensions appears not related by an acute recovery in LV dyssynchrony. An acute reduction in septal-to-lateral delay occurred after initiation of CRT (from 114±57 ms at baseline to 37±32 ms immediately after CRT, P<0.01), but this reduction was not accompanied by an acute reduction in RV dimensions (the baseline RV-SAX was 29±11 mm as compared to 30±10 mm immediately after CRT). It thus appears that a more coordinated motion of the interventricular septum following CRT was not responsible for the reduction in RV dimensions. Possibly, sustained improved LV performance has led to a reduction in pulmonary artery pressure (observed in the current study), resulting in an improved RV function (as evidenced also by a reduction in tricuspid regurgitation). Although improvement in RV size and function following CRT have

been demonstrated in the current study, the inclusion of a control group could potentially have contributed to a better understanding of the mechanism involved. Future studies are needed to further resolve these issues.

Conclusion

The clinical benefit of CRT on improvement in LV function was confirmed in the current study. The benefit from CRT was related to the presence of LV dyssynchrony before CRT. In addition, this is the first study to demonstrate reverse RV remodeling following CRT, which was associated with a reduction in tricuspid regurgitation and a decrease in pulmonary artery pressure; reverse RV remodeling was most outspoken in severely dilated RVs and only observed when LV dyssynchrony was present at baseline. These findings may lead to a better understanding of the beneficial effects of CRT on cardiac function as RV reverse remodeling, decreased tricuspid regurgitation and reduced pulmonary artery pressure are likely to contribute to the symptomatic benefit from CRT in patients with drug-refractory heart failure.

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Chapter 6

Left ventricular reverse remodeling but not clinical improvement predicts long-term survival after cardiac resynchronization therapy

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ABSTRACT

Background In patients with severe heart failure and dilated cardiomyopathy, cardiac resynchronization therapy (CRT) improves left ventricular (LV) systolic function associated with LV reverse remodeling and favorable 1-year survival. However, it is unknown whether LV reverse remodeling translates into a better long-term prognosis, and what extent of reverse remodeling is clinically relevant, which will be addressed by the present study.

Methods and Results 141 patients with advanced heart failure (mean age 64±11 years, 73% men) who received CRT were followed-up for a mean period of 695±491 days. The extent of reduction in LV end-systolic volume (LVESV) at 3-6 months relative to baseline was examined for its predictive value on long-term clinical outcome. The cut-off value of LV reverse remodeling in predicting mortality was derived from the ROC curve. Then the relationship between the potential predictors of mortality and heart failure hospitalizations were compared by Kaplan-Meier survival analysis, and followed by Cox regression analysis.

There were 22 (15.6%) deaths, mostly due to heart failure or sudden cardiac death. The ROC curve derived that a reduction of LVESV ≥9.5% has a sensitivity of 70% and specificity of 70% in predicting all-cause mortality, and 87% and 69% respectively for cardiovascular mortality. With this cut-off value, there were 87 (61.7%) responders of reverse remodeling. In Kaplan-Meier survival analysis, responders has significantly lower all-cause mortality (6.9% Vs 30.6%, Log-rank χ^2=13.26, p=0.0003), cardiovascular mortality (2.3% Vs 24.1%, Log-rank χ^2=17.1, p<0.0001), and heart failure events (11.5% Vs 33.3%, Log-rank χ^2=8.71, p=0.0032) than non-responders. In the Cox-regression analysis model, the change in LVESV is the single most important predictor of all-cause (β=1.048, CI=1.019-1.078, p=0.001) and cardiovascular mortality (β=1.072, CI=1.033-1.112, p<0.001). Clinical parameters were unable to predict any outcome event.

Conclusions A reduction in LVESV of 10% signifies clinically relevant reverse remodeling, which is a strong predictor of lower long-term mortality and heart failure events. This study suggests that assessing volumetric changes following an intervention in patients with heart failure provides information predictive of natural history outcomes.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is an established treatment for patients with advanced chronic heart failure with electromechanical delay.[1-4] Apart from the beneficial effects of CRT on symptoms and exercise capacity, left ventricular (LV) reverse remodeling[5,6] and improvement of clinical outcome were also observed in large, multicenter clinical trials.[2,4] Whether the observed LV reverse remodeling is clinically relevant is unclear.

However, large heart failure trials demonstrated that drug therapy limiting or reversing LV remodeling resulted in improved long-term survival.[7] In these studies, LV end-systolic volume (LVESV) was the strongest predictor of survival among clinical and echocardiographic parameters.[8] For example, in the multicenter trials of angiotensin converting enzyme inhibitors (e.g. the SAVE study), LV volumes were strong predictors of long-term mortality and cardiovascular events, independent of the effect of the ACE inhibitor captopril.[9] The extent of LV reverse remodeling after CRT was reported to be larger than 20% reduction in LVESV, which is much larger than that observed in medical therapy for heart failure.[10-12] This phenomenon was observed in the first 3 to 6 months after CRT. Since the mechanism of benefit of device therapy is somewhat different from medical therapy, it is currently unclear whether the LV reverse remodeling observed in patients undergoing CRT is predictive for improved long-term clinical outcome. Moreover, what extent of LV reverse remodeling is needed to result in an improved survival is also not clear. Therefore, the aims of the current study were: 1. to examine whether the LV reverse remodeling observed at 3-6 months is associated with better long-term clinical outcome in heart failure patients who received CRT, and 2. to determine what extent of LV reverse remodeling predicts improved outcome in this population.

METHODS

Patients

This is a prospective, follow-up study which involved 2 University Hospitals. The study population included 141 heart failure patients (mean age 64±11 years, 73% men) who underwent CRT and had a baseline and 3-6 months follow-up echocardiographic study to assess potential LV reverse remodeling. The inclusion criteria included severe symptomatic heart failure despite optimized medical therapy, LV systolic dysfunction with a LV ejection fraction <40%, and QRS duration >120 ms. Serial echocardiographic studies with tissue Doppler imaging (TDI) were performed before and 3-6 months after CRT to assess LV reverse remodeling. These patients have been put on optimal medical therapy before considering for CRT. Medication was unchanged within the first 6 months of CRT, and any changes afterwards were avoided unless clinically mandatory. Clinical assessment were also performed at the same time points including New York Heart Association (NYHA) class, Minnesota Living With Heart

Failure quality of life questionnaire and 6-minute hall walk distance. Two patients died (one refractory heart failure, one sudden cardiac death) before the 3-6 months echocardiographic follow up and. Since these patients did not have follow-up echocardiographic evaluation to assess LV reverse remodeling, they were excluded from the study. The study was approved and conducted in compliance with the regulations of the local Ethics Committees of both institutions and informed consent was obtained in all patients.

Pacemaker implantation

CRT devices were implanted as previously described.[10,13] The LV pacing lead was inserted by a transvenous approach through the coronary sinus into either the lateral or postero-lateral cardiac vein whenever possible. All patients received CRT devices had biventricular stimulation of the heart with implantation of right ventricular leads.

Echocardiography

Standard echocardiography, including TDI studies, was performed using commercially available equipment (Vivid 7, GE Vingmed Ultrasound, Horten, Norway). The LV end-diastolic volume (LVEDV), LVESV and LV ejection fraction were assessed by biplane Simpson's equation using the apical 4-chamber and 2-chamber views. The intra- and interobserver variability for volumetric assessment were 4% and 5%, respectively.[12] The severity of mitral regurgitation was assessed by the percentage jet area relative to the left atrial size in the apical 4-chamber view. At least 3 consecutive beats of sinus rhythm were measured and the average value was taken.

TDI was performed using the apical 4-chamber view for the long-axis motion of the ventricle as previously described.[5,10,14,15] Two-dimensional echocardiography with TDI-color imaging 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 the images were analyzed off-line by a customized software package (EchoPac 6.1 for PC, GE Vingmed Ultrasound, Horten, Norway). The myocardial velocity curves were constructed off-line, and the septal-to-lateral delay at the basal segments was measured as an index of systolic dyssynchrony using the beginning of the QRS complex as the reference point.[14,15]

Long-term follow-up and assessment of cardiovascular events

All the patients were followed-up regularly (typically every 2-3 months) in the heart failure clinic, with regular clinical assessment, ECG and device interrogation to ensure biventricular pacing was maintained. Only outcomes occurring after the 3-6 months follow-up echocardiogram were related to echocardiographic changes of LV volume. The occurrence of cardiovascular events was adjudicated by cardiologists blinded to the echocardiographic findings. The cause of death was ascertained by reviewing the clinical record and investigation results,

report of the close relatives and post-mortem findings. For cardiovascular hospitalization, the diagnosis of heart failure was based on clinical symptoms (limitation of activity, fatigue, and dyspnea or orthopnea), physical signs (edema, elevated jugular venous pressure, rales, or third heart sound with gallop), or radiological evidence of pulmonary congestion.[16] Acute coronary syndrome was defined according the current guidelines based on the presence of typical chest pain or discomfort, and elevation of cardiac enzymes such as CK-MB, troponin I or troponin T. ECG changes were not employed as a criterion since these patients had baseline LBBB, and subsequent ventricular pacing which hampers assessment of myocardial ischemia or infarction.

Statistical analysis

Results are presented as mean values ±SD. Data were compared using the paired and unpaired Student t-test when appropriate. Comparison of proportions was performed using Chi-square analysis with Yates' correction. Receiver operating characteristic (ROC) curves were analyzed to assess the best cut-off value of LVESV to predict mortality. Life table estimated actuarial survival was calculated by Kaplan-Meier curves where the Log-rank χ^2 values were presented. Cox-regression multivariable survival analysis was used to evaluate the predictive value of multiple factors on mortality. The data from patients in this dataset have not been published. A P-value <0.05 was considered statistically significant.

RESULTS

Among 141 patients, 12 were in NYHA class II, 106 in class III and 23 in class IV. The etiology of heart failure was ischemic in 68 (48%) and non-ischemic in 73 (52%) patients. Medications included diuretics in nearly all patients, angiotensin converting enzyme inhibitors or angiotensin receptor blockers in 91%, β-blockers in 75%, spironolactone in 49% and digoxin in 16% of patients. The echocardiographic studies demonstrated LV reverse remodeling after 3-6 months of CRT. The LVESV decreased significantly by 17.6±18.4% (P<0.001) whereas LVEDV decreased by 11.0±14.3% (P<0.001). LV ejection fraction increased by 6.3±6.9% (P<0.001).

Clinical outcome of patients during long-term follow-up

The mean duration of follow-up was 695±491 days (range 90 to 1992 days). There were 22 (15.6%) deaths. The causes of death included heart failure in 9 patients, sudden cardiac death in 6, myocardial infarction in 1, cerebrovascular accident in 1 and non-cardiac related deaths in 5 patients. Accordingly, 17 patients had cardiovascular mortality. Table 1 compares the clinical and echocardiographic parameters between the survivors and the patients who died during follow-up. All baseline characteristics were comparable, except for a slightly higher mean NYHA class in the patients who died during follow-up. Also, the extent of LV dyssyn-

Table 1. Comparison of baseline clinical and echocardiographic parameters between survivors and patients who died after cardiac resynchronization therapy.

	Survivors (N = 119)	Deaths (N = 22)	P value
Age, years	64±11	65±12	NS
Male / female, %	74 / 26	68 / 32	χ^2=0.39, p=NS
Ischemic vs Non-ischemic	57 vs 62	11 vs 11	NS
QRS duration, ms	157±38	151±34	NS
NYHA class	3.0±0.5	3.3±0.5	0.038
6-min hall walk, m	302±124	278±142	NS
Quality of life score	37±21	39±20	NS
LVESV, cm^3	165±67	181±77	NS
LVEDV, cm^3	217±76	232±80	NS
LV ejection fraction, %	24.9±7.3	24.0±11.2	NS
LV dyssynchrony, ms	62.9±47.3	28.3±23.5	<0.001
Medications, %			
Diuretics	98	100	χ^2=0.02, P=NS
ACE inhibitor or angiotensin receptor blocker	90	95	χ^2=0.34, P=NS
β-Blocker	75	77	χ^2=0.03, P=NS
Spironolactone	48	55	χ^2=0.58, P=NS
Digoxin	16	18	χ^2=0.08, P=NS

ACE, angiotensin converting enzyme; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association.

chrony at baseline was larger in the survivors. The reduction in clinical parameters (NYHA class, quality of life score, 6-minute walking distance) tended to improve more in survivors, although the differences were not statistically different. The extent of LV reverse remodeling and the improvement in LV ejection fraction were significantly larger in survivors. The mean reduction in LVESV in survivors was 19.8±17.7% as compared to 5.9±18.0% (P=0.001) in the patients who died during follow-up; the mean reduction of LVEDV in survivors was 12.4±14.2% versus 3.0±12.6% (P=0.004) in the patients who died during follow-up. Nineteen patients were hospitalized for decompensated heart failure. Twenty-one patients were hospitalized for other cardiovascular causes, including acute coronary syndrome in 7, arrhythmias in 11, stroke in 2, and percutaneous coronary intervention in 1 patient.

What extent of LV reverse remodeling predicts survival?

This study attempted to determine a clinically useful cut-off value of change in LVESV to assess whether LV reverse remodeling after CRT may predict a favorable long-term clinical outcome. Based on ROC curve analysis, a reduction in LVESV of 9.5% was identified as the optimal cut-off value to predict long-term survival (AUC 0.711, P=0.002, see Figure 1A). Using this cut-off value, a sensitivity and specificity of 70% were obtained to predict all-cause mor-

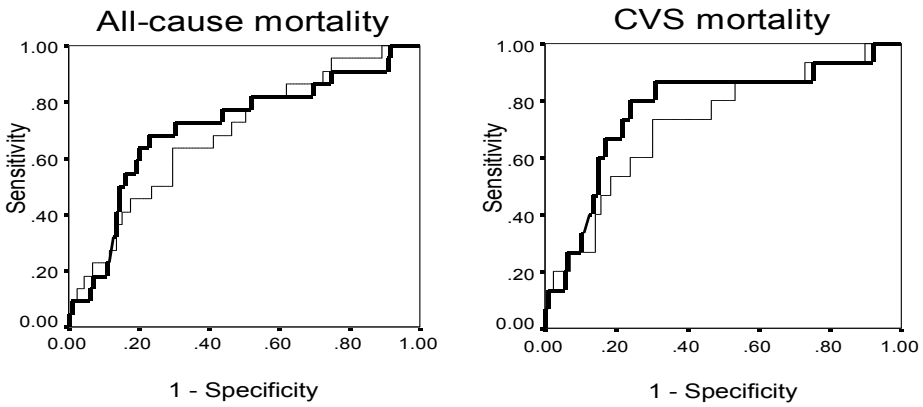

Figure 1. The ROC curve of predicting all cause (A) and cardiovascular (B) mortality by left ventricular reverse r emodeling as reflected by the reduction of LVESV (dark line) and LVEDV (light line) volumes.

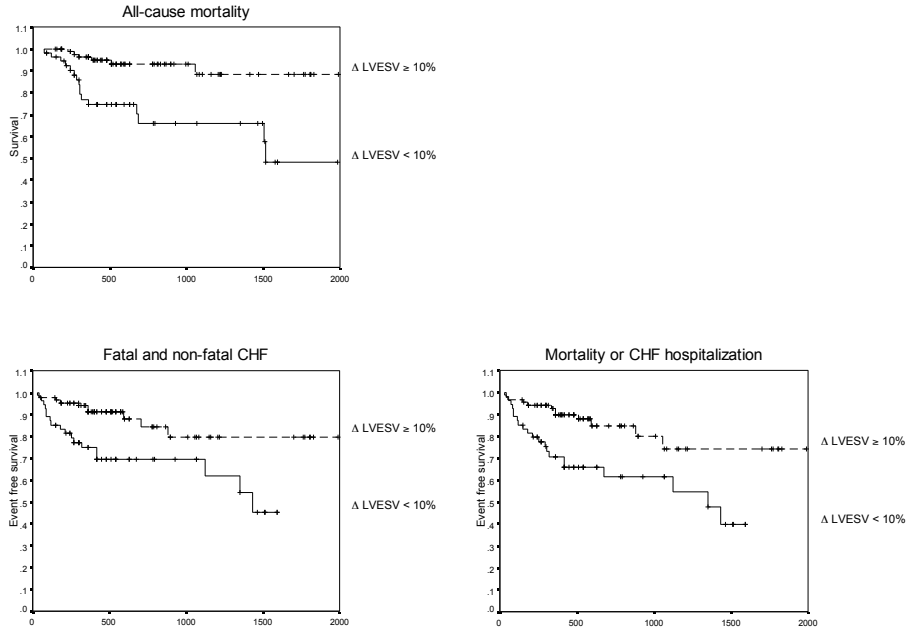

Figure 2. Kaplan Meier curves for all-cause mortality (A), fatal and non-fatal heart failure hospitalizations (B) and mortality or heart failure hospitalizations (C) dichotomized by the status of left ventricular reverse remodeling. Responders are defined as a reduction of LV end-systolic volume (LVESV) for ≥10% while non-responders has a <10% reduction of LV end-systolic volume (LVESV)

tality. Similarly, a reduction in LVESV of 9.5% had a sensitivity and specificity of 87% and 69% respectively, to predict cardiovascular mortality (AUC 0.774, P=0.001, see Figure 1B). Furthermore, the change in LVESV was consistently better than the change in LVEDV in predicting all-cause and cardiovascular mortality (Figures 1A and 1B). The AUC for LVEDV to predict all-cause and cardiovascular mortality were 0.688 (P=0.005) and 0.720 (P=0.005), respectively.

LV reverse remodeling after CRT and prediction of long-term prognosis

Based on the aforementioned findings, a reduction of LVESV ≥10% was used as the cut-off value to define patients with clinically relevant LV reverse remodeling. There were 87 (61.7%) patients with a reduction of LVESV ≥10% (called "responders") and 54 (38.3%) patients with <10% reduction in LVESV (called "non-responders"). During long-term follow-up, 81 of 87 (93.1%) responders of LV reverse remodeling survived, as compared to only 38 of 54 (70.4%) non-responders (χ^2=13.1, P<0.001). By Kaplan-Meier life-table survival analysis demonstrated that responders of LV reverse remodeling (reduction in LVESV ≥10%) were associated with significantly lower all-cause (N=22 who had the censored event) (6.9% Vs 30.6%, Log-rank χ^2=13.26, P=0.0003) (Figure 2A) and cardiovascular (N=17) mortality (2.3% Vs 24.1%, Log-rank χ^2=17.1, P<0.0001) as compared to non-responders. Furthermore, patients with reverse remodeling had a lower rate of heart failure events (both fatal and non-fatal, N=28) (11.5% Vs 33.3%, Log-rank χ^2=8.71, P=0.0032) (Figure 2B), all-cause mortality or heart failure hospitalization (N=33 who had the censored event) (13.8% Vs 38.9%, Log-rank χ^2=9.92, P=0.0016) (Figure 2C) and the composite end-point of all-cause mortality or cardiovascular hospitalization (N=54 who had the censored event) (29.1% Vs 55.8%, Log-rank χ^2=9.18, P=0.0025).

The baseline assessment of LV dyssynchrony was also compared with long-term survival. It was observed that survivors were associated with significantly more severe dyssynchrony than those who died (P<0.001) (Table 1). Patients who had baseline dyssynchrony >60 ms predicted a lower all-cause mortality (6.6% Vs 21.8%, Log-rank χ^2=4.46, P=0.03).

Table 2. Comparison of changes in clinical and echocardiographic parameters between survivors and patients who died after cardiac resynchronization therapy.

	Survivors (N = 119)	Deaths (N = 22)	P value
ΔNYHA class	-0.87±0.66	-0.75±0.79	NS
Δ6-min hall walk, m	85±104	56±103	NS
ΔQuality of life score	-13.7±17.5	-12.0±20.0	NS
ΔLVESV, %	-19.8±17.7	-5.9±18.0	0.001
ΔLVEDV, %	-12.4±14.2	-3.0±12.6	0.004
ΔLV ejection fraction, %	7.0±6.7	2.8±7.4	0.008

Δ indicated change

Clinical parameters were evaluated for their predictive values on mortality. However, only the NYHA class at baseline was significantly higher (P=0.038) in those who died. There was no difference in 6-minute hall walk distance or Minnesota Living-With-Heart-Failure quality of life score between the two groups, or the changes in these parameters after CRT for 3-6 months (Table 2). Therefore, clinical parameters for heart failure assessment were unable to predict the long-term outcome in these patients.

The predictive values of clinical / echocardiographic parameters on all-cause mortality were compared by the Cox-regression multivariable analysis model. It was found that the reduction of LVESV is the only independent predictor of all-cause mortality (β=1.048, CI=1.019-1.078, P=0.001) and cardiovascular mortality (β=1.072, CI=1.033-1.112, P<0.001), while the LV dyssynchrony at baseline, etiology (ischemic Vs non-ischemic) and other clinical or echocardiographic parameters listed in Table 1 became insignificant.

DISCUSSION

This study examined the relationship between LV reverse remodeling and long-term clinical outcome. Patients who died during follow-up exhibited less LV reverse remodeling as compared to survivors. Based on the ROC curve, a cut-off value of <10% reduction of LVESV yielded the best prediction of all-cause and cardiovascular mortality. Besides the LV reverse remodeling, baseline LV dyssynchrony was also predictive of survival. On multivariable analysis however, LV reverse remodeling was the best predictor of long-term survival. Of note, improvement of clinical status after 3-6 months of CRT was not predictive of long-term clinical outcome.

Definition of LV reverse remodeling after CRT and its prognostic significance

Previous studies observed that CRT not only improves clinical status (NYHA class, quality of life and exercise capacity),[1,2,4] but also reverses LV remodeling and improves systolic function.[6,10,11] However, lack of a favorable response to CRT was observed in about one-third of patients in clinical studies; the definition of non-responders is difficult, but has been defined as the lack of clinical response or absence of LV reverse remodeling.[2,10,11,17] Initial studies arbitrarily defined responders of LV reverse remodeling by a reduction of LVESV>15% after 3 to 6 months of CRT.[10,11] However, there is no study that examined the potential link between LV reverse remodeling and long-term clinical outcome; and it is not known if such arbitrarily defined cut-off value of 15% is clinically relevant. Since improvement in LVESV represents favorable structural and functional changes of the LV after CRT, this may potentially predict a favorable long-term clinical outcome. In pharmacological trials, LV reverse remodeling (in particular reduction of LVESV) was associated with a better prognosis, in particular in clinical

trials with angiotensin converting enzyme inhibitors and β-blockers.[9,18,19] Since CRT benefits cardiac function by a different mechanism that involves primarily the coordination of the regional contraction rather than direct tackling of neurohormonal pathways,[10,14] it has not been explored if reduction of LV volume in patients received CRT will also predict a better long-term clinical outcome.

The present study is the largest study directly examining the relation of LV reverse remodeling to outcomes among patients with heart failure in the contemporary treatment era. A new cut-off value derived from the ROC curves of mortality prediction concluded that a reduction of LVESV≥10% was clinically relevant since this cut-off value has a high sensitivity and specificity for prediction of long-term all-cause and cardiovascular mortality. Furthermore, this cut-off value of LV reverse remodeling also predicts heart failure events and composite end-points of cardiovascular hospitalization or mortality. Therefore, volumetric assessment by echocardiography is not only a surrogate marker of favorable cardiac response to CRT, but also an objective measure that predicts the long-term clinical outcome.

Lack of predictive value of clinical parameters on long-term outcome

Another important observation in the current study is the lack of predictive value of baseline clinical status or change in clinical status after CRT on long-term clinical outcome. The clinical parameters in the current study included NYHA class, 6-minute hall walk distance and heart failure quality of life score. These parameters are frequently used as standard soft clinical end-points for assessment of treatment efficacy in heart failure trials including CRT,[1-4] and have been employed as criteria to assess "clinical" response to CRT.[20] However, in the present study, clinical improvement of quality of life and walking distance were not significantly different between those who survived and died during long-term follow-up, whereas the difference in NYHA class was only marginal. Therefore, the evaluation of volumetric response provides complementary information to clinical assessment, especially in predicting the long-term clinical outcome after CRT. Since the measurement of LV volume was performed offline in a blinded fashion, the influence of a placebo effect was minimized.

Clinical implications and conclusion

The present study established the missing link between LV reverse remodeling response and long-term clinical outcome in CRT. Therefore, reduction of LV volume consistently translated into a better clinical outcome disregarding the modality of therapy (medical or device). The results indicated that LV reverse remodeling after 3-6 months of CRT does not only explain the structural and functional benefits of the ventricle as result of resynchronization, but also implied the translation of cardiac structural benefit into a lower clinical hard event rate. Of note, improvement in clinical parameters was not predictive for long-term survival. The baseline LV dyssynchrony was predictive of long-term survival, but multivariable analysis identified

reverse LV remodeling as the best predictor for long-term survival. Accordingly, LV reverse remodeling response is a useful criterion that also determines long-term clinical outcome, and provides complementary information to clinical parameters such as NYHA class, 6-minute walking distance or quality of life score. Moreover, ROC curve analysis demonstrated that 10% improvement in LVESV had the best predictive accuracy for long-term survival, and may be considered as an objective measure to assess a clinically useful response to CRT in future clinical trials.

Limitations of the study

In this study, the number of events is relatively small. This probably reflects the benefit of CRT in the improvement of clinical outcome, which is recently proven by the CARE-HF study.[21] However, with the relatively large sample size of patients undergoing CRT, we were able to achieve the objective of examining and confirming that LV reverse remodeling is an independent predictor of long-term clinical outcome. Large, multicenter trials are needed to confirm our findings and validate whether a 10% reduction in LVESV is the best volumetric parameter to predict a favorable clinical outcome.

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Chapter 7

Hemodynamic effects of long-term cardiac resynchronization therapy – Analysis by pressure-volume loops

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ABSTRACT

Background Acute hemodynamic effects of cardiac resynchronization therapy (CRT) were reported previously, but detailed invasive studies showing hemodynamic consequences of long-term CRT are not available.

Methods and Results We studied 22 patients scheduled for implantation of a CRT device based on conventional criteria (NYHA class III-IV, left ventricular (LV) ejection fraction <35%, left bundle-branch block, QRS duration >120ms). During diagnostic catheterization prior to CRT we acquired pressure-volume loops using conductance catheters during atrial pacing at 80, 100, 120 and 140 beats/min. Studies were repeated during biventricular pacing at the same heart rates after 6 months of CRT. Our data show significant clinical benefit of CRT (NYHA class: 3.1±0.5 to 2.1±0.8; Quality-of-Life score: 44±12 to 31±16; 6-min hall-walk: 260±149 to 396±129m; all $p<0.001$), improved LV ejection fraction (29±10 to 40±13%, $p<0.01$), decreased end-diastolic pressure (18±8 to 13±6mmHg, $p<0.05$), and reverse remodeling (end-diastolic volume: 257±67 to 205±54mL, $p<0.01$). Previously reported acute improvements in LV function remained present at 6 months: dP/dt_{MAX} (+18%, $p<0.01$), $-dP/dt_{MIN}$ (+13%, $p<0.01$), stroke work (+34%, $p<0.01$). Effects of increased heart rate were improved towards more physiological responses for LV ejection fraction, cardiac output and dP/dt_{MAX}. Moreover, our study showed improved ventricular-arterial coupling (+69%, $p<0.01$) and improved mechanical efficiency (+44%, $p<0.01$).

Conclusions Hemodynamic improvements with CRT, previously shown in acute invasive studies, are maintained long-term. In addition, ventricular-arterial coupling, mechanical efficiency, and chronotropic responses are improved after 6 months of CRT. These findings may help to explain the improved functional status and exercise tolerance in patients treated with CRT.

INTRODUCTION

Cardiac resynchronization therapy (CRT) improves quality of life, symptoms, and exercise capacity in patients with heart failure and intraventricular conduction delay.[1] A recent study confirmed these favorable effects and also demonstrated that CRT significantly reduced the risk of death.[2] Whereas previous randomized controlled trials have clearly demonstrated beneficial clinical effects over a period of up to 6 months, small-scaled studies suggest that these clinical improvements are maintained long-term.[3-5] The primary working mechanism of CRT is the optimization of the mechanical activation pattern of the left ventricle (LV), which is achieved by pre-excitation of the region which is otherwise activated late due to delayed intrinsic conduction.[6] In addition to this intraventricular resynchronization, additional benefit may be obtained by optimizing the delay between atrial and ventricular systole, and the timing of LV and right ventricular (RV) stimulation. Acute improvements in mechanical dyssynchrony resulting in enhanced systolic function have been demonstrated by various studies.[7-10] Invasive studies have shown increased LV ejection fraction and stroke volume, accompanied by increased systolic pressure, dP/dt_{MAX}, and stroke work, and reduced diastolic pressure.[9;11] Interestingly, these improvements in cardiac function are obtained at diminished energy cost.[12] In the long-term, CRT is associated with LV reversed remodeling[13] and improved myocardial efficiency.[14] However, currently no invasive studies are available regarding the effects of long-term CRT on systolic and diastolic hemodynamic parameters. In this study we assessed the long-term hemodynamic effects of CRT, and investigated the underlying mechanisms. To this end, we acquired pressure-volume loops prior to CRT during right atrial pacing at 80, 100, 120 and 140 beats/min, and these studies were repeated during biventricular pacing at the same heart rates after 6 months of CRT.

METHODS

Patients

Twenty-two patients (mean age, 66±11 years; 17 men) with NYHA class III or IV heart failure despite optimized medical treatment, echocardiographic LV ejection fraction <35% and QRS duration >120ms scheduled for implantation of a CRT device were included. The protocol was approved by our institutional review committee and all patients gave informed consent. The etiology of heart failure was ischemic in 14 and non-ischemic in 8 patients. All patients received stable medical therapy for chronic heart failure, including diuretics (n=19), spironolactone (n=8), β-blockers (n=10), ACE inhibitors (n=20), and amiodarone (n=6). Medication was unchanged and no new therapies were installed during the 6-months follow-up period. In addition to the invasive studies described in detail below, we performed echocardiography, 6-minute hall-walk tests, and quality of life assessments by

the Minnesota Living with Heart Failure Questionnaire at baseline and after 6 months of CRT.

Protocol

Baseline (i.e. pre-CRT) hemodynamic data were obtained during routine diagnostic right and left heart catheterization, including thermodilution cardiac output, left ventriculography and coronary angiography. To acquire pressure-volume loops at incremental heart rates, a 7F combined pressure-conductance catheter (CD Leycom, Zoetermeer, The Netherlands) was placed in the LV via the femoral artery, and a temporary pacing lead was placed in the right atrium. Pressure-volume signals were displayed on-line and digitized at a sample frequency of 250Hz (Leycom CFL, CD Leycom). LV volume was calibrated using thermodilution and hypertonic saline dilution as previously described.[15;16] Right atrial pacing was performed at 80, 100, 120 and 140 beats/min. Data were acquired consecutively approximately 60s after changing to a higher rate, and periods of at least 20s were selected for off-line analysis. All measurements were repeated during recatheterization after at least 6 months of chronic CRT. During this session biventricular pacing was performed at 80, 100, 120 and 140 beats/min by reprogramming the CRT device. The atrioventricular (AV) delay was kept fixed at the optimal clinical setting based on Doppler mitral flow velocity recordings obtained previously at the outpatient clinic.

Data analysis

Analysis of the steady state pressure-volume loops was performed using custom software as previously described.[17] Briefly, for each patient and each pacing rate hemodynamic indexes were calculated as the mean of all beats during a steady state period of approximately 20s. LV function was quantified by cardiac output and stroke volume, end-diastolic and end-systolic volume, LV ejection fraction, end-systolic and end-diastolic pressure, maximal and minimal rate of LV pressure change (dP/dt_{MAX}, dP/dt_{MIN}). The time constant of relaxation (τ) was determined using phase-plot analysis.[18] Stroke work was calculated as the area of the pressure-volume loop. LV end-systolic elastance (E_{ES}) was estimated by end-systolic pressure divided by end-systolic volume, and end-diastolic stiffness (E_{ED}) by end-diastolic pressure divided by end-diastolic volume. Effective arterial elastance (E_A) was calculated as end-systolic pressure divided by stroke volume.[19] Ventricular-arterial coupling was quantified as E_{ES}/E_A,[20] and mechanical efficiency was calculated as the ratio of external stroke work and pressure-volume area (a measure of total mechanical work).[21] Nonuniform LV performance was determined from the segmental LV conductance signals and quantified by calculating the percentage of time within the cardiac cycle that a specific segment is dyssynchronous (i.e. opposite in phase with the global LV volume signal). Overall LV mechanical dyssynchrony was determined as the mean of the segmental dyssynchronies. In addition, we calculated the internal flow fraction, which quantifies the ineffective shifting of blood volume within the

LV due to nonuniform contraction and filling. This approach was described and validated in a previous study.[17] Time-varying wall stress, WS(t), was calculated from the instantaneous LV pressure and volume signals (P(t) and V(t), respectively) as described by Arts et al.[22]: WS(t) = P(t)·(1+3·V(t) / LVM). LV mass (LVM) was calculated from M-mode echocardiography according to the conventions proposed by the American Society of Echocardiography.[23] Atrioventricular delay was determined as the time between the right atrial pacing and the start of left ventricular contraction.[24]

Statistical analysis

We used a linear mixed-effects model to account for repeated measurements on each patient. In this model, patients were included as random effects and conditions (baseline, CRT), pacing (80, 100, 120, and 140 beats/min), and their interaction as fixed effects.[25] To assess statistical significances between pacing levels and conditions, appropriate contrasts were selected. Data are presented as mean±SD. A p-value <0.05 was considered statistically significant. The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

RESULTS

Clinical assessment and atrioventricular delay

All patients were successfully implanted with a CRT device (Contak Renewal, Guidant (n=21), or InSync III, Medtronic (n=1)). All patients received CRT for at least 6 months (7.2±1.6 months). Table 1 shows the clinical parameters which all improved significantly, consistent with previous reports[1]. AV delay was optimized based on Doppler mitral flow velocity recordings at our outpatient clinic shortly after pacemaker implantation: The AV delay was set to achieve the longest left ventricular filling time without premature truncation of the A-wave by mitral valve closure[26]. Baseline AV delay (during right atrial pacing at 80 beats/min) was 184±96 ms and tended to decrease at higher pacing rates. Mean optimized AV delay with biventricular pacing was 97±15 ms and was unchanged at the higher pacing rates (Table 2).

Table 1: Clinical parameters at baseline (pre-CRT) and after 6 months of CRT

	Baseline	6-mo CRT
NYHA class	3.05±0.49	2.05±0.79 *
Quality of life score	44±12	31±16 *
6-min hall-walk, m	260±149	396±129 *

* p<0.001 vs. baseline by paired t-tests.

Table 2: Left ventricular function indexes at baseline (pre-CRT) and at 6 months of CRT

		Changes vs. p80				P-values of Effects		
		p80	p100	p120	p140	Condition	Pacing	Interaction
HR (beats/min)	BL	78.6±4.4	21.6±0.7**	43.8±0.8**	62.7±0.8**	0.308	<0.001	0.093
	CRT	80.1±2.2	20.6±0.7**	41.1±0.7**	61.8±0.8**			
AVD (ms)	BL	184±96	-12±16	-20±16	-28±17	<0.001	0.832	0.472
	CRT	97±15##	0.4±12	2±12	3±13			
CO (L/min)	BL	4.36±0.70	0.09±0.17	-0.25±0.19	-1.14±0.20**	<0.001	<0.001	0.026
	CRT	4.98±0.86##	0.45±0.17**	0.08±0.17	-0.32±0.19			
ESV (mL)	BL	195±72	4.1±13.6	-5.3±14.7	-15.0±15.9	<0.001	0.615	0.947
	CRT	137±52##	-2.6±12.4	-5.6±12.4	-9.5±14.1			
EDV (mL)	BL	257±67	0.6±15.2	-25.7±16.5*	-44.9±17.8**	<0.001	0.005	0.814
	CRT	205±54##	-4.3±14.0	-14.2±14.0	-21.9±15.8*			
EF (%)	BL	29.1±10.4	-3.5±2.4	-8.9±2.6**	-12.6±2.8**	<0.001	<0.001	0.235
	CRT	39.5±12.8##	-0.2±2.2	-2.3±2.2	-7.4±2.5**			
SW (mmHg·L)	BL	4.37±2.07	-0.82±0.39*	-1.91±0.42**	-2.62±0.49**	<0.001	<0.001	0.468
	CRT	5.87±2.26##	-0.43±0.35	-1.06±0.35**	-2.24±0.39**			
ESP (mmHg)	BL	105±29	-1.2±3.5	-7.0±3.8	-17.6±4.1**	<0.001	<0.001	0.701
	CRT	108±22	-1.8±3.3	-5.7±3.3	-12.1±3.7**			
EDP (mmHg)	BL	17.9±8.2	0.9±1.9	1.7±2.0	3.0±2.2	<0.001	0.013	0.614
	CRT	13.2±6.4#	-0.4±1.8	2.1±1.8	5.7±2.1**			
dP/dt_{MAX} (mmHg/s)	BL	807±264	51±42	39±45	-42±48	<0.001	0.045	0.296
	CRT	953±287##	79±39*	98±39*	77±44			
$-dP/dt_{MIN}$ (mmHg/s)	BL	829±237	5±34	-36±37	-84±40	<0.001	0.105	0.650
	CRT	936±281##	17±32	6±32	-25±37			
τ (ms)	BL	83.1±12.6	-7.0±2.9*	-7.5±3.1*	-13.2±3.3**	0.637	<0.001	0.653
	CRT	81.4±12.7	-3.2±2.7	-8.0±2.7**	-10.7±3.0**			
PWS (mmHg)	BL	342±89	-2.5±20	-22±21	-54±23*	0.149	0.012	0.940
	CRT	331±99	-9.5±18	-19±18	-43±21*			
WS_{ED} (mmHg)	BL	61±26	1.4±8.0	-3.1±8.6	-3.5±9.3	0.142	0.323	0.105
	CRT	47±31	-2.5±7.3	8.5±7.3	19.7±8.2			
DYS (%)	BL	31.4±3.2	-0.2±1.1	-0.5±1.2	-1.4±1.3	<0.001	0.960	0.346
	CRT	27.4±4.5##	-0.5±1.0	-0.1±1.0	1.2±1.2			
IFF (%)	BL	71±23	-0.7±6.4	-1.0±6.8	-3.2±7.3	<0.001	0.979	0.959
	CRT	42±23##	-0.8±6.0	-2.5±6.0	0.6±6.7			
E_A (mmHg/mL)	BL	1.94±0.33	0.43±0.11**	1.03±0.12**	2.06±0.12**	<0.001	<0.001	<0.001
	CRT	1.78±0.41	0.25±0.10*	0.74±0.10**	1.29±0.11**			
E_{ES} (mmHg/mL)	BL	0.67±0.43	-0.03±0.10	-0.04±0.11	-0.11±0.12	<0.001	0.902	0.936
	CRT	1.00±0.67##	-0.02±0.09	-0.03±0.09	-0.02±0.10			
E_{ED} (mmHg/mL)	BL	0.074±0.038	0.002±0.011	0.014±0.012	0.035±0.014*	0.777	<0.001	0.810
	CRT	0.067±0.029	0.001±0.010	0.020±0.010	0.050±0.012**			
PVA (mmHg·L)	BL	14.5±4.4	-1.50±0.79	-2.90±0.85**	-5.20±1.06**	0.056	<0.001	0.505
	CRT	13.1±3.2	-0.62±0.71	-1.64±0.71*	-3.44±0.78**			
ME	BL	0.31±0.14	-0.03±0.03	-0.09±0.03**	-0.09±0.04*	<0.001	<0.001	0.470
	CRT	0.45±0.15##	-0.02±0.02	-0.03±0.02	-0.08±0.03**			
E_{ES}/E_A	BL	0.34±0.21	-0.08±0.04	-0.14±0.04**	-0.22±0.05**	<0.001	<0.001	0.841
	CRT	0.57±0.39##	-0.09±0.04*	-0.19±0.04**	-0.23±0.04**			

Table 2 Legends: p80..p140 indicates paced at 80..140 beats/min; BL, baseline (i.e. pre-CRT) ; CRT, 6-months cardiac resynchronization therapy; Condition effect, BL vs. CRT; Pacing effect, effect of incremental paced heart rate; Interaction effect, condition-pacing interaction; HR, heart rate; AVD, atrioventricular delay; CO, cardiac output; ESV, end-systolic volume; EDV, end-diastolic volume; EF, ejection fraction; SW, stroke work; ESP, end-systolic pressure; EDP, end-diastolic pressure; τ, relaxation time constant; PWS, peak wall stress; WS_{ED}, end-diastolic wall stress; DYS, mechanical dyssynchrony; IFF, internal flow fraction; E_A, effective arterial elastance; E_{ES}, end-systolic elastance; E_{ED}, end-diastolic stiffness; PVA, pressure-volume area; ME = SW/PVA, mechanical efficiency; and E_{ES}/E_A, ventricular-arterial coupling. Statistical significances and contrasts (changes vs. p80) were determined by using a linear mixed-effects model (see text for details). CRT-p80 vs. BL-p80: $^{\#}$ p<0.05, $^{\#\#}$ p<0.01. Changes vs. p80 at same condition (BL or CRT): * p<0.05, ** p<0.01.

Left ventricular function

Figure 1 shows typical examples of pressure-volume loops at 80 beats/min at baseline and after 6 months of CRT from two patients. Full hemodynamic data including the effects of increased pacing rate from all patients are summarized in Table 2. Comparison of 6 months of CRT vs. baseline at the lowest pacing rate (80 beats/min, p80) shows that cardiac output and LV ejection fraction improved significantly, whereas end-diastolic volume and end-systolic volume were significantly reduced. The latter indicates substantial reversed remodeling consistent with previous reports.[13] Improved systolic function was evidenced by a significantly increased dP/dt_{MAX}, E_{ES} and stroke work. In addition, end-diastolic pressure was significantly reduced. Diastolic stiffness E_{ED} and τ showed a non-significant tendency to reduce. dP/dt_{MIN} was significantly improved indicating improved active relaxation. The increase in E_{ES} combined with a modest decrease in E_A resulted in a significantly improved ventricular-arterial coupling ratio (E_{ES}/E_A). The significant increase in external stroke work with unchanged total mechanical work resulted in a significantly improved mechanical efficiency. Mechanical dyssynchrony and internal flow fraction were significantly reduced. Mechanical dyssynchrony was improved at all segmental levels except for the apical segment (Figure 2). Despite the

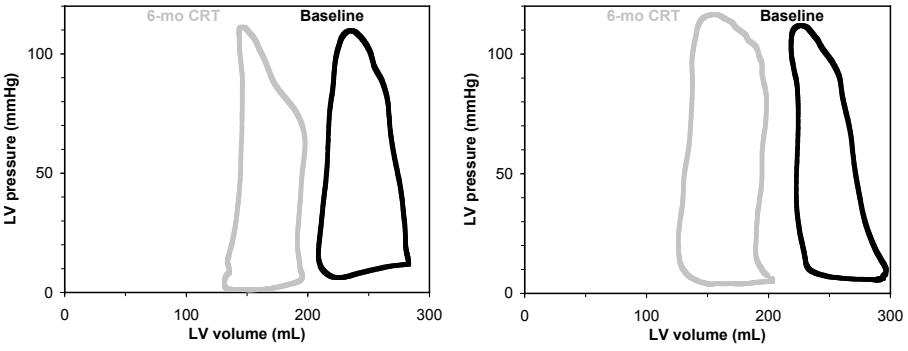

Figure 1: Effects of chronic CRT in two patients. Typical pressure-volume loops at baseline (grey) and after 6 months of chronic CRT (black) are shown (in all cases at a heart rate of 80 beats/min). Note the left ward shift of the pressure-volume loops indicating substantial reversed remodeling

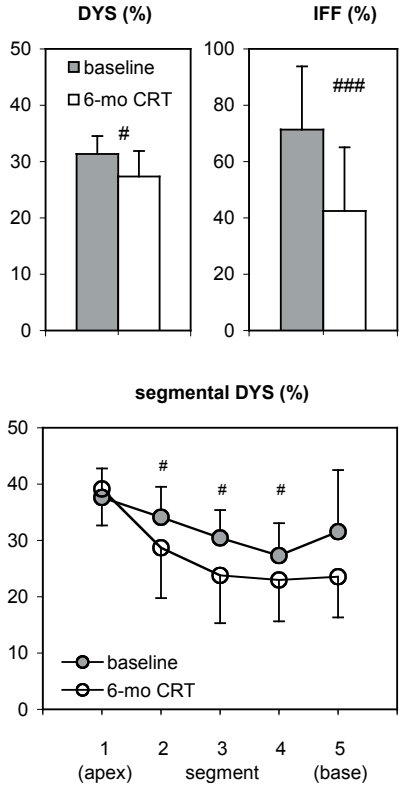

Figure 2: Mechanical dyssynchrony (DYS) and internal flow fraction (IFF) at baseline and after 6 months of CRT (at 80 beats/min). DYS is also shown per segment. Significances vs. baseline: # $p<0.05$, ### $p<0.005$.

significant reduction in LV volumes, LV wall stress was not significantly reduced. This was due to a concomitant significant reduction in LV mass from 324±92g at baseline to 290±107g ($p<0.001$) after 6 months of CRT.

Responses to increased heart rate

Table 2 shows mean values at baseline and 6-months CRT for all hemodynamic indexes at 80 beats/min, and the related changes during pacing at 100, 120 and 140 beats/min. The mean values of the main indexes are also graphically displayed in Figure 3. At baseline, cardiac output did not increase with incremental pacing, but rather cardiac output was significantly reduced at 140 beats/min, indicating an exhausted chronotropic reserve in these heart failure patients. In contrast, at 6 months follow-up, cardiac output, which was significantly higher at 80 beats/min compared to the same heart rate at baseline, increased further at 100 beats/min and remained stable at higher rates (Figure 3A). Similarly, at follow-up, LV

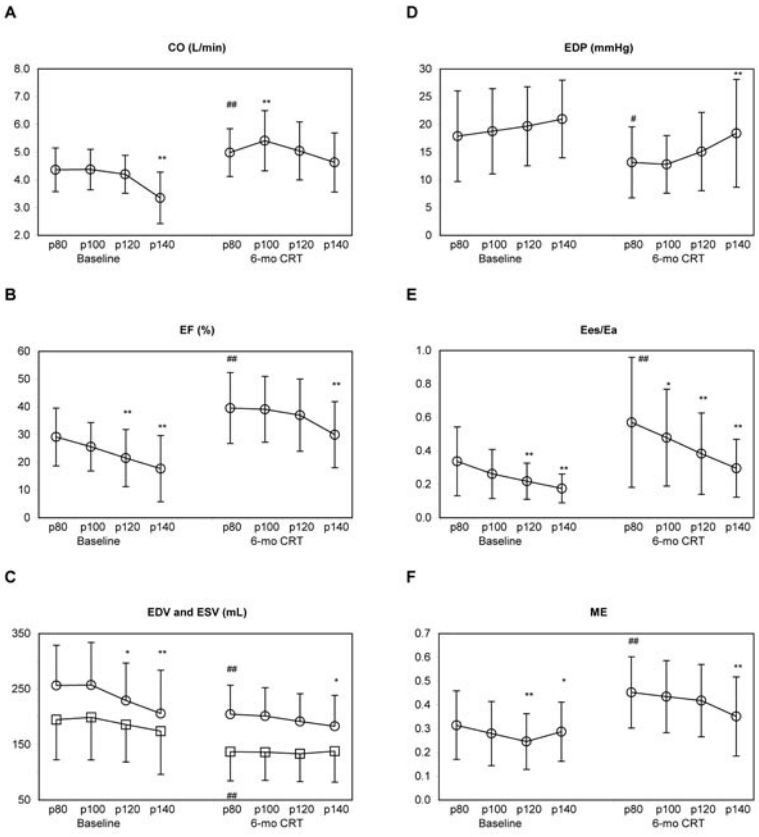

Figure 3: Main hemodynamic indexes at baseline and after 6 months of CRT. CO indicates cardiac output; EDP, end-diastolic pressure; EF, LV ejection fraction; E_{ES}, end-systolic elastance; E_A, arterial elastance; EDV, end-diastolic volume; ESV, end-systolic volume; ME, mechanical efficiency. The Figures show mean±SD at 80, 100, 120 and 140 beats/min (p80, p100, p120 and p140). Significances vs. p80 at the same condition (baseline or CRT): * $p<0.05$, ** $p<0.01$. Significances at p80 for CRT vs. baseline: # $p<0.05$, ## $p<0.01$.

ejection fraction was significantly higher at 80 beats/min, and the reduction in LV ejection fraction at incremental pacing was substantially less pronounced than at baseline (Figure 3B). The negative chronotropic responses at baseline mainly resulted from a rapid decrease in end-diastolic volume with incremental pacing, with a less pronounced drop in end-systolic volume. After 6 months of CRT, the reduction in end-diastolic volume was more limited (only significant at 140 beats/min) whereas end-systolic volume remained unchanged (Figure 3C). At the same time systolic pressure dropped significantly at 140 beats/min both at baseline and at 6 months of CRT, and diastolic pressure tended to increase with pacing rate at both time-points. These effects are clearly shown by the average (i.e. based on mean end-systolic and end-diastolic pressures and volumes) pressure-volume loops in Figure 4. Note the substantial reverse remodeling evidenced by the leftward shift of all pressure-volume loops at

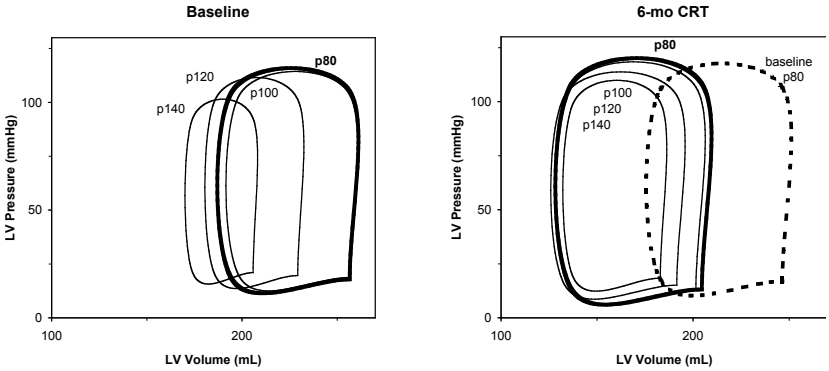

Figure 4: Mean pressure-volume loops at baseline and after 6 months of CRT. Mean pressure-volume loops are based on mean end-systolic and end-diastolic pressures and volumes and are shown at heart rates 80, 100, 120 and 140 beats/min. At baseline we used right atrial pacing via a temporary pacing lead; at follow-up biventricular pacing was performed by reprogramming the CRT device.

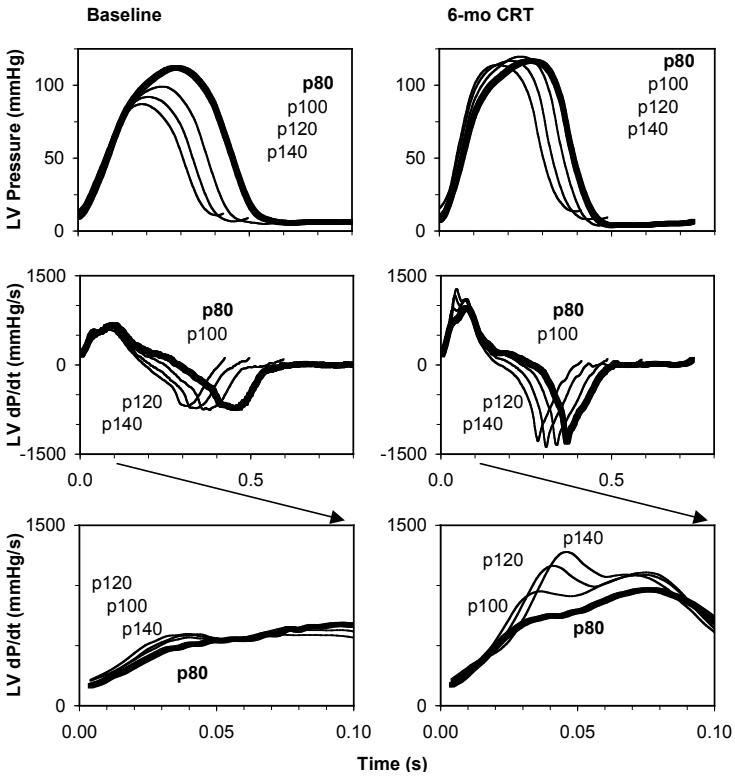

Figure 5: Typical examples of LV pressure and LV dP/dt during incremental pacing rate at baseline and after 6 months of CRT. Note that dP/dt_{MAX} was unchanged with increasing heart rate at baseline, whereas dP/dt_{MAX} substantially increased after CRT (See the bottom panels which extent the first 100ms of the dP/dt tracings).

6 months of CRT, and the fact that stroke volume (the width of the pressure-volume loops) was better maintained during increased heart rate after 6 months of CRT. Interestingly, after 6 months of CRT, dP/dt_{MAX} showed a significant increase at higher pacing levels as compared to the value at 80 beats/min, whereas at baseline no significant increases were found during incremental pacing. This indicates a more physiological response after 6 months of CRT. This is illustrated in Figure 5, which shows LV pressure and LV dP/dt for the different heart rates at baseline and after 6 months of CRT in a typical patient. Note the higher dP/dt_{MAX} after 6 months of CRT and the gradual increase in dP/dt_{MAX} with increased pacing rate, which was absent at baseline. This change towards normalization of chronotropic response was not found for dP/dt_{MIN}. Ventricular-arterial coupling, quantified by the ratio of ventricular and arterial elastance, was highly abnormal in the heart failure patients, but improved significantly after 6 months of CRT. The drop in E_{ES}/E_A with increased heart rate was still present after CRT (Figure 3E). Likewise, mechanical efficiency was improved at follow-up, but dropped significantly at 140 beats/min both at baseline and after 6 months of CRT (Figure 3F).

DISCUSSION

CRT is a highly effective new therapy in patients with left bundle-branch block and severe heart failure. Large-scale studies have reported long-term clinical benefit with improved LV function and reverse LV remodeling.[1;6;13;27] In these studies, follow-up is generally performed with echocardiography, and improvements in LV function are reported mainly in terms of increased ejection fraction. Detailed invasive hemodynamic studies of the acute effects of CRT, including analyses with pressure-volume loops[12;28], have been published previously, but to our best knowledge no such data are available for chronic CRT. In the present study we obtained invasive hemodynamics by pressure-volume loops at baseline and after 6 months of CRT. Our data confirm previous findings regarding clinical benefit, improved LV ejection fraction and reverse remodeling. In addition, it shows that hemodynamic improvements in terms of increased dP/dt_{MAX}, dP/dt_{MIN} and stroke work, and reduced end-diastolic pressure, previously found in acute studies[6;11;28;29], are still present at 6 months follow-up.

Moreover, our study shows improved ventricular-arterial coupling and improved mechanical efficiency. These hemodynamic findings are consistent with the observed improvements in clinical and functional status. The altered responses to increased heart rate may partly explain the improved exercise capacity of patients treated with CRT. At baseline, cardiac output was unchanged when heart rate was increased illustrating the exhausted LV function reserve of these patients. At follow-up this is converted to a more physiological response although the capacity to increase cardiac output is still limited. The latter presumably is partly due to an abnormal relaxation reflected by a relatively long isovolumic relaxation time (τ), which did not improve after CRT. In the normal heart, τ substantially shortens at higher heart rate,

which enables adequate filling despite a shortened diastolic period. This response is largely lost in heart failure, and did not normalize after 6 months of CRT in our patients. Consistent with our findings, previous studies failed to show improvements in isovolumic relaxation neither with acute biventricular pacing[29;30] nor at long-term.[13] A theoretical model by Hay et al.[31] shows a close correlation between increased τ and increased diastolic pressure, which is most evident at high heart rates. Our data are consistent with this prediction and show that the phenomenon is still present after 6 months of CRT. The improved mechanical efficiency found in our study is in line with previous studies on acute effects of CRT by Nelson et al.[12] and is consistent with studies by, e.g., Sundell et al.[14] in patients treated long-term. Most likely, the improved mechanical intraventricular synchrony underlies the more efficient conversion of total mechanical energy to external stroke work. This is most evident from a highly significant reduction in internal flow fraction from 71 to 42%, which indicates that segmental volume changes are more efficiently used for effective ejection rather than for energy-wasting shifting of blood volumes between segments within the ventricle. In addition, ventricular-arterial coupling was significantly improved which further optimizes production of external work[32;33]. However, whereas in the normal heart optimal ventricular-arterial coupling is maintained with increased heart rate[34], E_{ES}/E_A significantly dropped in our patients and this abnormal response was still present after long-term CRT. The baseline values for mechanical efficiency and ventricular-arterial coupling found in our study (0.31 and 0.34, respectively) were in the same range but somewhat lower than values reported by Kim et al.[35]: 0.38 and 0.42, respectively. However, the patients in their study had less severe heart failure evidenced by an average NYHA classification of 1.8±0.7 and an LV ejection fraction of 37±13%. Asanoi et al.[36] reported that in the failing heart homeostatic mechanisms maintain arterial blood pressure within the normal range, but that this blood pressure level causes a deviation from energetically optimal conditions in hearts with a severely reduced contractile state. This discrepancy results from worsening of ventricular-arterial coupling and decreased mechanical efficiency. Conversely, the improved ventricular-arterial coupling and mechanical efficiency after 6 months of CRT, as found in our study, constitutes a more optimal energetic condition. Interestingly, despite the substantial reverse remodeling in our study, wall stress was not significantly reduced after 6 months of CRT. This was due to a concomitant reduction in LV mass. We would hypothesize that the regression in LV volumes initially leads to a reduction in wall stress, which then in turn may cause a reduction in LV hypertrophy. Note however that, although not statistically significant, diastolic wall stress was reduced by 23% at 80 beats/min and by 30% at 100 beats/min. At higher heart rates, wall stress was virtually unchanged or even increased compared to baseline (-5% at 120 beat/min, and +24% at 140 beats/min). This finding is explained by the fact that at baseline end-diastolic volume drops substantially at the high heart rates (which also limits the increase in end-diastolic pressure), whereas end-diastolic volume is better maintained at 6-months follow-up. Furthermore, the global model to calculate wall stress does not take into account spatial dyssynchrony, and

conversion to a more uniform contraction pattern at 6-months follow-up may lead to reductions in wall stress at a regional level.

In our study we used simultaneous biventricular pacing in all patients. Sequential biventricular pacing has been proposed to optimize CRT, and either right ventricular or left ventricular pre-excitation may optimize hemodynamics in individual patients.[8;37] However, Hay et al.[28] demonstrated that sequential biventricular stimulation offered minimal benefit and that, on the average, most systolic and diastolic function parameters reached a maximum with simultaneous pacing. In addition to improvement of intra- and interventricular dyssynchrony, the patients may also have benefited from optimization of the AV delay. In our study the AV delay was reduced from a baseline value of 184±96 ms to a mean value of 97±15 ms during CRT. Studies by Auricchio et al.[24] showed that the maximal increases in pulse pressure and dP/dt_{MAX} were obtained at 45% of the intrinsic AV interval. Consistently, most studies report optimal AV delays of 100-120 ms, but small differences in delay have far less influence than pacing site.[29]

Because our baseline studies were performed prior to implantation of the CRT device we could not assess the acute hemodynamic effects of CRT. However, these effects were documented in previous studies. Acute improvements in CO or SV, in most studies assessed by changes in aortic pulse pressure, were reported to be in the range of 7 to 15% [3;11;24;28;29;38;39], which is comparable to the 14% increase found at 6-months in our study. Previous studies show an acute reduction of 10 to 18% in end-systolic volume, and a relatively smaller reduction in end-diastolic volume of 5 to 9% [8;30;39] , which lead to 15 to 33% relative improvement in EF. The reductions in end-systolic and end-diastolic volume at 6 months in our study were 30 and 20%, respectively. Apparently, the acute improvement in cardiac output is maintained long-term, but both end-systolic and end-diastolic volume show a gradual, more or less parallel, further reversed remodeling, as previously documented over a 3-months period by Yu et al.[27] With regard to dP/dt_{MAX}, previous studies fairly consistently showed an acute increase of 13 to 21% [3;7;11;24;28;29;38], which is close to the 18% increase found in our study at 6-months follow-up. Yu's study revealed that more than 60% of the gain in dP/dt_{MAX} obtained after 3 months CRT is lost immediately after turning off the pacemaker, whereas 4 weeks after cessation of CRT dP/dt_{MAX} had completely returned to pre-CRT values. Their study also showed that left ventricular volumes increased and other echocardiographic benefits were gradually lost over the 4-week period. We did not systematically investigate the effects of turning off the pacemaker, but in a few patients we registered pressure-volume loops during temporary cessation of pacing in the follow-up study. Figure 6 shows two typical examples: The pressure-volume loops show an immediate reduction in stroke volume, whereas dP/dt_{MAX} was decreased by 20 and 7%, respectively. These immediate on-off responses are very similar to those registered previously in acute studies.[29]

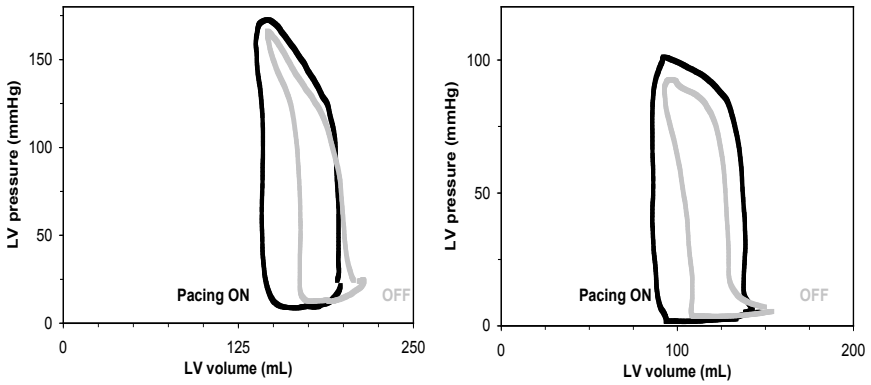

Figure 6: Immediate effects of cessation of biventricular pacing after 6-months CRT in two patients. Typical pressure-volume loops during pacing ON (black) and OFF (grey). Note the immediate reduction in stroke volume.

Study limitations

The number of patients included in this study was relatively small in comparison to the number of outcome variables. Thus, some differences that reached statistical significance might be spurious due to the relatively large number of statistical tests. Moreover, the sample size was too small to justify a meaningful responder/non-responder analysis. Only 4 patients did not show an improved clinical status: 3 patients with NYHA class III remained in class III, one class III patient deteriorated to class IV. All other patients improved by 1 or 2 NYHA classes. In the 'non-responder' group the baseline end-diastolic volume and end-systolic volume (282±73 and 228±70 mL, respectively) appeared to be somewhat higher than in the group as a whole, and ejection fraction somewhat lower (21±6%).

In conclusion, our study shows that hemodynamic improvements that were previously shown in acute studies are maintained with long-term CRT. In addition, ventricular-arterial coupling, mechanical efficiency, and chronotropic responses are improved after 6 months of CRT. These findings may help to explain the improved functional status and exercise tolerance in heart failure patients treated with cardiac resynchronization.

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Chapter 8

Left ventricular resynchronization is mandatory for response to cardiac resynchronization therapy

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Submitted

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, P=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, P=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 ≤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), LV ejection fraction ≤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 exer-

cise 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, end-diastolic) and LV ejection fraction 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 LV end-systolic volume 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 between 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.

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 LV ejection fraction from 23±7% to 33±10% ($P<0.001$) and significant LV reverse remodeling with a decrease in LV end-diastolic volume from 243±76 ml to 204±73 ml ($P<0.001$) and a decrease in LV end-systolic volume from 188±71 ml to 136±63 ml ($P<0.001$).

Table 1. Baseline characteristics (n=100)

Age (yrs)	67±11
Gender	
male	86 (86%)
female	14 (14%)
Etiology	
ischemic	59 (57%)
non-ischemic	41 (43%)
QRS duration (ms)	168±27
Rhythm	
Sinus rhythm	89 (89%)
Atrial fibrillation	11 (11%)
NYHA functional class	
III	95 (95%)
IV	5 (5%)
Medication	
Diuretics	88 (88%)
ACE inhibitors	92 (92%)
Beta-blockers	77 (77%)
Qol-score	38±16
6-MWT	292±108
LVEF (%)	23±7
LVEDV (ml)	243±76
LVESV (ml)	188±71
LV dyssynchrony (ms)	114±36

6-MWT: 6-minute walking distance; LV: left ventricular; LVEF: left ventricular ejection fraction; LVEDV left ventricular end-diastolic volume; LVESV left ventricular end-systolic volumes; NYHA: New York Heart Association; Qol: quality-of-life score.

Eighty-five patients (85%) showed a reduction >10% in LV end-systolic volume 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 versus baseline and P=NS versus 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 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).

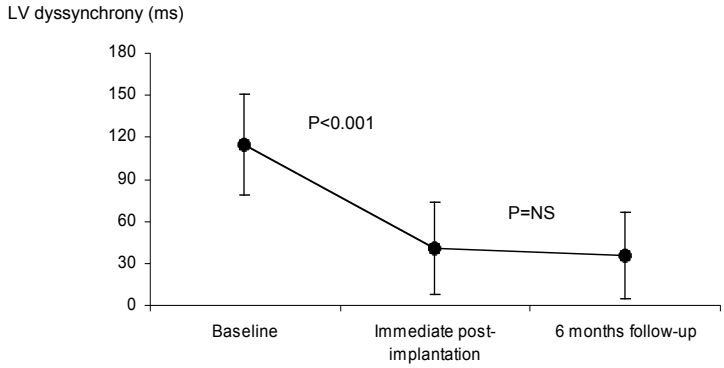

Figure 1. Time course of LV resynchronization following CRT implantation in all patients (n=100).

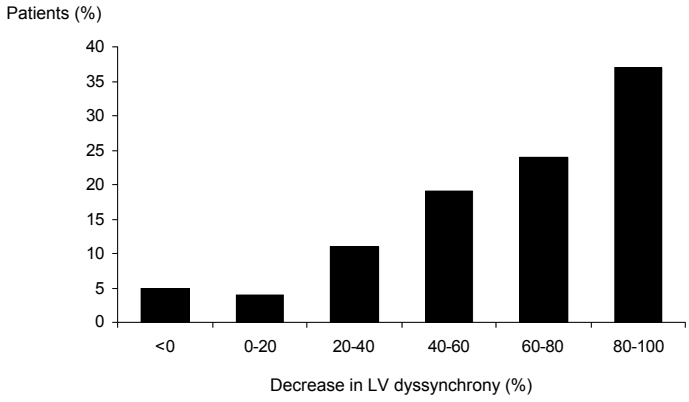

Figure 2. Extent of the decrease in LV dyssynchrony immediately following CRT implantation.

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 LV end-systolic volume and 1 patient died from progressive heart failure before 6 months follow-up; these patients were classified as non-responders to CRT (15%).

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%, P=NS).

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

	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
Etiology (isch/non-isch)	47/38	12/3	NS
QRS duration (ms)	169±28	158±18	NS
LV dyssynchrony (ms)			
Baseline	115±37	106±29	NS
follow-up (acute)	32±23*	79±44	<0.05
NYHA class			
baseline	3.0±0.2	3.1±0.3	NS
follow-up	2.0±0.5*	2.6±0.5*	<0.05
6-MWT (m)			
baseline	295±110	264±89	NS
follow-up	419±85*	337±151*	<0.05
QoL score			
Baseline	37±17	42±13	NS
follow-up	18±14*	28±16*	<0.05
LVESV (ml)			
Baseline	190±69	170±79	NS
follow-up	130±59*	177±73	<0.05
LVEDV (ml)			
Baseline	245±75	220±84	NS
follow-up	200±72*	231±80	NS
LVEF (%)			
Baseline	23±7	24±7	NS
follow-up	34±9*	25±7	<0.05

6-MWT: 6-minute walking distance; LV: left ventricular; LVEF: left ventricular ejection fraction; LVEDV left ventricular end-diastolic volume; LVESV left ventricular end-systolic volumes; NYHA: New York Heart Association; Qol: quality-of-life score. *: P<0.05 follow-up vs. baseline value, # 1 patient died before 6 months follow-up.

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

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, P=NS), whereas the re-

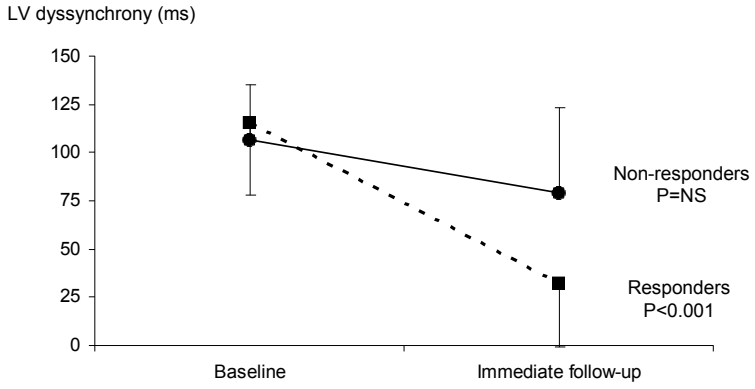

Figure 3. Immediate decrease in LV dyssynchrony in the patients with response to CRT (n=85, 85%, defined as >10% reduction in LV end-systolic volume) versus the patients without response (n=15, 15%).

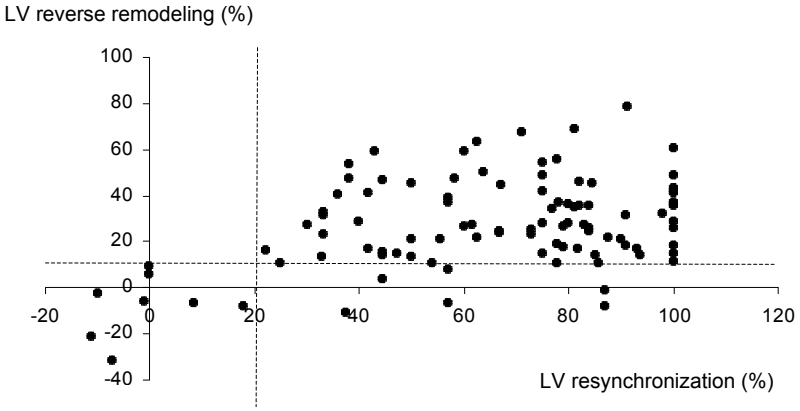

Figure 4. Relationship between immediate LV resynchronization and reduction in LV end-systolic volume at 6 months follow-up (y=0.29x+8, n=99, r=0.41, P<0.001).

sponders 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).

DISCUSSION

The main findings of the current study can be summarized as follows:
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].

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
Etiology (isch/non-isch)	53/38	6/3	NS
QRS duration (ms)	169±28	157±17	NS
LV dyssynchrony (ms)	114±37	112±24	NS
NYHA class	3.0±0.2	3.1±0.3	NS
LVESV (ml)	187±70	197±79	NS
LVEDV (ml)	241±76	255±84	NS
LVEF (%)	23±7	23±7	NS

LV: left ventricular; LVEF: left ventricular ejection fraction; LVEDV left ventricular end-diastolic volume; LVESV left ventricular end-systolic volumes; NYHA: New York Heart Association
1 patient died before 6 months follow-up

In the current study, all patients had echocardiographic evidence of LV dyssynchrony and the echocardiographic response rate (defined as a decrease >10% in LV end-systolic volume 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 LV end-systolic volume 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 LV end-systolic volume 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.

In 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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Part III

Prediction of response to CRT

Chapter 9

Relationship between QRS duration and left ventricular dyssynchrony in patients with end-stage heart failure

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ABSTRACT

Introduction Patients with end-stage heart failure and a wide QRS complex are considered candidates for cardiac resynchronization therapy (CRT). However, 20-30% of patients do not respond to CRT. Lack of left ventricular dyssynchrony may explain non-response. Accordingly, we have evaluated the presence of left ventricular dyssynchrony using tissue Doppler imaging (TDI) in 90 consecutive patients with heart failure.

Methods Ninety patients with severe heart failure (left ventricular ejection fraction<35%, NYHA class III-IV) were prospectively evaluated. Based on the QRS duration, 30 consecutive patients with a narrow QRS complex were included (QRS duration ≤120 ms), 30 patients with an intermediate QRS duration (120-150 ms), and 30 patients with a wide QRS complex (>150 ms). All patients underwent TDI to assess left ventricular dyssynchrony. Extensive left ventricular dyssynchrony was defined as an electro-mechanical delay on TDI between the septum and lateral wall, the so-called septal-to-lateral delay, of more than 60 ms.

Results Severe dyssynchrony was observed in 27% of patients with narrow QRS complex, in 60% of patients with intermediate QRS duration and in 70% of patients with wide QRS complex. No relation existed between QRS duration and septal-to-lateral delay.

Conclusions 30-40% of heart failure patients with QRS duration >120 ms do not exhibit left ventricular dyssynchrony, which may explain non-response to CRT. Alternatively, 27% of patients with heart failure and a narrow QRS complex show significant left ventricular dyssynchrony and may be candidates for CRT.

INTRODUCTION

Over the past decades end-stage heart failure has emerged as a growing health-care problem in the Western World with an almost "epidemic" increase in the number of patients with end-stage heart failure [1-3].

A relatively new option of therapy for patients with end-stage heart failure and a wide QRS complex, is atrial synchronized biventricular pacing or cardiac resynchronization therapy (CRT). Promising results were demonstrated in recent large randomized controlled trials [4-7]. In these trials the clinical benefit of CRT has been shown, as evidenced by improvement in heart failure symptoms and functional class, quality of life, exercise capacity and left ventricular systolic performance.

In these trials however, approximately 20-30% of the patients fails to improve during CRT (referred to as non-responders), although they are selected according to traditional patient selection criteria (QRS >120 ms, left bundle branch block, NYHA class III-IV and left ventricular ejection fraction <35%) [6-8].

In order to avoid unnecessary medical expenses and procedure risks, the number of non-responders should be reduced. To achieve this goal, traditional selection criteria must be refined. It has recently been suggested that dyssynchrony within the left ventricle may be the most important predictor of response to CRT [8-11]. However, a wide QRS complex may not be synonymous with substantial left ventricular dyssynchrony. This consideration is supported by the fact that recent studies demonstrated poor prediction of success when the QRS duration was used. In contrast, preliminary studies that used tissue Doppler imaging (TDI) to assess left ventricular dyssynchrony demonstrated that identification of responders was possible before implantation of a CRT system [8,11-14]. Thus, QRS duration may not adequately reflect left ventricular dyssynchrony and some patients with a wide QRS complex may not have substantial left ventricular dyssynchrony. In addition, it is also unclear whether patients with a narrow QRS complex may have left ventricular dyssynchrony.

Therefore, we have evaluated the relationship between the QRS duration on the surface ECG and left ventricular dyssynchrony in a large group of patients with end-stage heart failure using tissue Doppler echocardiography; a subset of patients with a narrow QRS complex was also studied.

METHODS

Study Population

A total of 90 consecutive patients with severe heart failure were prospectively included. The inclusion criteria were:

-severe heart failure (NYHA class III or IV)

-left ventricular ejection fraction ≤35%.
Patients with a paced rhythm were excluded.
Based on the QRS duration, 30 consecutive patients with a narrow QRS complex were included (QRS duration ≤120 ms), 30 patients with an intermediate QRS duration (between 120 and 150 ms) and 30 patients with a wide QRS complex (>150 ms).

Electrocardiographic analysis

In all patients, QRS duration was measured from the surface ECG using the widest QRS complex from the leads II, V1 and V6. The electrocardiograms were recorded at a speed of 25mm/sec. The ECGs were evaluated by two independent observers without knowledge of the clinical status of the patient.

Echocardiography and tissue Doppler imaging

Patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed system FiVe/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 colour Doppler data, triggered to the QRS complex were saved in cine loop format. The left ventricular volumes (end-systolic, end-diastolic) and left ventricular ejection fraction were calculated from the conventional apical 2- and 4-chamber images, using the biplane Simpson's technique [15].

For TDI, color Doppler frame rates varied between 80 and 115 frames/s depending on the sector width of the range of interest; pulse repetition frequencies were between 500 Hz and 1 KHz, resulting in aliasing velocities between 16 and 32 cm/s. Tissue Doppler parameters were measured from color images of 3 consecutive heart beats by offline analysis. Data were analyzed using commercial software (Echopac 6.1, General Electric - Vingmed). To determine left ventricular dyssynchrony, the sample volume was placed in the basal portions of the septum and the lateral wall; peak systolic velocities and time-to-peak systolic velocities were obtained and the septal-to-lateral delay in peak velocity was calculated as an indicator of left ventricular dyssynchrony. Based on previous observations, a cut-off point of 60 ms delay between peak systolic velocity of the septum and lateral wall was used to identify patients with severe left ventricular dyssynchrony [8]. Inter- and intra-observer agreement for assessment of septal-to-lateral delay were 90% and 96%, respectively.
All echocardiographic measurements were obtained by two independent observers without knowledge of the clinical status of the patient.

Statistical analysis

Data are presented as mean ± SD, and compared using (un-)paired Student's t-test when appropriate. Univariate analysis for categorical variables was performed using the chi-square

test with Yates' correction. Simultaneous comparison of >2 mean values was performed by using 1-way ANOVA with Bonferoni correction. Linear regression analysis was performed to determine the relationship between QRS duration and septal-to-lateral delay. For all tests a P-value <0.05 was considered statistically significant.

RESULTS

Study population

A total of 90 patients were included (69 men, mean age 62.1 ± 12 years); the underlying etiology of heart failure was idiopathic dilated cardiomyopathy in 31 % and ischemic cardiomyopathy in 69 %. Mean QRS duration was 144 ms and varied from 78 to 238 ms; 93 % of patients with a QRS of more than 120 ms had left bundle branch block. The majority (84%) of patients were in sinus rhythm. All patients were in NYHA class III (94%) or IV (6%). The left ventricular ejection fraction was 22 ± 7% (range 11-35 %) with a left ventricular end-systolic volume of 190 ± 76 ml and a left ventricular end-diastolic volume of 240 ± 86 ml.

The characteristics of the 3 groups (divided according to QRS duration) are summarized in Table 1. By definition, the mean QRS duration was longest in group 3, and shortest in group 1 (187±9 ms vs 106±12 ms). Among those patients with QRS width > 120ms, over 90% had left bundle branch block.

Patients with a narrow QRS complex had less severe heart failure symptoms.

Left ventricular volumes increased in parallel to the QRS duration; since both left ventricular end-systolic and end-diastolic volume increased, left ventricular ejection fraction was comparable between the different between the 3 groups (Table 2).

QRS duration versus left ventricular dyssynchrony

The septal-to-lateral delays for the 3 different groups are shown in Figure 1. A stepwise increase in septal-to-lateral delay was noted over the 3 groups, with a mean septal-to-lateral delay of 43ms in the patients with narrow QRS complex and 97ms with a wide QRS complex ($P<0.05$).

Significant left ventricular dyssynchrony was observed in the vast majority (70%) of patients with wide QRS complex. Also, 60% of the patients with an intermediate QRS duration exhibited significant left ventricular dyssynchrony. Of interest, 27% of patients with a narrow QRS complex also demonstrated left ventricular dyssynchrony. The precise distribution of dyssynchrony in relation to the 3 groups is displayed in Figure 2. Linear regression failed to show a significant relation between the QRS duration and the septal-to-lateral delay (Figure 3).

Table 1: Baseline patient characteristics

	QRS ≤ 120 (n= 30)	QRS 120 –150 (n=30)	QRS > 150 (n=30)	
M/F	26/4	21/9	22/8	NS
Age (years)	59.0 ± 14.3 (20-77)	61.2 ± 11.9 (31-80)	65.9 ± 8.6 (46-81)	<0.05
Ischemic	22 (73%)	20 (67%)	20 (67%)	NS
Nonischemic	8 (27%)	10 (33%)	10 (33%)	
QRS duration (ms)	106.2 ± 12.3 (78-120)	139.5 ± 9.2 (122-150)	186.7 ± 8.6 (158-238)	_
QRS configuration:				
LBBB	0	27 (90%)	29 (97%)	NS
RBBB	0	3 (10%)	1 (3%)	NS
Rhythm:				
Sinus rhythm	24 (80%)	26 (87%)	26 (87%)	NS
Atrial fibrillation	6 (20)	4 (13%)	4 (13%)	NS
NYHA class III	29	28	28	NS
NYHA class IV	1	2	2	NS
Medication:				
Diuretics	20 (67%)	24 (80%)	26 (87%)	NS
ACE-inhibitors	24 (80%)	26 (87%)	27 (90%)	NS
Beta-blockers	17 (57%)	18 (60%)	19 (63%)	NS
Anticoagulants/Aspirin	27 (90%)	28 (93%)	27 (90%)	NS

LBBB: left bundle branch block ,RBBB: right bundle branch block M/F: male/female

Table 2: Left ventricular ejection fraction and left ventricular volumes

	QRS < 120 (n= 30)	QRS 120 –150 (n=30)	QRS > 150 (n=30)	
LVEF (%)	22 ± 6 (13-35)	22 ± 7 (11-34)	21 ± 7 (11-34)	NS
ESV	164 ± 63 (84-305)	188 ± 67 (86-320)	218 ± 88 (94-487)	<0.05
EDV	210 ± 71 (105-350)	236 ± 73 (130-387)	273 ± 101 (140-559)	<0.05

EDV: end-diastolic volume
ESV: end-systolic volume
LVEF: left ventricular ejection fraction

Etiology versus dyssynchrony

To evaluate the effect of underlying etiology on left ventricular dyssynchrony, the patients with ischemic and non-ischemic cardiomyopathy were analyzed separately.

The 2 subsets of patients showed similar findings. A gradual increase in septal-to-lateral delay paralleled the increase in QRS duration (Figure 4). The shortest septal-to-lateral delays were observed in the patients with a narrow QRS complex (44 and 40ms for patients with ischemic

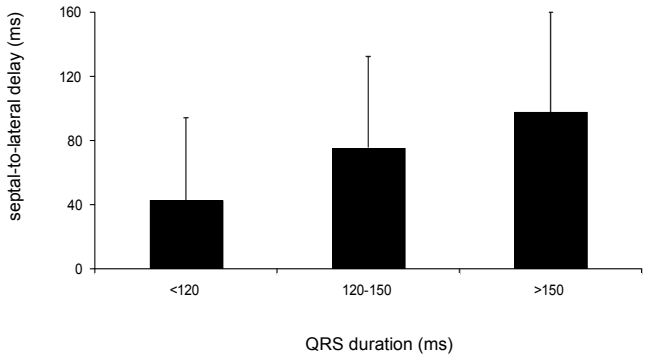

Figure 1. Mean septal-to-lateral delay in the different patient groups according to QRS duration. ($P < 0.05$ by ANOVA).

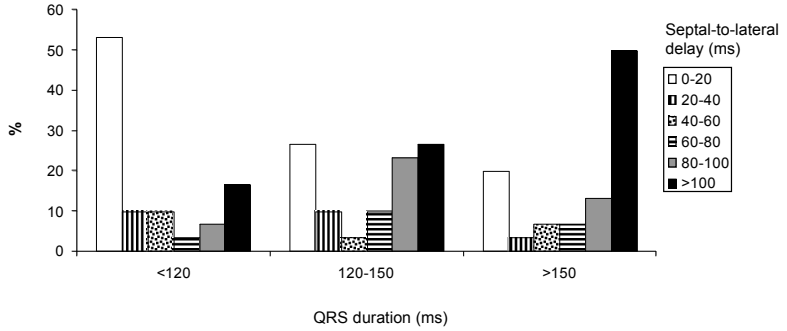

Figure 2. Distribution of septal-to-lateral delay (as marker of left ventricular dyssynchrony) and QRS duration.

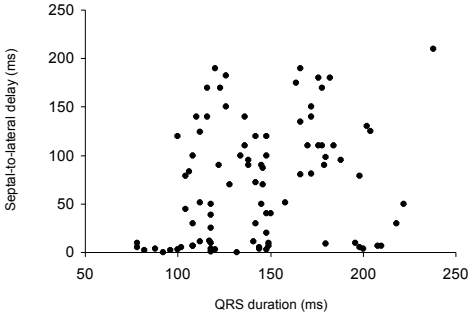

Figure 3. Relationship between septal-to-lateral delay and QRS duration. No significant relation existed between QRS duration and septal-to-lateral delay. ($y = 0.44\,x + 9.1$, n=90, r=0.26, ns)

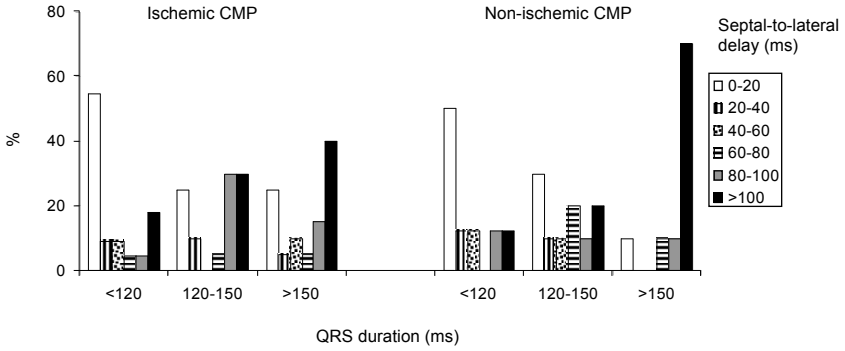

Figure 4. Distribution of septal-to-lateral delay and QRS duration. Ischemic versus non-ischemic cardiomyopathy.

and non-ischemic cardiomyopathy respectively).The largest delays were observed in the patients with wide QRS complex: 87ms for patients with ischemic cardiomyopathy and 118ms for non-ischemic cardiomyopathy.

In both groups, the majority of patients (60% and 90% respectively) with a wide QRS complex had substantial dyssynchrony. In the narrow QRS group, 27% and 25% (ischemic and non-ischemic cardiomyopathy respectively) had substantial left ventricular dyssynchrony.

Linear regression demonstrated no relation between QRS duration and septal-to-lateral delay in the patients with ischemic cardiomyopathy ($y = 0.30 x + 28.0$, n=62, r=0.18, ns), whereas a weak relation between these 2 parameters existed in the patients with non-ischemic cardiomyopathy ($y = 0.79 x -40.0$, n=28 r=0.48, $P<0.05$).

Influence of NYHA class and left ventricular ejection fraction

Patients with NYHA class IV (n=5) had a wider QRS complex (although not significant) as compared to the patients in NYHA class III (154 vs. 144ms, ns). Also, patients in NYHA class IV had more extensive dyssynchrony as compared to the NYHA class III patients (85 vs. 71ms, ns). Linear regression demonstrated no relation between left ventricular ejection fraction and septal-to-lateral delay ($y = 1.79 x + 33.4$, n=90, r=0.19, ns).

DISCUSSION

Currently, CRT is considered a major breakthrough in treatment of patients with dilated cardiomyopathy and end-stage heart failure. Various studies have demonstrated the immediate benefit of CRT on hemodynamics [16-18] and systolic performance of the left ventricle [19]. Moreover, the immediate benefits were accompanied by an improvement in symptoms, exercise capacity, and left ventricular ejection fraction at mid-term follow-up [7,20]. Multicenter

large trials have clearly confirmed the findings from smaller studies [4-6]. In addition, duration and number of hospitalisations for decompensated heart failure is reduced after CRT [21]. Finally, meta-analysis of the available studies demonstrated an improved survival (over 6 months) after CRT as compared to optimal medical therapy [22].

The indications for use of CRT include, severe heart failure (NYHA class III or IV), dilated cardiomyopathy with depressed left ventricular ejection fraction (<35%), and wide QRS complex on the ECG with left bundle branch block configuration [4-6]. Some patients do not improve during CRT, these patients are referred to as non-responders. Careful analysis of data from the MIRACLE Trial revealed that 20-30% of patients (selected according to these criteria) did not improve in symptoms [6]. This percentage of non–responders has also been reported in other studies [7,8]. The definition of a non-responder is difficult: some patients do not improve in symptoms, but do also not deteriorate in symptoms. Despite the absence of improvement, these patients may still be considered as responders since without CRT these patients may have worsened in symptoms. Still, additional selection criteria for CRT are needed to enhance the likelihood of response to CRT.

Recently, it has been proposed that the most important predictor of response to CRT may be the presence of dyssynchrony within the left ventricle [8,11,23]. Patients with extensive dyssynchrony within the left ventricle appeared to respond well to CRT, whereas patients without dyssynchrony did not respond to CRT [8,11]. Assessment of dyssynchrony is possible with a variety of techniques including magnetic resonance imaging [24], scintigraphy [25], and various echocardiographic techniques [12-14,26-30]. Among the echocardiographic approaches, most experience has been obtained with TDI [8,10,12-14,26,27]. Yu et al demonstrated the feasibility of TDI to assess left ventricular dyssynchrony in patients eligible for CRT [10,11]. Moreover, these authors showed a significant reduction in left ventricular dyssynchrony after CRT [8,10-14]. Besides TDI, strain and strain rate analyses have also been used to assess left ventricular dyssynchrony. In particular, Sogaard et al. have shown the value of these approaches for predicting response to CRT [26,27].

Potentially, the combination of the traditional selection criteria for CRT combined with the assessment of left ventricular dyssynchrony may be ideal to select the best candidates for CRT. In the current study, we have evaluated patients meeting the traditional selection criteria for CRT, and we have assessed the presence or absence of left ventricular dyssynchrony with TDI. The parameter to assess dyssynchrony used in the present study, the septal-to-lateral delay, has been used in previous studies. It represents the delay in long-axis function between the septum and the lateral wall. In patients with non-ischemic cardiomyopathy, it was demonstrated that CRT resulted in a substantial reduction in septal-to-lateral delay, indicating resynchronization after CRT [8,10-14]. In a subsequent study, it was shown that a septal-to-lateral delay >60 ms was highly predictive of response to CRT [8].

Using this cut-off of 60 ms, the data in the present study showed that 70% of patients with a wide QRS complex (>150 ms) had substantial left ventricular dyssynchrony. However, 30%

of patients with a wide QRS complex did not have substantial dyssynchrony; this percentage of patients without dyssynchrony is very similar to the percentage non-responders in the various CRT trials[6-8]. Similarly, in the patients with an intermediate QRS duration (120-150 ms), 40% did not show substantial left ventricular dyssynchrony. Additional evaluation of patients with and without dyssynchrony after CRT to further determine the relation between dyssynchrony and outcome after CRT is needed.

The majority (73%) of patients with a narrow QRS complex (≤120 ms) did not exhibit dyssynchrony, but interestingly, 27% of patients had significant dyssynchrony. Whether these patients also benefit from CRT needs further testing.

In addition, other factors may influence response to CRT, including LV lead positioning, and optimisation of the AV and V-V delay.

Conclusion

TDI allows assessment of left ventricular dyssynchrony. Patients with a wide QRS complex frequently have substantial left ventricular dyssynchrony, although 30%-40% did not exhibit dyssynchrony. The combination of the traditional selection criteria, complemented by demonstration of left ventricular dyssynchrony, may allow more accurate prediction of response to CRT.

In addition, 27% of patients with heart failure, dilated cardiomyopathy and a narrow QRS complex had dyssynchrony, suggesting that a subset of these patients may also benefit from CRT.

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Chapter 10

Frequency of left ventricular dyssynchrony in patients with heart failure and a narrow QRS complex

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ABSTRACT

Cardiac resynchronization therapy (CRT) is considered a major advance in the treatment of patients with heart failure. The presence of left ventricular (LV) dyssynchrony seems mandatory for a positive response to CRT. Currently only patients with a wide QRS complex are considered for CRT, although patients with a narrow QRS complex may also have LV dyssynchrony. In the present study we prospectively evaluated the incidence of LV dyssynchrony in 64 patients with heart failure and a narrow QRS complex using tissue Doppler imaging.

INTRODUCTION

It is unclear how many patients with a narrow QRS complex have substantial dyssynchrony and may thus be considered for cardiac resynchronization therapy (CRT). Accordingly, the incidence of left ventricular (LV) dyssynchrony in patients with heart failure and a narrow QRS complex was evaluated using tissue Doppler imaging (TDI).

METHODS

Patients and study protocol

A total of 64 consecutive patients with known heart failure, severe impairment of LV systolic function (LV ejection fraction ≤ 35%) and a narrow QRS complex (≤ 120 ms) on the surface electrocardiogram were prospectively included in the study. Patients with a recent myocardial infarction (< 3 months) or decompensated heart failure, and a permanent pacemaker were excluded. In the patients, the clinical status was assessed and QRS duration was measured from the surface electrocardiogram. Two-dimensional echocardiography was conducted to assess LV volumes and LV ejection fraction. LV dyssynchrony was determined by TDI, calculating the delay between peak systolic velocities of the septum and the lateral wall (referred to as the septal-to-lateral delay). The level of inter-ventricular dyssynchrony was derived from conventional pulsed-wave Doppler echocardiography.

Electrocardiographic analysis

The QRS duration was measured from the surface ECG using the widest QRS complex in the leads II, V1 and V6. The electrocardiograms were recorded at a speed of 25 mm/sec. The electrocardiograms were evaluated by 2 independent observers without knowledge of the clinical status of the patient.

Echocardiography and tissue Doppler imaging

Patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed system FiVe/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 images and color Doppler data, triggered to the QRS complex were saved in cine-loop format. The LV volumes (end-systolic, end-diastolic) and LV ejection fraction were calculated from the conventional apical 2- and 4-chamber images, using the biplane Simpson's technique [1].
The severity of mitral regurgitation was graded semi-quantitatively from color-flow Doppler in the conventional parasternal long-axis and apical 4-chamber images. Mitral regurgitation was characterized 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%) [2].

For TDI, color Doppler frame rates varied between 80 and 115 frames/s depending on the sector width of the range of interest; 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 images of 3 consecutive heart beats by offline analysis. Data were analyzed using commercial software (Echopac 6.1, General Electric - Vingmed).

To assess LV dyssynchrony, the sample volume was placed in the basal portions of the septum and the lateral wall; peak systolic velocities and time-to-peak systolic velocities were obtained and the septal-to-lateral delay in peak velocity was calculated as an indicator of LV dyssynchrony. Based on previous observations, a cut-off point of 60 ms delay between peak systolic velocity of the septum and lateral wall was used to identify patients with severe LV dyssynchrony; the 60 ms cut-off value was not derived from a normal population [3]. Inter- and intra-observer agreement for assessment of septal-to-lateral delay were 90% and 96%, respectively.

The delay between the systolic contraction of the left and the right ventricle (inter-ventricular dyssynchrony) was calculated using Doppler flow signals. The aortic and pulmonary ejection flows were measured respectively in the apical four-chamber and parasternal views. The aortic pre-ejection time interval was defined as the time interval between the onset of the QRS complex on surface electrocardiogram and the onset of the aortic ejection flow, whereas the pulmonary pre-ejection time interval was defined as the time duration between the onset of the QRS complex on surface electrocardiogram and the onset of pulmonary ejection flow. The difference between the aortic and the pulmonary pre-ejection times represents the delay between left and right ventricular systolic contraction (inter-ventricular dyssynchrony). Based on recent data, a delay of >50ms between left and right ventricular contraction was considered to represent substantial inter-ventricular dyssynchrony [4,5]. The echocardiographic data were analyzed by two independent observers without knowledge of the clinical status of the patient.

Statistical analysis

Data are presented as mean ± SD, and compared using the (un-)paired Student's t-test when appropriate. Univariate analysis for categorical variables was performed using the chi-square test with Yates' correction. Linear regression analysis was performed to determine the relationship between QRS duration and the septal-to-lateral delay and the relationship between QRS duration and inter-ventricular dyssynchrony. For all tests, a p-value <0.05 was considered statistically significant.

RESULTS

A total of 64 patients were included in this study (50 male, mean age 61 ± 14 years). Baseline characteristics are summarized in Table 1.

Left ventricular dyssynchrony

The mean LV dyssynchrony was 45 ± 38 ms (range 0-140 ms) Of these patients, 21 (33%) showed a septal-to-lateral delay of ≥ 60 ms, representing severe LV dyssynchrony, and 43 patients (67%) showed minor (< 60 ms) LV dyssynchrony.

An example of a patient with a narrow QRS complex and severe LV dyssynchrony is shown in Figure 1. There was no relation between the QRS duration and the extent of LV dyssynchrony

Table 1: Patient characteristics and echocardiographic data (n=64)

Variable	Value
Male/Female	50/14
Age (years)	61 ± 14
Etiology	
Ischemic	44 (69%)
Nonischemic	20 (31%)
QRS duration (ms), (range)	105 ± 12 (78-120)
Rhythm	
Sinus rhythm	56 (88%)
Atrial fibrillation	6 (9%)
Atrial flutter	2 (3%)
New York Heart Association class	
II	20 (31%)
III	39 (61%)
IV	5 (8%)
Medication:	
Diuretics	53 (83%)
ACE-inhibitors	56 (88%)
Beta-blockers	44 (69%)
Anticoagulants/aspirin	58 (91%)
Left ventricular ejection fraction (%) (range)	24 ± 6 (12-34)
End-diastolic volume (ml), (range)	209 ± 67 (105-37
End-systolic volume (ml), (range)	160 ± 59 (82-323)
Mitral regurgitation	1.6 ±1.0
Septal-to-lateral delay (ms), (range)	45 ± 38 (0-140)
Septal-to-lateral delay > 60ms	21 (33%)
Interventricular delay (ms), (range)	17 ± 15 (0-65)
Interventricular delay > 50ms	3 (5%)

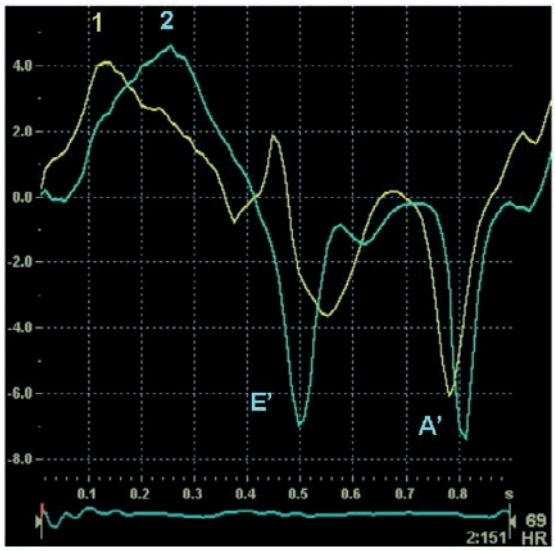

Figure 1. An example of a patient with a narrow QRS duration (112 ms) and extensive LV dyssynchrony. The septal-to-lateral delay was 120 ms. The tracing shows peak systolic velocities (1: basal septum, 2: basal lateral wall) and diastolic parameters (E' and A').

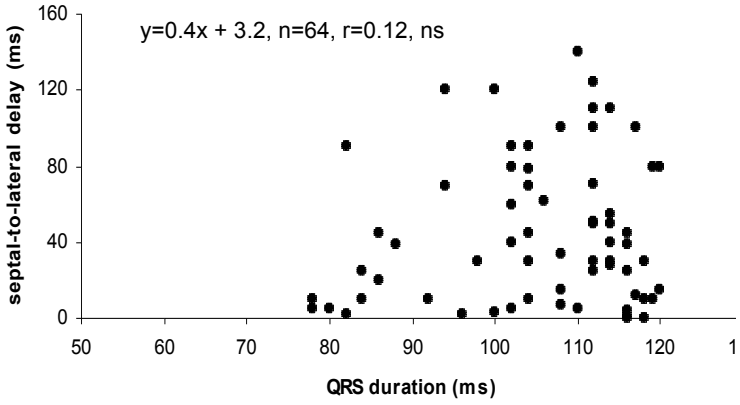

Figure 2. No significant relationship existed between QRS duration and septal-to-lateral delay. (y=0.4x + 3.2, n=64, r=0.12, ns)

(Figure 2, y=0.4x + 3.2, n=64, r=0.12, ns). In Table 2, the characteristics of patients with and without substantial LV dyssynchrony are compared. All characteristics were comparable, only the LV ejection fraction was slightly but significantly higher in the patients with LV dyssynchrony (22% vs 26%, $p<0.05$).

Table 2: Patient characteristics: left ventricular dyssynchrony (n=43) versus no left ventricular dyssynchrony (n=21)

Variable	group 1: s-l delay ≤ 60 ms	group 2: s-l delay > 60 ms
Male/Female	32/11	18/3
Age (years)	60 ± 15	64 ± 13
Etiology		
Ischemic	28 (64%)	16 (76%)
Nonischemic	15 (36%)	5 (24%)
QRS duration (ms)	105 ± 13	106 ± 9
Rhythm:		
Sinus rhythm	36 (84%)	18 (86%)
Atrial fibrillation	5 (12%)	3 (14%)
Atrial flutter	2 (4%)	0
New York Heart Association class		
II	11 (26%)	9 (43%)
III	28 (65%)	11 (52%)
IV	4 (9%)	1 (5%)
Medication:		
Diuretics	37 (86%)	16 (76%)
ACE-inhibitors	39 (91%)	17 (81%)
Beta-blockers	31 (73%)	13 (62%)
Anticoagulants/Aspirin	39 (91%)	19 (90%)
LV ejection fraction (%) (range)	22 ± 6 * (12-34)	26 ± 6 * (13-33)
End-diastolic volume (ml), (range)	209 ± 70 (105-372)	209 ± 50 (114-322)
End-systolic volume (ml), (range)	162 ± 63 (85-323)	155 ± 62 (82-252)
Mitral regurgitation grade	1.6 ± 0.9	1.4 ± 1.1
Septal-to-lateral delay (ms), (range)	22 ± 17 (0-55)	93 ± 22 (60-140)
Interventricular delay (ms), (range)	18 ± 14 (0-65)	15 ± 16 (0-57)

* = $P < 0.05$

Inter-ventricular dyssynchrony

Mean inter-ventricular delay was 17 ± 15 ms (range 0-65 ms) for the patients in this group. Only 3 patients (5%) showed severe inter-ventricular dyssynchrony (>50 ms). There was no relationship between the QRS duration and the extent of inter-ventricular dyssynchrony (y=0.2x – 8.6, n=64, r=0.20, ns).

DISCUSSION

In the present study, the incidence of LV dyssynchrony in patients with a narrow QRS complex was specifically addressed. Sixty-four consecutive patients with heart failure and a narrow QRS complex were prospectively evaluated for the presence of LV dyssynchrony using TDI. Severe LV dyssynchrony was observed in one third of the patients. This percentage is in line

with previous studies, reporting an incidence varying between 27% and 56%, although these studies did not specifically focus on patients with a narrow QRS complex. The differences in incidence of LV dyssynchrony in the various studies may be related to differences in study population, but also in methodology and analysis of echo data; in particular, the definition of substantial LV dyssynchrony varied among the studies [6,7,8]. In particular, in the current study, only dyssynchrony between the septum and lateral wall was evaluated, whereas in some patients dyssynchrony may involve other regions. The issue of dyssynchrony in the patients with narrow QRS complex is intriguing, and could be due to electrical delay but also reflect scar tissue; this information cannot be derived from the current study, and further studies are needed.

Also in the present study, the relation between the QRS duration and LV dyssynchrony was evaluated, and no significant correlation was observed. Moreover, no baseline clinical parameters were able to predict the presence of LV dyssynchrony in these patients, except that the LV ejection fraction was slightly but significantly higher in the patients with LV dyssynchrony.

In conclusion, substantial dyssynchrony is present in one third of the patients with heart failure and a narrow QRS complex, implying that CRT should be considered in these patients. Initial data by Achilli et al. [8] indeed suggest that patients with narrow QRS may also benefit from CRT.

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Chapter 11

Relative merits of M-mode echocardiography and tissue Doppler imaging for prediction of response to cardiac resynchronization therapy in patients with heart failure secondary to ischemic or idiopathic dilated cardiomyopathy

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ABSTRACT

Both M-mode echocardiography (using the septal-to-posterior wall motion delay, SPWMD) and color-coded tissue Doppler imaging (TDI, using the septal-to-lateral delay in peak systolic velocity) have been proposed for assessment of left ventricular (LV) dyssynchrony and prediction of response to cardiac resynchronization therapy (CRT). In this study, a head-to-head comparison between M-mode echocardiography and color-coded TDI was performed for assessment of LV dyssynchrony and prediction of response to CRT. Consecutive (n=98) patients with severe heart failure (NYHA class III-IV), LV ejection fraction ≤35% and QRS duration >120 ms underwent CRT. Before pacemaker implantation, LV dyssynchrony was assessed by M-mode echocardiography (SPWMD) and color-coded TDI (septal-to-lateral delay). At baseline and 6 months after implantation, clinical and echocardiographic parameters were evaluated. SPWMD measurement was not feasible in 41% of patients due to akinesia of the septal and/or posterior walls or poor acoustic windows. Conversely, the septal-to-lateral delay could be assessed in 96% of patients. At 6 months follow-up, 75 patients (77%) were classified as responders to CRT (improvement ≥1 NYHA class). The sensitivity and specificity of SPWMD were lower as compared to the septal-to-lateral delay (66% vs. 90%, P<0.05 and 50% vs. 82%, P= NS respectively). LV dyssynchrony assessment was feasible in 59% of patients with M-mode echocardiography as compared to 96% (P< 0.05) when color-coded TDI was used. Color-coded TDI was superior over M-mode echocardiography for prediction of response to CRT.

INTRODUCTION

In the search for more optimal selection criteria for cardiac resynchronization therapy (CRT), left ventricular (LV) dyssynchrony has been defined as a promising parameter to predict a positive response [1,2]. Various echocardiographic techniques have been developed to identify LV dyssynchrony, ranging from simple measurements obtained with routine echocardiography to more sophisticated techniques using tissue Doppler imaging (TDI) [1-3]. Recently, M-mode echocardiography has been proposed to quantify LV dyssynchrony, which is a simple and practical approach [3-5]. Pitzalis et al. reported promising results on the prediction of response to CRT with M-mode echocardiography [3,4], whereas Marcus et al. recently reported less optimistic data [5]. The current study was designed to evaluate feasibility and value of M-mode echocardiography for the prediction of response to CRT; moreover in the same patients TDI was performed, allowing for a head-to-head comparison between the 2 techniques for the prediction of 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 severe heart failure (NYHA class III or IV), LV ejection fraction ≤35% and QRS duration >120 ms. 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. LV dyssynchrony was assessed using both M-mode echocardiography [3,4] and color-coded tissue TDI [2,6]. Assessment of LV dyssynchrony was repeated at 1 day post-CRT implantation. 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 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. QRS duration was measured from the surface ECG using the widest QRS complex from the leads II, V1 and V6. Patients with an improvement of at least 1 grade in NYHA class were considered responders to CRT.

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, end-diastolic) and LV ejection fraction were calculated from the conventional apical 2- and 4-chamber images, using the biplane Simpson's technique [7].
All echocardiographic data were analyzed offline using commercial software (Echopac 4.0.3, General Electric). Echocardiographic data were analyzed by 2 independent observers, blinded to all other patient data.

LV dyssynchrony assessment using M-mode echocardiography

Assessment of LV dyssynchrony from M-mode echocardiography was performed according to the method described by Pitzalis et al. [3,4]. Briefly, a parasternal short-axis view was selected at the level of the papillary muscles. In this view, an M-mode recording was obtained through the septum and posterior LV wall. LV dyssynchrony was calculated by measuring the shortest interval between the maximal posterior displacement of the septum and the maximum displacement of the LV posterior wall. According to Pitzalis et al., a septal-to-posterior wall motion delay (SPWMD) >130 ms was considered to indicate substantial LV dyssynchrony [3]. Inter- and intra-observer agreement for assessment of SPWMD were 86% and 92% in the current study.

LV dyssynchrony assessment using color-coded TDI Assessment of LV dyssynchrony from color-coded TDI was performed according to methods described previously [2,6]. Briefly, 4-chamber color-coded TDI images were selected and sample volumes were placed in the basal portions of the septum and the LV lateral wall. The time-to-peak systolic velocities were obtained from both samples and the septal-to-lateral delay in peak systolic velocities was calculated as a marker of LV dyssynchrony. The analysis of peak systolic velocities was limited to the LV ejection period and post-systolic peaks were excluded. The opening and closure of the aortic valve were measured from the pulsed-wave Doppler signals in the LV outflow tract and subsequently superimposed on the TDI curves to mark the LV ejection period (using the "event-timing" function on the Echopac analysis software). Based on previous observations, a septal-to-lateral delay ≥65 ms was considered to indicate substantial LV dyssynchrony [6]. Inter- and intra-observer agreement for assessment of septal-to-lateral delay were 90% and 96%, respectively [8].
For color-coded TDI, frame rates were > 80 frames/s depending on the sector width of the range of interest; 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 images of three consecutive heart beats by offline analysis.

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 was 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.).

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.

The agreement between the presence/absence of substantial dyssynchrony on TDI (cut-off value 65 ms) and M-mode echocardiography (cut-off value 130 ms) was expressed as percentage with corresponding κ-value. In addition, sensitivity and specificity to assess response to CRT were calculated for both TDI and M-mode echocardiography; the 95% confidence intervals (95% CI) were calculated according to standard definitions. The optimal cut-off value for SPWMD to predict response to CRT was determined by receiver-operating characteristic (ROC) curve analysis. The output is an area-under-the (AUC) value ranging between 0 and 1. The performance can be classified using the AUC value with 0.90-1 = excellent, 0.80-0.90 = good, 0.70-0.80 = fair, 0.60-0.70 = poor, 0.50-0.60 test without value. The optimal cut-off value was defined as the optimal balance between sensitivity and specificity. For all tests a P-value <0.05 was considered statistically significant.

RESULTS

Study population

The study population comprised 98 patients (78 men, 20 women) with a mean age of 66±11 years. Mean NYHA class was 3.1±0.3, with 92% of patients in NYHA class III. Patients showed severe LV dilatation (LV end-diastolic volume 236±71 ml and LV end-systolic volume 184±64 ml), with a depressed LV ejection fraction of 23±8%.

Post-CRT implantation

Within 6 months after CRT, 2 patients (2%) died, (both due to refractory heart failure) and did not have the clinical and echocardiographic follow-up assessment at 6 months, but were

classified as non-responders to CRT. Following CRT implantation, QRS duration decreased from 168±30 ms to 151±24 ms (P<0.001). At 6 months follow-up, NYHA class improved from 3.1±0.3 to 2.2±0.7 (P<0.001). The quality of life score decreased from 39±18 to 25±18 (P<0.001) and the 6-minute walking distance increased from 290±136 m to 387±135 m (P<0.001). LV ejection fraction improved from 23±8% to 30±10% (P<0.001), associated with a significant reduction in LV volumes; the LV end-systolic volume decreased from 184±64 ml to 151±69 ml (P<0.001) and the LV end-diastolic volume decreased from 236±71 ml to 208±76 ml (P<0.001).

Feasibility of LV dyssynchrony assessment: M-mode echocardiography versus color-coded TDI

The feasibility to assess LV dyssynchrony before CRT implantation was evaluated for both M-mode echocardiography using the SPWMD and for TDI using the septal-to-lateral delay. Assessment of the SPWMD was not feasible in a relatively high proportion of patients (n=40, 41%, Figure 1). The reasons for lack of interpretability of the SPWMD were: absence of systolic motion of the myocardium on M-mode echocardiography due to akinesia of the inter-ventricular septum (n=21, 53%), the posterior wall (n=5, 12%), or both walls (n=1, 3%) or a poor acoustic window of the parasternal view (n=13, 32%).

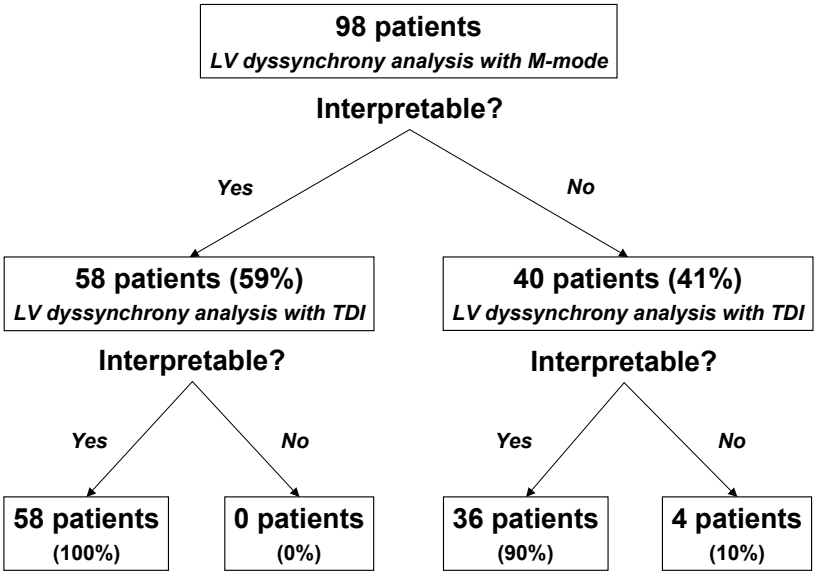

Figure 1. Feasibility of left ventricular (LV) dyssynchrony assessment using M-mode echocardiography and color-coded tissue Doppler imaging (TDI).

In contrast, assessment of septal-to-lateral delay using TDI was feasible in the majority of patients (n=94, 96%, P<0.05 versus M-mode echocardiography, Figure 1). The reasons for lack of interpretablity of the TDI curves were: akinesia of the inter-ventricular septum (n=3, 75%) or poor acoustic window of the apical view (n=1, 25%).

Assessment of the septal-to-lateral delay on TDI was feasible in all patients with an interpretable SPWMD (n=58, Figure 1). Importantly, assessment of the septal-to-lateral delay using TDI was also feasible in 36 of 40 (90%) patients without an interpretable SPWMD (Figure 1). An example of a patient in whom interpretation of the SPWMD was not feasible is shown in Figure 2. The SPWMD could not be measured due to absence of a clear systolic excursion of both the inter-ventricular septum and the posterior wall on M-mode echocardiography. Measurement of the septal-to-lateral delay using TDI however was possible (Figure 3). The baseline characteristics of the patients with (n=58) and without (n=40) an interpretable SPWMD are summarized in Table 1. No differences in clinical or echocardiographic parameters were present between both patient groups. In particular, the incidence of ischemic cardiomyopathy was not higher in the patients without an interpretable SPWMD.

Prediction of response to CRT: M-mode echocardiography versus TDI

A total of 23 patients (23%) were classified as clinical non-responder at 6 months follow-up (n=21 patients without improvement in NYHA class and 2 patients who died from progressive heart failure before 6 months follow-up). Besides a lack of improvement in NYHA class, the non-responders also failed to improve in 6-minute walking distance (from 290±158 m

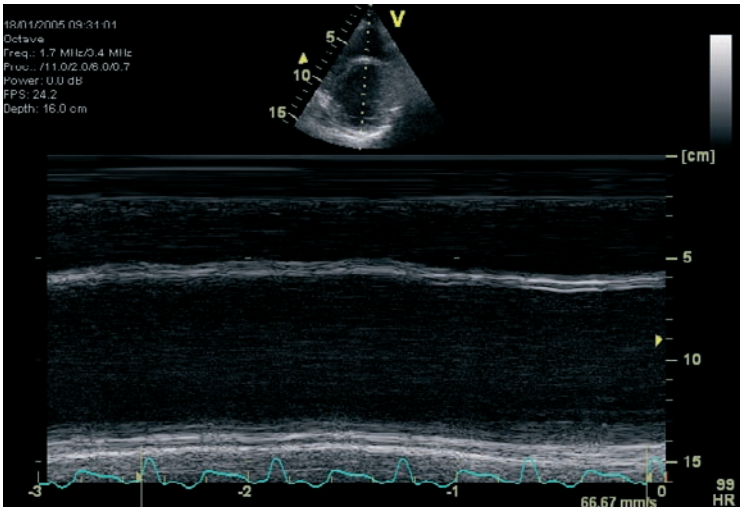

Figure 2. Example of a patient in whom assessment of left ventricular dyssynchrony using M-mode echocardiography was not feasible due to akinesia of both the inter-ventricular septum and the posterior wall.

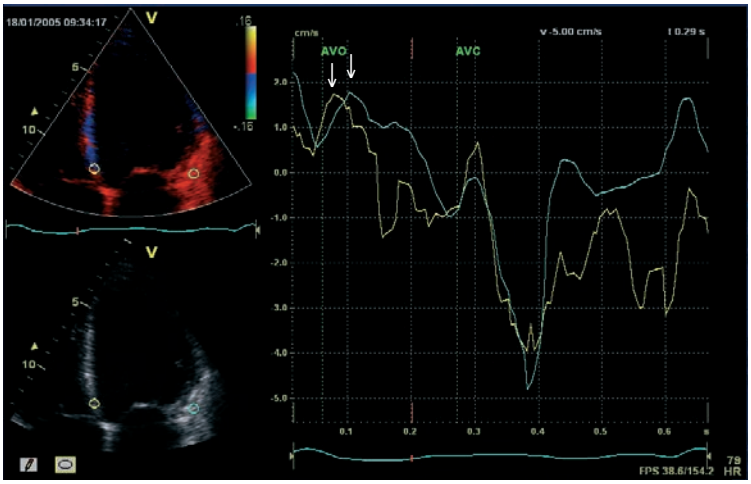

Figure 3. Left ventricular dyssynchrony assessment using color-coded tissue Doppler imaging. The sample volumes are placed in the basal part of the septum and lateral wall, and tracings are derived. The arrows indicate the peak systolic velocity (first peak = septum and second peak = lateral wall (AVO = aortic valve opening, AVC = aortic valve closure). The septal-to-lateral delay is 40 ms, indicating the absence of substantial left ventricular dyssynchrony (same patient as in Figure 2).

to 277±155 m, NS), quality-of-life score (from 45±22 to 45±21, NS) and LV function (LV end-systolic volume from 173±58 ml to 182±75 ml and LV ejection fraction from 25±9% to 24±8%, both NS).

The baseline clinical and echocardiographic characteristics of the clinical responders and non-responders are compared in Table 2. Baseline LV dyssynchrony assessment using TDI showed that responders had a significantly larger septal-to-lateral delay as compared to patients without response to CRT (103±42 ms vs. 41±37 ms). The SPWMD was slightly larger in the responders, but the difference was not statistically significant (188±123 ms vs. 155±103 ms, NS). Other differences in baseline characteristics between responders and non-responders included the patient's age and gender (Table 2). Figure 4 shows the agreement between TDI (using the septal-to-lateral delay, cut-off value 65 ms) and M-mode echocardiography (using the SPWMD, cut-off value 130 ms) for assessment of LV dyssynchrony. In 50% of patients both methods detected substantial LV dyssynchrony, and in 17% of patients both methods indicated the absence of LV dyssynchrony. Accordingly, the agreement between the 2 techniques was 67% (κ= 0.27, Figure 4).

The predictive accuracy of TDI (using the septal-to-lateral delay) for response to CRT was excellent; using the previously validated cut-off value of 65 ms, a sensitivity of 90% (95% CI 83% - 97%) and specificity of 82% (95% CI 66% - 98%) were obtained. The sensitivity and specificity of M-mode echocardiography (using the SPWMD) were substantially lower; using the previously published cut-off value of 130 ms, a sensitivity of 66% (95% CI 53% - 79%, P<0.05 vs. TDI) and specificity of 50% (95% CI 24% - 76%, P = NS vs. TDI) were obtained (Table 3).

Table 1. Baseline characteristics of patients with interpretable septal-to-posterior wall motion delay (n=58) vs. patients with non-interpretable septal-to-posterior wall motion delay (n=40)

Variable	Septal to posterior wall motion delay Interpretable	Septal to posterior wall motion delay Non-interpretable
Age (years)	65±10	67±12
Male/female	46/12	32/8
NYHA class	3.0±0.3	3.1±0.3
Etiology		
Ischemic	33 (56%)	24 (60%)
Idiopathic	25 (44%)	16 (40%)
QRS-duration (ms)	165±30	174±29
6-minute walking distance (m)	292±144	280±130
LV ejection fraction (%)	24±8	22±7
LV end-diastolic volume (ml)	225±67	252±74
LV end-systolic volume (ml)	175±60	198±68

Table 2. Baseline characteristics of responders (n=75) vs. non-responders (n=23)

Variable	Responders	Non-responders	P-value
Age (years)	68±11	60±11	<0.05
Male/female	65/10	13/10	<0.05
NYHA class	3.1±0.3	3.1±0.3	NS
Etiology			
Ischemic	45 (60%)	11 (48%)	NS
Idiopathic	30 (40%)	12 (52%)	
QRS duration (ms)	170±30	162±28	NS
6-minute walking distance (m)	240±28	273±160	NS
LV ejection fraction (%)	23±8	24±9	NS
LV end-diastolic volume (ml)	238±73	231±64	NS
Left ventricular end-systolic volume (ml)	186±66	177±58	NS
TDI:			
Septal-to-lateral delay (ms)	103±42	41±37	<0.05
non-interpretable patients	3 (4%)	1 (4%)	NS
Mmode:			
Septal-to-posterior wall motion delay (ms)	188±123	155±103	NS
non-interpretable patients	31 (41%)	9 (39%)	NS

Next, ROC-curve analysis was performed to define the optimal cut-off value for the SPWMD in the current patient group. The optimal cut-off value for SPWMD was 148 ms and the area under the curve was 0.57. The cut-off value of 148 ms yielded a sensitivity and a specificity of 55% (Figure 5).

When a decrease in LV end-systolic volume >10% at 6 months follow-up was applied as a measurement of response to CRT, 35 patients (36%) were classified as non-responders (in-

Table 3: Sensitivity, specificity, positive and negative predictive values of septal-to-lateral delay ≥65 ms and septal-to-posterior wall motion delay >130 ms for prediction of response to cardiac resynchronization therapy.

	Septal-to-lateral delay ≥65 ms	Septal-to-posterior wall motion delay >130 ms
Sensitivity	90%	66%
Specificity	82%	50%
Positive predictive value	94%	81%
Negative predictive value	72%	32%

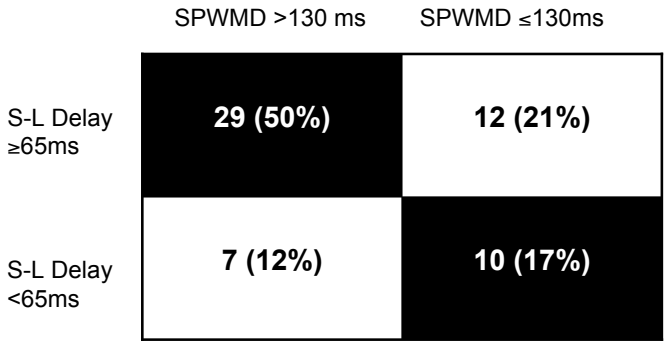

Figure 4. Agreement between left ventricular dyssynchrony using the septal-to-lateral delay (S-L delay, derived from color-coded tissue Doppler imaging, cut-off value 65 ms) and the septal-to-posterior-wall-motion delay (SPWMD, derived from M-mode echocardiography, cut-off value 130 ms).

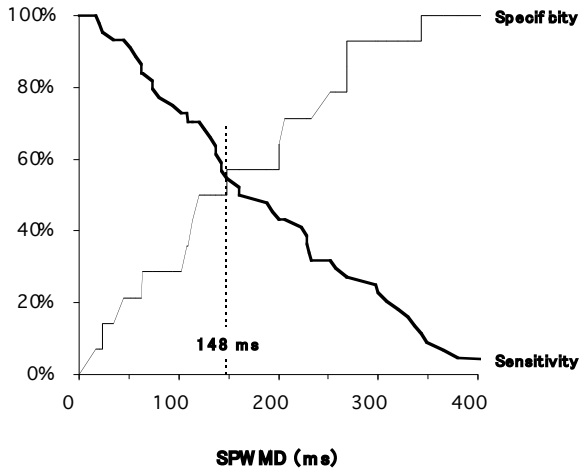

Figure 5. Receiver-operating characteristic (ROC) curve analysis demonstrated a sensitivity and specificity of 55% to predict response to CRT at a cut-off value of 148 ms for septal-to-posterior-wall-motion-delay (SPWMD). The AUC is 0.57.

cluding the 2 patients who died before 6 months follow-up).
The predictive accuracy of TDI for echocardiographic response to CRT was excellent with a sensitivity of 92% (95% CI 81%-97%) and a specificity of 74% (95% CI 55%-87%). The predictive accuracy of M-mode echocardiography was lower with a sensitivity of 65% (95% CI 47% - 79%, P<0.05 vs. TDI) and a specificity of 48% (95% CI 26%-70%, P=NS vs. TDI).

DISCUSSION

The main results of the present study are: 1) analysis of LV dyssynchrony using M-mode echocardiography was not feasible in 41% of patients; conversely, LV dyssynchrony was feasible in 96% of patients when color-coded TDI was used. 2) the accuracy of color-coded TDI to predict response to CRT was superior over M-mode echocardiography.
In recent large CRT trials including patients based on established CRT selection criteria (NYHA class III-IV, LV ejection fraction ≤35% and QRS duration >120 ms), 20-30% of patients did not respond to CRT [9,10]. Recent studies revealed that the likelihood of response to CRT is related to the presence of substantial LV dyssynchrony and various (echocardiographic) techniques have been developed to detect LV dyssynchrony [3,4,6,11-13].
A relatively simple and elegant echocardiographic approach is M-mode echocardiography where an M-mode recording is used to measure the delay between the systolic excursion of the inter-ventricular septum and the posterior wall (SPWMD) [3,4]. Another frequently used echocardiographic technique is color-coded TDI. With color-coded TDI different segments can be evaluated simultaneously and the segment with the latest mechanical activity can be identified. Studies have indicated that most patients demonstrate LV dyssynchrony between the septum and lateral or posterior wall [6,11,14].
The ideal technique for assessment of LV dyssynchrony to screen heart failure patients for eligibility for CRT should be non-time consuming, technically feasible with interpretable results in a high number of patients and have a high predictive value for response to CRT.
Recent studies from Pitzalis et al. [3,4] have demonstrated the use of SPWMD for assessment of LV dyssynchrony. In 20 patients with severe heart failure (20% ischemic cardiomyopathy), assessment of SPWMD was feasible in all patients [3]. In a subsequent study [4], the same authors evaluated another 60 patients (22% ischemic cardiomyopathy) and indicated that in 2 (3%) patients an akinetic septum prevented assessment of the SPWMD.
The feasibility of assessing the SPWMD was recently evaluated retrospectively in a large cohort (n=79 patients, 72% ischemic cardiomyopathy) of heart failure patients who were included in the CONTAK-CD trial [5]. The authors reported difficulties in interpretation of M-mode recordings in more than 50% of patients due to the absence of a clear definition of the systolic deflection of the septal and/or posterior walls. Similarly, de Sutter et al. [15] evaluated

138 patients with heart failure (with 77% ischemic cardiomyopathy) and were unable to assess the SPWMD in 56% of patients.
In the current study (with 58% of patients having ischemic cardiomyopathy), the SPWMD could not be assessed in 41% of patients. The lack of interpretability was due to the absence of a clear systolic excursion of the inter-ventricular septum, the posterior wall or both in 53%, 12% and 3% of patients respectively and a poor acoustic window in 32% of patients. Accordingly, these data in larger groups of patients consistently report a high number of non-interpretable M-mode recordings; this may in part be related to the inclusion of a larger proportion of patients with ischemic cardiomyopathy who frequently have large areas of scar tissue. Still, in the current study, 40% of the patients with non-interpretable SPWMD had non-ischemic cardiomyopathy. Moreover, in the clinical setting, a large percentage of patients with heart failure have ischemic heart disease underlying the cardiomyopathy [16].
In contrast, LV dyssynchrony assessment using TDI was feasible in 96% of patients. The non-interpretability was due to septal akinesia in 3 patients and a poor acoustic window in 1 patient. Importantly, in many patients with a non-interpretable SPWMD, assessment of LV dyssynchrony with color-coded TDI is possible. In addition, a poor acoustic window is more frequently encountered in the parasternal view as compared to the apical view in heart failure patients (13% vs. 1%, $P<0.05$, in the current patient population).
Besides a high percentage of interpretable results, the ideal technique for screening of CRT patients should have a high predictive accuracy to predict response to CRT. Pitzalis et al. [3,4] demonstrated that responders to CRT had a significantly larger SPWMD as compared to non-responders. Using a cut-off value of 130 ms, SPWMD yielded an accuracy of 85% (sensitivity 100%, specificity 63%) to predict response after CRT. Recent data however, revealed less favourable results of SPWMD to predict response to CRT. Retrospective analysis of the CONTAK-CD data, yielded a sensitivity of 24% with a specificity of 66% [5], and results from the current study showed a sensitivity of 66% with a specificity of 50% to predict clinical response to CRT. In contrast, color-coded TDI using the septal-to-lateral delay yielded significantly higher values: a sensitivity of 90% and specificity of 82% were obtained, which is in line with other studies using TDI for prediction of response to CRT [6,12,17].
Several factors can be considered to explain this substantial difference between M-mode echocardiography and color-coded TDI. First, the 2 techniques use different myocardial segments to quantify LV dyssynchrony. The SPWMD measures the delay between the anteroseptum and the posterior wall, whereas color-coded TDI measures the delay between the basal septum and lateral wall, and recent studies have suggested that the benefit of CRT may be predominantly related to correction of LV dyssynchrony in the septal-lateral direction, rather than the antero-posterior direction [6,17,18]. Moreover, color-coded TDI permits interrogation of many different segments (although only 2 were used in the current study) whereas the SPWMD is derived from 2 regions. Alternatively, M-mode echocardiography and color-coded TDI measure different dyssynchronies: SPWMD provides information on delay

in *systolic motion*, whereas color-coded TDI provides information on delay in *peak systolic velocities*. The fact that both techniques measure a different "type" of LV dyssynchrony is also reflected by the relatively poor agreement (67%, κ=0.27, Figure 4) between both techniques for identification of LV dyssynchrony.

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Chapter 12

Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy

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ABSTRACT

Objectives To predict the response and prognosis after cardiac resynchronization therapy (CRT) in patients with end-stage heart failure.

Background CRT improves heart failure symptoms, exercise capacity and left ventricular (LV) function. Since not all patients respond, pre-implantation identification of responders is needed. In the present study, response to CRT was predicted by the presence of LV dyssynchrony assessed by tissue Doppler imaging (TDI). Moreover, the prognostic value of LV dyssynchrony in patients undergoing CRT was assessed.

Methods Eighty-five patients with end-stage heart failure, QRS duration >120 ms and LBBB were evaluated by TDI before CRT. At baseline and 6 months follow-up, NYHA class, quality of life and 6-minute walking distance, LV volumes and LV ejection fraction (EF) were determined. Events (death, hospitalization for decompensated heart failure) were obtained during 1-year follow-up.

Results Responders (74%) and non-responders (26%) had comparable baseline characteristics, except for a larger dyssynchrony in responders (87±49 ms versus 35±20 ms, P<0.01). ROC curve analysis demonstrated that an optimal cutoff value of 65 ms for LV dyssynchrony yielded a sensitivity and specificity of 80% to predict clinical improvement and of 92% to predict LV reverse remodeling. Patients with dyssynchrony ≥65 ms had an excellent prognosis (6% event-rate) after CRT, as compared to a 50% event-rate in patients with dyssynchrony <65 ms (P<0.001).

Conclusion Patients with LV dyssynchrony ≥65 ms respond to CRT and have an excellent prognosis after CRT.

INTRODUCTION

Cardiac resynchronization therapy (CRT) has been proposed as an alternative treatment in patients with drug-refractory heart failure [1-3]. Initial studies demonstrated acute improvement in hemodynamics immediately after CRT [4]. Other studies have demonstrated the sustained clinical benefit of CRT at longer follow-up, evidenced by improvement in heart failure symptoms, quality-of-life, exercise capacity and left ventricular (LV) systolic performance [1-3,5-7]. However, it has also become clear that 20-30% of patients do not respond to CRT [1-3]. Therefore, interest has shifted towards identification of potential responders to CRT before implantation of the pacemaker [8-14]. It is hypothesized that LV dyssynchrony is the most important determinant of response to CRT and various techniques to detect and quantify LV dyssynchrony are currently under investigation [8-14]. However, no large studies have focused on the prediction of benefit from CRT based on the degree of LV dyssynchrony. More important, it is unclear whether patients with LV dyssynchrony who respond to CRT have a better prognosis as compared to patients without dyssynchrony.

Accordingly, we have related the extent of LV dyssynchrony prior to implantation of the CRT device (assessed by tissue Doppler imaging, TDI) to clinical outcome and LV reverse remodeling after CRT, in 85 consecutive patients. The accuracy of this approach (and the cutoff value for LV dysynchrony) to predict outcome was determined using receiver operator characteristic (ROC) curve analysis. Finally, the most important issue was addressed: would identification of responders prior to pacemaker implantation translate in a favourable prognosis during follow-up?

METHODS

Patients and study protocol

Eighty-five consecutive patients with end-stage heart failure, scheduled for implantation of a biventricular pacemaker, were included in the current study. The patients were selected according to the established selection criteria for CRT: 1. severe heart failure (New York Heart Association (NYHA) class III or IV), 2. severely depressed LV ejection fraction (LVEF ≤35%), QRS exhibiting left bundle branch block configuration with a duration ≥120 ms [1-3].

Patients with atrial fibrillation or with a previously implanted pacemaker were excluded.

The study protocol was as follows: before pacemaker implantation, resting two-dimensional (2D) and color Doppler transthoracic echocardiography were performed to measure LVEF and LV volumes, and analyze the severity of mitral regurgitation. Next, myocardial TDI was performed to assess inter- and intraventricular dyssynchrony.

Clinical status was assessed at baseline and 6 months follow-up, including assessment of NYHA class, quality of life (using the Minnesota Living with Heart Failure questionnaire) [15],

and evaluation of exercise capacity using the 6-minute walking test [16]. At 6 months follow-up, LVEF and LV volumes and severity of mitral regurgitation were re-assessed by echocardiography; LV dyssynchrony was also re-assessed.
Hospitalization for heart failure and survival were assessed during 1 year follow-up after pacemaker implantation.

Echocardiography and data acquisition/analysis

Patients were imaged in the left lateral decubitus position using a commercially available system (Vivid Seven, General Electric – Vingmed, Milwaukee, WI, 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-chamber and 4-chamber images). Standard 2-dimensional and color Doppler data (3 consecutive beats), triggered to the QRS complex, were saved in cineloop format. For TDI, color Doppler frame rates varied between 100 and 120 frames/sec depending on the sector width of the range of interest, and pulse repetition frequencies between 500 Hz to 1 KHz, resulting in aliasing velocities between 16 and 32 cm/sec. Tissue Doppler parameters were measured from color images by off-line analysis.
The LV volumes and the LVEF were calculated from the apical 2- and 4-chamber images, using the biplane Simpson's rule [17]. The severity of mitral regurgitation was graded semi-quantitatively from color-flow Doppler in the conventional parasternal long-axis and apical 4-chamber images. Mitral regurgitation was characterized 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%) [18].
For TDI analysis, the digital cineloops were analyzed using commercial software (Echopac 6.1, General Electric – Vingmed, Milwaukee, WI, USA) by 2 independent observers, blinded to the clinical outcome. The sample volume was placed in the LV basal portions of the anterior, inferior, septal and lateral walls (using the 2- and 4-chamber images), and per region, the time interval between the onset of the QRS complex and the peak systolic velocity was derived. LV dyssynchrony was defined as the maximum delay between peak systolic velocities among the 4 walls within the LV (most frequently observed between the interventricular septum and the lateral wall) [19]. Interventricular dyssynchrony was assessed by comparing the delay between peak systolic velocity of the right ventricular free wall and the LV lateral wall [8]. The time required to analyze the tissue Doppler data was 10-15 min.

Pacemaker Implantation

The LV pacing lead was inserted transvenously via the subclavian route. First, a coronary sinus venogram was obtained using the balloon catheter. Next, the LV pacing lead was inserted via the coronary sinus using an 8F guiding catheter and positioned preferably in a (postero-)lateral vein.

The right atrial and ventricular leads (with separate connectors) were positioned conventionally. The atrioventricular delay was optimized by 2D echocardiography so that it provided the longest filling time for completion of the end-diastolic filling flow before LV contraction [20]. A dedicated resynchronization device was used in all patients. When a conventional indication for an ICD existed, a combined device was implanted.

Statistical Analysis

Results are presented as mean ± SD. Data were compared using paired or unpaired Student's t-test when appropriate. Proportions were compared using Chi-square analysis with Yates' correction. Optimal cutoff values of parameters to predict response to CRT were determined by ROC curve analysis. The optimal cutoff value was defined as that providing the maximal accuracy to distinguish between responders/non-responders.

Differences in cardiac event-rates (death and hospitalization for heart failure) over time were analyzed by the method of Kaplan-Meier, and log-rank test. For all tests, a P-value <0.05 was considered significant.

RESULTS

Study Population

Eighty-five patients were included. The patient characteristics are summarized in Table 1. Patients had severe LV dysfunction (mean LVEF 23±7%, range 9-34%), with extensive dilatation (LV end-diastolic volume 258±56 ml). Approximately equal numbers of patients had heart failure of ischemic and non-ischemic etiology. The QRS duration was prolonged, ranging from 120 to 240 ms.

The mean LV dyssynchrony was 73±49 ms (range 0 - 221 ms) before CRT. The site of latest activation was the lateral wall in 89% of patients; in the remaining 11%, the site of latest activation was the septum (n=4, although this may also be due to passive motion rather than true late activation), anterior wall (n=2) or the inferior wall (n=3). The mean RV-LV dyssynchrony was 47±38 ms.

Thirty-seven patients received a resynchronization pacemaker (Contak TR (n=27), Guidant, MN, USA or InSync III (n=10), Medtronic Inc., MN, USA) and 48 a combined CRT-ICD device (Contak CD (n=15) or Contak Renewal (n=30), Guidant, MN, USA and InSync III CD (n=3), Medtronic Inc., MN, USA). Two types of LV leads were used (Easytrack 4512-80 (n=73), Guidant, MN, USA or Attain-SD 4189 (n=12), Medtronic Inc., MN, USA). The procedure was successful in all patients and no procedure related complications were observed.

Following CRT, the QRS-duration was reduced from 178±36 ms to 155±22 ms (P<0.01).

The optimized atrioventricular delay was 115±32 ms.

Table 1. Patient characteristics (n=85).

Age (yrs)	66±12
Gender (M/F)	64/21
Previous MI	39 (46%)
NYHA class	
III	n=68
IV	n=17
Etiology	
Ischemic	47 (55%)
Idiopathic	38 (45%)
QRS (ms)	178±36
LVEF (%)	23±7
LVEDV (ml)	258±56
LVESV (ml)	200±53
Severe MR	21 (25%)
Medication	
Diuretics	83 (98%)
ACE inhibitors	81 (95%)
Spironolactone	46 (54%)
B-blockers	71 (84%)
Amiodarone	35 (41%)

LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; MI: myocardial infarction; MR: mitral regurgitation; NYHA: New York Heart Association.

Within 6 months after CRT, 5 patients died of worsening heart failure. Since these patients did not have the 6 month follow-up assessment, they were could not be included in the prediction of response to CRT, but they were included in the prognostic evaluation.

Clinical Improvement Following CRT

At baseline and 6 months follow-up, the clinical status of the patients was assessed.
NYHA class improved from 3.2±0.4 to 2.1±0.7 ($P<0.01$). In addition, the Minnesota score decreased from 42±16 to 29±16 ($P<0.01$), and the 6-minute walking distance increased from 278±132 m to 399±149 m ($P<0.01$). The LVEF demonstrated a modest improvement (from 23±7% to 28±8%, $P<0.05$), with a reduction in LV end-diastolic volume (259±57 ml to 237±58 ml, $P<0.05$) and end-systolic volume (201±54 ml to 173±53 ml, $P<0.05$). Mitral regurgitation improved by at least 1 grade in 12 of 19 (63%) patients with severe regurgitation (2 patients of the 21 patients with severe mitral regurgitation at baseline died before echocardiographic follow-up).

Responders and Non-responders

The patients were subsequently divided into responders and non-responders, based on an improvement in NYHA class by ≥1 score and an improvement by ≥25% in 6-minute walking

distance (Tables 2 and 3). In the responders, the mean NYHA class improved from 3.2±0.4 to 1.7±0.5, whereas it remained unchanged in the non-responders (by definition). The 6-minute walking distance improved from 291±122 m to 438±116 m and remained unchanged in the non-responders (279±155 m vs 254±175 m) (by definition).

At baseline, no significant differences were observed between responders and non-responders, except that the non-responders tended to have larger LV end-diastolic and end-systolic volumes, although these differences were not significant (Table 2). The only variable that was significantly different between the 2 groups was the LV dyssynchrony, which was extensive in the responders and minimal in the non-responders (Table 2). Of note, RV-LV dyssynchrony was not different between responders and non-responders.

The responders showed a significant improvement in clinical parameters after CRT (Table 3), whereas none of the clinical parameters improved in the non-responders after CRT. Furthermore, the LVEF improved in the responders, and reverse remodeling was observed after CRT. In the non-responders, the LVEF did not improve and the LV volumes did not decrease after CRT.

In the responders, 12 patients had severe mitral regurgitation and 11 (92%) patients improved in mitral regurgitation by at least 1 grade after CRT. In the non-responders, 7 patients had severe mitral regurgitation, and only 1 (14%, P<0.05 vs responders) improved at least 1 grade after CRT.

Table 2. Responders (n=59) vs non-responders (n=21), baseline characteristics.

	Responders (n=59)	Non-responders (n=21)	P-value
Age (yrs)	64±9	66±12	ns
Gender (M/F)	46/13	14/7	ns
Previous MI	27 (46%)	9 (43%)	ns
NYHA class (III/IV)	81%/29%	90%/10%	ns
Etiology			
Ischemic	33 (56%)	11 (52%)	ns
Idiopathic	26 (44%)	10 (48%)	ns
QRS (ms)	174±29	171±26	ns
6-MWT	291±122	279±155	ns
QoL score	40±15	43±16	ns
LVEF (%)	23±6	22±8	ns
LVEDV (ml)	254±57	272±55	ns
LVESV (ml)	197±55	214±55	ns
Severe MR	12 (20%)	7 (33%)	ns
RV-LV dyssynchrony (ms)	47±34	49±29	ns
LV dyssynchrony (ms)	87±49	35±20	<0.01

LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; MI: myocardial infarction; MR: mitral regurgitation; 6-MWT: 6-minute walk test; NYHA: New York Heart Association; QoL: quality of life score.

Table 3. Responders (n=59) vs non-responders (n=21), clinical and echocardiographic variables before and after 6 months CRT.

	Responders (n=59)	Non-responders (n=21)	P-value
NYHA class			
baseline	3.2±0.4	3.3±0.2	ns
follow-up	1.7±0.5*	3.1±0.3	<0.01
6-MWT (m)			
baseline	291±122	279±155	ns
follow-up	438±116*	254±175	<0.01
QoL score			
Baseline	40±15	43±16	ns
follow-up	24±12*	44±17	<0.01
QRS (ms)			
baseline	174±29	171±26	ns
follow-up	142±27*	165±31	<0.01
LVEF (%)			
baseline	23±6	22±8	ns
follow-up	29±8*	23±9	<0.05
LVEDV (ml)			
baseline	254±57	272±55	ns
follow-up	225±53*	271±60	<0.01
LVESV (ml)			
baseline	197±55	214±55	ns
follow-up	160±46*	211±56	<0.01
Severe MR			
Baseline	12 (20%)	7 (33%)	ns
follow-up	1 (2%)*	6 (29%)	<0.05

LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; MR: mitral regurgitation; 6-MWT: 6-minute walk test; QoL: quality of life score. *:P<0.05 follow-up vs baseline value.

In responders, the LV dyssynchrony had decreased from 87±49 ms to 21±28 ms (P<0.01), whereas in the non-responders, the LV dyssynchrony tended to increase, although the difference was not significant (35±20 ms vs 42±23 ms, ns).

Prediction of Response

The only variable at baseline that was significantly different between responders and non-responders was the LV dyssynchrony. To define the optimal cutoff value to predict clinical response, ROC curve analysis was performed. When responders were defined as patients exhibiting an improvement in NYHA class ≥1 score and an improvement ≥25% in 6-minute walking distance, an optimal sensitivity and specificity of 80% were obtained at a cutoff level of 65 ms for LV dyssynchrony (Figure 1).

ROC curve analysis was also performed to define the optimal cutoff value for LV dyssynchrony to predict reverse LV remodeling. At a cutoff value of 65 ms for LV dyssynchrony a sensitivity

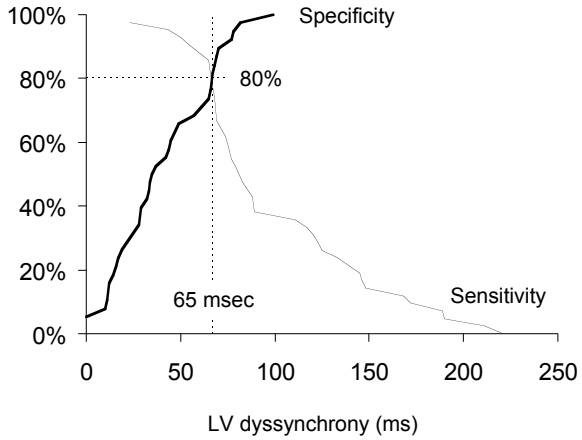

Figure 1. ROC curve analysis demonstrated a sensitivity and specificity of 80% to predict response to CRT (defined as an improvement in NYHA class ≥1 score and an improvement ≥25% in 6-minute walking distance) at a cutoff level of 65 ms for LV dyssynchrony.

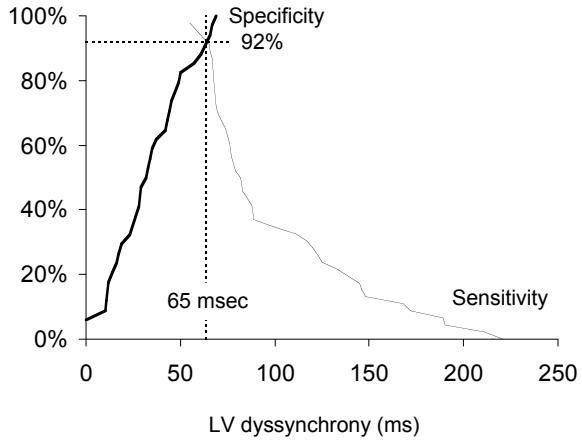

Figure 2. ROC curve analysis demonstrated a sensitivity and specificity of 92% to predict reverse LV remodeling after CRT (defined as an improvement in LV end-systolic volume ≥15%) at a cutoff level of 65 ms for LV dyssynchrony.

and specificity of 92% were obtained to predict a reduction of ≥15% LV end-systolic volume (Figure 2).

The continuous relation between the LV dyssynchrony and the reduction in LV end-systolic volume is displayed in Figure 3. A linear relation existed between the LV dyssynchrony and the reduction in LV end-systolic volume until the LV dyssynchrony reached 100 ms. After this point, even if LV dyssynchrony increased further, no further reduction in LV end-systolic volume occurred (as evidenced by the horizontal line, y=55, Figure 3).

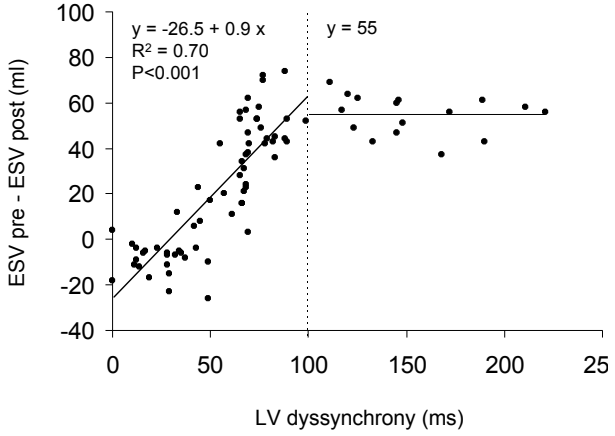

Figure 3. A linear relation existed between the extent of LV dyssynchrony and the change in LV end-systolic volume after CRT. However, LV dyssynchrony over 100 ms did not result in further reduction in LV end-systolic volume.

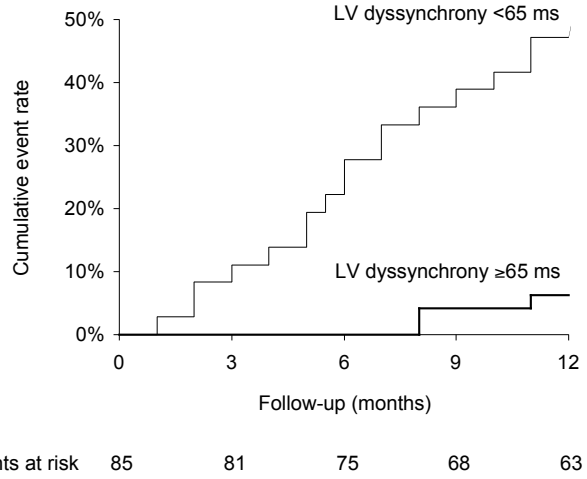

Figure 4. Cardiac events (cardiac death, hospitalization for decompensated heart failure) during 1-year follow-up after cardiac resynchronization therapy. Patients with left ventricular dyssynchrony ≥65 ms had a significantly lower event-rate after cardiac resynchronization therapy as compared to patients with dyssynchrony <65 ms (6% vs 50%, P<0.001).

Prediction of Prognosis

Follow-up was performed during 1 year after implantation. A total of 16 events occurred in the 80 patients, including 7 deaths (1 non-cardiac death, 6 worsening heart failure), and 9

hospitalizations for decompensated heart failure. The event-rate in responders was significantly lower than in non-responders (8% vs 52%, <0.01).
Moreover, when patients were divided according to the presence/absence of LV dyssynchrony (using a 65 ms cutoff value), only 3 (6%) events occurred in the 49 patients with dyssynchrony as compared to 13 (33%) in the 31 patients without dyssynchrony. None of the 5 patients who died before the 6 months follow-up assessment had LV dyssynchrony; inclusion of these patients resulted in a 50% event-rate during the 1-year follow-up in the patients without dyssynchrony (Figure 4).
Moreover, 6 of 48 (13%) patients with a combined CRT-ICD device experienced adequate shocks (for ventricular arrhythmias) during the 1-year follow-up; all of these patients were non-responders.

DISCUSSION

The findings in the current study can be summarized as follows:
1. all baseline characteristics are comparable in responders and non-responders to CRT, except for the LV dyssynchrony, which was larger in responders; 2. baseline LV dyssynchrony of 65 ms or more has a sensitivity and specificity of 80% to predict clinical response and 92% to predict reverse LV remodeling; 4. patients with extensive dyssynchrony who undergo CRT have an excellent prognosis (6% event-rate) whereas patients who do not have dyssynchrony and undergo CRT have a poor prognosis (event-rate 50%).

Benefit of CRT

In the entire study population, an improvement in all clinical parameters was observed, in line with previous studies concerning CRT [5-7]. Comparable to recent randomized clinical trials (MIRACLE, MUSTIC, PATH-CHF), a reduction in NYHA class and quality of life score were noted and an increase in 6-minute walking distance was observed [5-7]. Moreover, in the present study, a modest improvement in LVEF was shown, comparable to results of the MIRACLE trial [6]. In addition, significant reverse remodeling was demonstrated, also in line with data from the MIRACLE trial [21].
However, not all patients responded equally to CRT, and when patients were divided in responders and non-responders, based on improvement in NYHA class, it became evident that an improvement in clinical parameters was only observed in the responders. Moreover, improvement in LVEF and reverse remodeling were also observed only in the responders. When individual results were analyzed, it became clear that 21 (26%) patients did not respond to CRT. When the 5 patients who died before the 6-month follow-up were also included, the percentage of non-responders was 31%. This observation is in agreement with previous studies [8,14]. For example, in the MIRACLE trial, 20% of patients did not experience an improvement

in symptoms and 32% did not improve in NYHA class [6]. Similarly, Reuter and coworkers [22] demonstrated that 18% of 102 consecutive patients undergoing CRT did not improve in NYHA class and quality of life score.

In the current study and in most of the large clinical trials, the selection criteria included severe heart failure (NYHA class III or IV) with severely depressed LVEF (≤35%), and wide QRS complex (≥120 ms). Thus, additional selection criteria are needed to reduce the high number of non-responders.

Left ventricular dyssynchrony to select candidates for CRT

When baseline characteristics were compared between responders and non-responders (Table 2), the only variable that was different among the 2 groups was the LV dyssynchrony (whereas the RV-LV dyssynchrony was also not different). This finding was not unexpected, since various studies have recently emphasized the importance of LV dyssynchrony for the response to CRT [8-14]. Pitzalis et al [23] have used M-mode echocardiography to assess LV dyssynchrony by measuring the septal-to-posterior wall motion delay. Although this is an elegant and simple method to assess LV dyssynchrony, in patients with ischemic heart disease and previous anterior infarction, assessment of septal movement is frequently not possible. Recent studies have therefore focused on TDI applications to assess dyssynchrony. Sogaard and colleagues [10] have used tissue tracking in 25 patients to detect regions with delayed longitudinal contraction. The authors demonstrated that the extent of delayed longitudinal contraction predicted response to CRT. Breithardt and coworkers [11] used strain rate imaging in 18 patients to assess dysynchrony. More recent studies have focused on timing of peak systolic velocities of different myocardial regions to assess LV dyssynchrony. Yu and colleagues [12] have evaluated 30 patients before and after CRT with TDI and demonstrated that LV dyssynchrony allowed separation between patients with and without LV remodeling as expressed by a reduction in end-systolic volume by more than 15%. Assessment of dyssynchrony was comparable to the present analysis, with the exception that 12 segments were used, instead of 4 segments in the present study.

ROC curve analysis demonstrated a sensitivity and specificity of 80% for prediction of clinical status and 92% for the prediction of reverse LV remodeling. ROC curve analysis identified the cutoff value of 65 ms as optimal. Of interest, Gorcsan et al [13] have recently evaluated a small group of patients and also reported a similar value (65 ms) as optimal cutoff value to predict response to CRT. This cutoff level may now be used in further studies to prospectively select patients for CRT.

Prognostic Value of CRT and Left Ventricular Dyssynchrony

The typical patients who are eligible for CRT (heart failure, depressed LVEF and wide QRS complex) have a poor prognosis when treated conservatively [1-3]. Moreover, Bader et al [19] have recently shown that in these patients the presence of LV dyssynchrony is an important predictor of poor outcome.

Prognostic studies in patients undergoing CRT are still scarce. Various studies have evaluated patients after CRT; the initial studies have reported the acute benefit [4], other studies have demonstrated response after 6 months to 1 year, and preliminary data have shown sustained benefit over time [5-7]. A recent meta-analysis of the 11 published studies of 4 randomized trials (including 1634 patients) demonstrated a short-term (6-month) survival benefit after CRT as compared to optimized medical therapy [24].

However, none of the studies have evaluated the relation between baseline dyssynchrony in patients undergoing CRT and prognosis. In the current study, 1-year follow-up was obtained and the results demonstrated a low event-rate (6%) after CRT in patients with LV dyssynchrony at baseline as compared to patients without dyssynchrony (50% event-rate). This observation further supports the hypothesis that the degree of LV dyssynchrony is not only predictive of response to CRT but is also related to favourable prognosis when treated by CRT.

It is most likely that both patients with and without LV dyssynchrony have a poor prognosis if untreated, and possibly the patients with LV dyssynchrony have an even worse prognosis. If treated by CRT, the hemodynamic improvements observed after CRT in responders (i.e. the patients with LV dyssynchrony) may result in an improved prognosis as observed in the current study. The patients without LV dyssynchrony do not improve in hemodynamics, resulting in poor long-term survival.

Conclusion

Patients with extensive LV dyssynchrony responded well to CRT. Using a cutoff level of 65 ms, a sensitivity and specificity of 80% were obtained to predict clinical response and of 92% to predict reverse LV remodeling. Moreover, patients with LV dyssynchrony ≥65 ms had an excellent prognosis after CRT, in contrast to patients with <65 ms who had a high event-rate (50%) during 1-year follow-up.

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Chapter 13

Effect of postero-lateral scar tissue on clinical and echocardiographic improvement following cardiac resynchronization therapy

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ABSTRACT

Background Currently, one third of patients treated with cardiac resynchronization therapy (CRT) do not respond. Non-response to CRT may be explained by the presence of scar tissue in the postero-lateral left ventricular (LV) segments, which may result in ineffective LV pacing and inadequate LV resynchronization. In the current study the relationship between transmural postero-lateral scar tissue and response to CRT was evaluated.

Methods and Results Forty consecutive patients with end-stage heart failure (New York Heart Association (NYHA) class III/IV), LV ejection fraction (EF) ≤35%, QRS duration >120 ms, LBBB and chronic coronary artery disease were included. The localization and transmurality of scar tissue was evaluated with contrast-enhanced MRI. Next, LV dyssynchrony was assessed at baseline and immediately post-implantation using tissue Doppler imaging (TDI). Clinical parameters, LV volumes and LVEF were assessed at baseline and at 6 months follow-up.
Fourteen patients (35%) had a transmural (>50% of LV wall thickness) postero-lateral scar. In contrast to patients without postero-lateral scar tissue, these patients showed a low response rate (14% vs. 81%, P<0.05) and did not improve in clinical or echocardiographic parameters. In addition, LV dyssynchrony remained unchanged after CRT implantation (84±46 ms vs. 78±41 ms, ns).
Patients without postero-lateral scar tissue ***and*** severe baseline dyssynchrony (≥65 ms) showed an excellent response rate of 95%, compared to patients with a postero-lateral scar and/or absent LV dyssynchrony (11%).

Conclusion CRT does not reduce LV dyssynchrony in patients with transmural scar tissue in the postero-lateral LV segments, resulting in clinical and echocardiographic non-response to CRT.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is a rapidly evolving treatment option for patients with drug-refractory heart failure. Large clinical trials have reported the sustained benefit of CRT in patients with severe heart failure (New York Heart Association (NYHA) class III or IV), impaired left ventricular (LV) ejection fraction (EF) (≤35%) and a wide QRS complex (>120 ms) [1-3]. Beneficial effects of CRT include improvement in heart failure symptoms, quality-of-life, exercise capacity and LV systolic performance [1-4]. Simultaneously however, it was noted that 20-30% of patients did not respond to CRT, emphasizing the need for better selection criteria [2,5,6]. In search for new selection criteria it was demonstrated that the predominant mechanism determining the response to CRT is the resynchronization of pre-existent LV dyssynchrony [6-8].

Recently, new echocardiographic techniques, e.g. tissue Doppler imaging (TDI), have shown that QRS duration, which is traditionally considered as a marker of LV dyssynchrony, does not correlate well with LV dyssynchrony, thus explaining the low predictive value of the QRS duration for response to CRT [9,10]. Additional studies have indeed demonstrated that assessment of LV dyssynchrony using TDI was superior over electrocardiographically assessed QRS duration for prediction of response to CRT [7,8]. However, LV dyssynchrony may not be the only determinant of response to CRT, since some patients with LV dyssynchrony do not respond to CRT. Another potential reason for non-response to CRT (in patients with ischemic cardiomyopathy) may be the presence of extensive scar tissue in the region of the tip of the LV pacing lead (usually the postero-lateral LV region). Pacing the left ventricle in non-viable or scarred myocardium may result in less effective or even ineffective LV pacing, and as a consequence, failure of LV resynchronization and no response to CRT. Accordingly, the aim of the current study was to evaluate the response to CRT in relation to LV dyssynchrony on the one hand, and scar tissue in the postero-lateral wall on the other hand. To precisely determine the spatial and transmural extent of scar tissue, contrast-enhanced magnetic resonance imaging (MRI) was used.

METHODS

Patients and Study Protocol

Forty consecutive patients with severe heart failure and chronic coronary artery disease (ischemic cardiomyopathy), scheduled for the implantation of a CRT device were prospectively included. Patients were selected according to the traditional selection criteria for CRT: 1) severe heart failure (NYHA class III or IV), 2) severely depressed LV ejection fraction (LVEF) (≤35%), and 3) a QRS complex exhibiting left bundle branch block with a duration >120 ms.

Chronic coronary artery disease was defined as angiographically proven stenosis of more than 50% in ≥1 major epicardial coronary artery.

Patients with a recent myocardial infarction (<3 months), decompensated heart failure, a previous cardiac pacemaker or intracranial aneurysm clips were excluded.
The study protocol was as follows: before pacemaker implantation contrast-enhanced MRI was performed to determine the extent and transmurality of infarcted myocardial tissue. Next, clinical status was assessed and resting 2D transthoracic echocardiography was performed to measure LV volumes and LVEF. Also, TDI was performed to assess the extent of LV dyssynchrony.
LV dyssynchrony was re-assessed on the day after implantation, to assess the extent of resynchronization. Clinical status, LV volumes, and LVEF were re-assessed at 6 months follow-up.
The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Magnetic Resonance Imaging

Data acquisition. A clinical 1.5-T Gyroscan ACS-NT MRI scanner (Philips Medical Systems, Best, The Netherlands) equipped with Powertrack 6000 gradients, release 9.1 of the scanner software and a 5-element cardiac synergy coil was used. Patients were positioned in the supine position. Images were acquired during breathholds of approximately 15 seconds using vector ECG gating. The heart was imaged from apex to base [11] with 20 to 24 imaging levels (dependent on the heart size) in short-axis views. Contrast-enhanced images were acquired approximately 15 minutes after bolus injection of gadopentetate dimeglumine 0.15 mmol/kg (gadolinium-diethylenetriamine pentaacetic acid, Magnevist, Schering AG/Berlex Laboratories, Berlin, Germany) with an inversion-recovery gradient echocardiographic sequence; the inversion time was determined using a Look-Locker sequence [12,13]. Typical parameters were a field of view of 400 × 400 mm^2, a matrix size of 256 × 256, a slice thickness of 5 mm, a slice gap of -5 mm, a flip angle of 15°, a time to echo of 1.36 ms and a time to repeat of 4.53 ms [14].

Data analysis. The contrast-enhanced images were scored visually by 2 experienced observers (blinded to other MRI, echocardiographic and clinical data) using a 17-segment model [15]. Each segment was graded on a five point scale (segmental scar score; 0 = absence of hyperenhancement, 1 = hyperenhancement of 1% to 25% of LV wall thickness, 2 = hyperenhancement extending to 26% to 50%, 3 = hyperenhancement extending to 51% to 75%, and 4 = hyperenhancement extending to 76% to 100% of the LV wall thickness) [14].
A transmural scar in the postero-lateral region was defined as a segmental scar score of 3 or 4 (hyperenhancement extending to 51% to 100% of LV wall thickness) in ≥1 of the following LV segments: basal posterior, mid posterior, basal postero-lateral and mid postero-lateral.

Clinical Evaluation

Evaluation of clinical status included assessment of NYHA functional class, quality-of-life score (using the Minnesota quality-of-life questionnaire) and 6-minute hall-walk test. NYHA

functional class was scored by an independent physician, who was blinded to all other patient data. Patients with an improvement of ≥1 NYHA functional class **and** an improvement ≥25% in 6-min walking distance were classified as responders [8]. In addition, patients who died due to progressive heart failure before the 6-month follow-up assessment were classified as non-responders. In all patients, QRS duration was measured from the surface ECG using the widest QRS complex from the leads II, V1 and V6. Also, the QRS axis in the frontal plane was measured from the surface ECG immediately post-implantation. 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.

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 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-systolic, end-diastolic) and LVEF were calculated from the conventional apical two- and four-chamber images, using the biplane Simpson's technique [16].

Assessment of mitral regurgitation. The severity of mitral regurgitation was graded semi-quantitatively from color-flow Doppler images. For quantification of mitral regurgitation, the apical 4-chamber images were used. 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%) [17].

Tissue Doppler imaging to assess LV dyssynchrony. In addition to the conventional echocardiographic examination, TDI was performed to assess LV dyssynchrony. For TDI, color Doppler frame rates varied between 80 and 115 frames/s depending on the sector width of the range of interest; 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 images of three consecutive heart beats by offline analysis. Data were analyzed using commercial software (Echopac 6.1, General Electric - Vingmed). To determine LV dyssynchrony, the sample volume was placed in the basal portions of the septum and the LV lateral wall; peak systolic velocities and time-to-peak systolic velocities were obtained and the delay in peak velocity between the septum and the LV lateral wall was calculated as an indicator of LV dyssynchrony (referred to as the septal-to-lateral delay) [6,8]. Based on previous observations, a septal-to-lateral delay ≥65 ms was considered to represent severe LV dyssynchrony [8]. Inter- and intra-observer agreement for assessment of the septal-to-lateral delay were 90% and 96%, respectively [9].

Pacemaker Implantation

The LV pacing lead was inserted transvenously via the subclavian route. First, a coronary sinus venogram was obtained during occlusion of the coronary sinus using a balloon catheter. Next, the LV pacing lead was inserted in the coronary sinus with the help of an 8Fr-guiding catheter, and positioned as far as possible in the venous system, preferably in the (postero-) lateral vein. The right atrial and right ventricular leads were positioned conventionally. When a conventional indication for an internal defibrillator existed, a combined device was implanted. At implant both sensing and pacing threshold (at pulse duration of 0.5 ms) of the LV pacing lead were measured. For each patient the atrio-ventricular interval was adjusted to maximize the mitral inflow duration using pulsed-wave Doppler echocardiography. No adjustments were made to the V-V interval during the first 6 months of CRT. The final position of the LV pacing lead was assessed using cine fluoroscopy.

Statistical Analysis

Continuous data are presented as mean ± SD, and dichotomous data are presented as numbers and percentages. Data **within** patient groups (to compare the effect of CRT) are compared using paired Student's t-tests (continuous variables) and Wilcoxon signed ranks tests (NYHA classification). Differences in baseline characteristics and 6-months follow-up **between** independent patient groups are evaluated using unpaired Student's t-tests (continuous variables) and Mann-Whitney tests (NYHA classification).

Multivariable linear regression analyses were applied to evaluate the relation between clinical and echocardiographical variables (quality-of-life score, 6-minute walking distance, LVEF, LV end-diastolic and end-systolic volumes) at 6 months follow-up and the presence of postero-lateral scar tissue and/or LV dyssynchrony at baseline. We included a postero-lateral scar * LV dyssynchrony interaction term to study to what extent these variables modify each others relationship with improvement at 6-months follow-up.

Finally to compare response rate to CRT in different patient groups the chi-square tests with Yates' correction (dichotomous variables) are used. All tests are 2-sided, and a P-value <0.05 was considered statistically significant.

RESULTS

Forty consecutive patients were included in this study (35 men, mean age 67±10 years). Baseline patient characteristics are summarized in Table 1.

Pacemaker implantation

CRT-device and lead implantation was successful in all patients without major complications (Contak TR or CD, Guidant, Minneapolis, Minnesota, USA and Insync III or CD, Medtronic

Table 1. Patient characteristics (n=40).

Age (yrs)	67±10
Gender (M/F)	35/5
NYHA class	
III	36 (90%)
IV	4 (10%)
QRS duration (ms)	160±29
Rhythm	
sinus rhythm	34 (85%)
atrial fibrillation	6 (15%)
Previous MI	27 (68%)
Multi-vessel disease	30 (75%)
Previous revascularization	23 (58%)
LVEF (%)	23±7
LVEDV (ml)	245±82
LVESV (ml)	191±77
Severe MR (grade 3-4+)	8 (20%)
LV dyssynchrony (ms)	90±43
Medication	
Diuretics	35 (88%)
ACE inhibitors	38 (95%)
Beta-blockers	33 (83%)

LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; MI: myocardial infarction; MR: mitral regurgitation; NYHA: New York Heart Association.

Inc., Minneapolis, Minnesota, USA). Two types of LV leads were used (Easytrack 4512 to 80, Guidant, or Attain-SD 4189, Medtronic Inc.).

The LV pacing lead was positioned in the mid lateral region in 20 patients (50%) and in the postero-lateral region in 20 patients (50%).

Post-implantation

Following CRT implantation, QRS duration decreased from 160±29 ms to 149±24 ms ($P<0.05$). TDI demonstrated a reduction in LV dyssynchrony immediately after implantation of the CRT device from 90±43 ms to 47±39 ms ($P<0.001$).

Clinical and echocardiographic improvement following CRT

One patient died at 4 months after CRT implantation due to worsening heart failure. Accordingly, this patient did not have a clinical follow-up assessment at 6 months.

In the remaining 39 patients, a significant improvement in NYHA class was observed, 5 patients showed an improvement of 2 NYHA classes, 18 patients improved by 1 NYHA class, 14 patients did not improve and 2 patients showed a worsening in NYHA class. In addition,

the quality-of-life score decreased from 39±15 to 23±20 (P<0.001) and the 6-minute walking distance increased from 290±99 m to 357±169 m (P<0.01).
Based on a lack of improvement in NYHA class at 6 months or a lack of improvement ≥25% in 6-minute walking distance, 16 patients (40%) were classified as non-responders. The patient who died before 6 months follow-up showed a gradual decline in his clinical situation following CRT implantation and was therefore also classified as non-responder.
A modest improvement in LVEF from 23±7% to 29±11 (P<0.01) was observed. Significant reverse remodeling occurred after 6 months of CRT. The LV end-systolic volume decreased from 191±77 ml at baseline to 157±54 ml after 6 months of CRT (P<0.05). Similarly, LV end-diastolic volume decreased from 245±82 ml at baseline to 226±77 ml at 6 months follow-up (P<0.05).

Postero-lateral scar tissue

Of the 680 segments that were evaluated, 314 segments (46%) revealed hyperenhancement on MRI. In particular, 102 (15%) showed minimal hyperenhancement (score 1), 86 (13%) had hyperenhancement score 2, 82 (12%) had score 3, and 44 (6%) score 4.
Fourteen patients (35%) had a transmural scar (hyperenhancement score 3 or 4) in the postero-lateral region (basal posterior, mid posterior, basal postero-lateral and/or mid postero-lateral segments). An example of a patient with a transmural scar in the postero-lateral region is shown in Figure 1.
Baseline characteristics between patients with (n=14) and without postero-lateral scar tissue (n=26) were comparable, in particular QRS duration was similar (158±42 ms vs. 164±26 ms respectively, ns). At implantation both LV sensing (14.3±8.6 mV vs. 13.6±9.9 mV respectively, ns) and the LV pacing threshold (1.1±1.1 V vs. 1.3±0.9 V, respectively, ns) were comparable between both groups. In addition, the direction of the QRS axis on surface ECG immediately following implantation was comparable between the patients with and without postero-lateral scar tissue.

Postero-lateral scar tissue and response following CRT (Table 2)

Baseline values of both clinical (NYHA class, 6-minute walking distance and quality-of-life score) and echocardiographic parameters (LVEF, LV end-systolic volume, LV end-diastolic volume) were comparable between patients with (n=14) and without postero-lateral scar tissue (n=26) (Table 2). In the patients without transmural postero-lateral scar tissue (n=26), 21 patients (81%) were classified as responders.
In these patients there was an immediate reduction in LV dyssynchrony following CRT implantation (from 93±41 ms to 31±27 ms, P<0.05), indicating resynchronization of LV contraction. At 6 months follow-up there was a significant improvement in NYHA class, 6-minute walking distance and quality-of-life score. In addition, LVEF improved significantly (from 24±7% to 32±10%, P<0.05), and significant LV reverse remodeling was observed (Table 2).

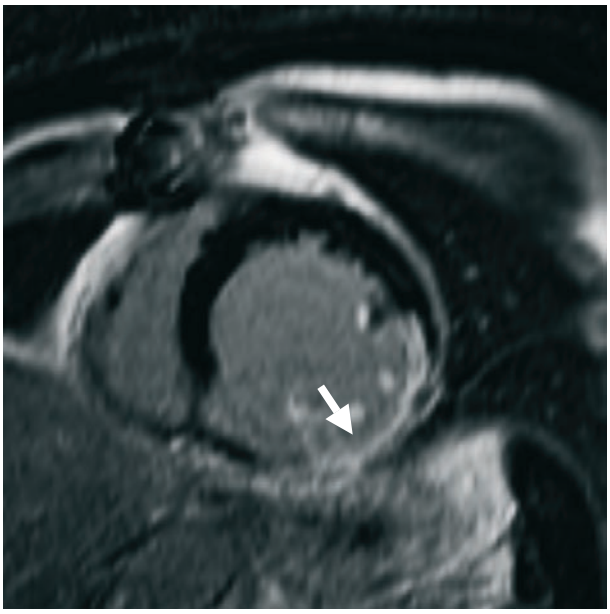

Figure 1. Contrast-enhanced MRI of a patient with transmural scar tissue in the postero-lateral wall.

In the patients with a transmural scar in the postero-lateral region (n=14), only 2 patients (14%) were classified as a responder at 6 months follow-up (P<0.05 vs. patients without scar tissue).

Baseline LV dyssynchrony in these patients was not statistically different compared to the patients without a transmural postero-lateral scar (84±46 ms vs. 93±41 ms respectively, ns). However, in the patients with a transmural postero-lateral scar, LV dyssynchrony remained unchanged following implantation of the CRT device (84±46 ms vs. 78±41 ms, ns), indicating absence of LV resynchronization. At 6 months follow-up no improvement was observed in NYHA class, 6-minute walking distance, and quality-of-life score. Also, LVEF failed to improve (from 22±7% to 23±10%, ns) and LV reverse remodeling was not observed.

LV dyssynchrony and response following CRT (Table 3)

Mean LV dyssynchrony in all patients was 90±43 ms (range 5-182 ms) before CRT. Thirty-three patients (83%) showed severe baseline LV dyssynchrony (≥65 ms). The site of latest activation was the postero-lateral region in all patients. No differences were observed in baseline clinical and echocardiographic parameters between patients with (n=33) and patients without (n=7) severe baseline LV dyssynchrony (Table 3).

In the patients with severe baseline LV dyssynchrony (≥65 ms, n=33), 23 patients (70%) were classified as responders at 6 months follow-up. In these patients, LV dyssynchrony decreased

Table 2. Patients with (n=14) and without (n=26) postero-lateral scar tissue; clinical and echocardiographic variables before and after 6 months CRT.

	No Scar (n=26)	Scar (n=14)**	P-value
NYHA class (I/II/III/IV)			
baseline	0/0/23/3	0/0/13/1	ns
follow-up	3/18/4/1*	0/2/9/2*	<0.05
6-MWT (m)			
baseline	276±99	320±99	ns
follow-up	398±146*	275±187	<0.05
QoL score			
baseline	40±14	37±18	ns
follow-up	18±18*	33±20	<0.05
LVEF (%)			
baseline	24±7	22±7	ns
follow-up	32±10*	23±10	<0.05
LVEDV (ml)			
baseline	239±82	257±87	ns
follow-up	205±64*	270±86	<0.05
LVESV (ml)			
baseline	184±76	205±82	ns
follow-up	138±32*	204±62	<0.05

LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; NYHA: New York Heart Association; 6-MWT: 6-minute walk test; QoL: quality-of-life score. * = P<0.05 follow-up vs. baseline; ** = 1 patient died before 6 months follow-up.

from 103±32 ms to 50±41 ms after implantation (P<0.05). At 6 months follow-up, a significant improvement in both clinical and echocardiographic parameters was observed. NYHA class improved significantly, the 6-minute walking distance improved from 288±97 m to 383±164 m (P<0.05) and the quality-of life score improved from 39±13 to 19±18 (P<0.05). LVEF showed an increase from 23±6% to 31±11% (P<0.05), with a significant LV reverse remodeling (Table 3).

None of the 7 patients without severe baseline LV dyssynchrony (<65 ms), showed response to CRT at 6 months follow-up (P<0.05 vs. patients with LV dyssynchrony). No change was observed in LV dyssynchrony immediately after implantation (from 24±17 ms to 32±27 ms, ns). Quality-of-life, LVEF and LV end-diastolic volume remained unchanged and a significant deterioration was observed in the 6-minute walking distance (from 304±121 m to 239±147 m, P<0.05) and LV end-systolic volume at 6-months follow-up (from 171±95 ml to 197±70 ml, P<0.05).

Postero-lateral scar tissue and LV dyssynchrony versus response to CRT (Table 4)

Figure 2 shows the percentage of responders to CRT for 4 different patient categories based on the presence/absence of transmural postero-lateral scar tissue in combination with the presence/absence of severe baseline LV dyssynchrony (≥65 ms).

Only the patients with severe baseline LV dyssynchrony and without a transmural postero-lateral scar (n=22) showed an excellent response rate (95%). Of interest, the non-responding patient in this category had a non-transmural scar in the postero-lateral region (hyperenhancement score 2). In contrast, all other patients showed a low response rate following CRT. Patients with severe LV dyssynchrony and a transmural postero-lateral scar (n=11) had a response rate of 18%. The patients without severe LV dyssynchrony at baseline had a response rate of 0%, irrespective of the presence (n=4) or absence (n=3) of postero-lateral scar tissue. The baseline clinical and echocardiographic parameters of the 22 patients with severe baseline LV dyssynchrony and without postero-lateral scar tissue were comparable to the baseline parameters of the other patients (Table 4).

The patients with severe baseline LV dyssynchrony and without a transmural postero-lateral scar (n=22) showed a significant reduction in LV dyssynchrony (from 105±31 ms to 30±28 ms,

Table 3. Patients with (n=33) and without (n=7) baseline LV dyssynchrony; clinical and echocardiographic variables before and after 6 months CRT.

	Dyssynchrony (n=33)**	No Dyssynchrony (n=7)	P-value
NYHA class (I/II/III/IV)			
baseline	0/0/29/4	0/0/7/0	ns
follow-up	3/20/6/3*	0/0/7/0	<0.05
6-MWT (m)			
baseline	288±97	304±121	ns
follow-up	383±164*	239±147*	<0.05
QoL score			
baseline	39±13	36±23	ns
follow-up	19±18*	39±20	<0.05
LVEF (%)			
baseline	23±6	24±8	ns
follow-up	31±11*	19±4	<0.05
LVEDV (ml)			
baseline	249±79	221±103	ns
follow-up	222±71*	242±111	ns
LVESV (ml)			
baseline	194±74	171±95	ns
follow-up	150±48*	197±70*	<0.05

LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; NYHA: New York Heart Association; 6-MWT: 6-minute walk test; QoL: quality-of-life score. * = P<0.05 follow-up vs. baseline; ** = 1 patient died before 6 months follow-up.

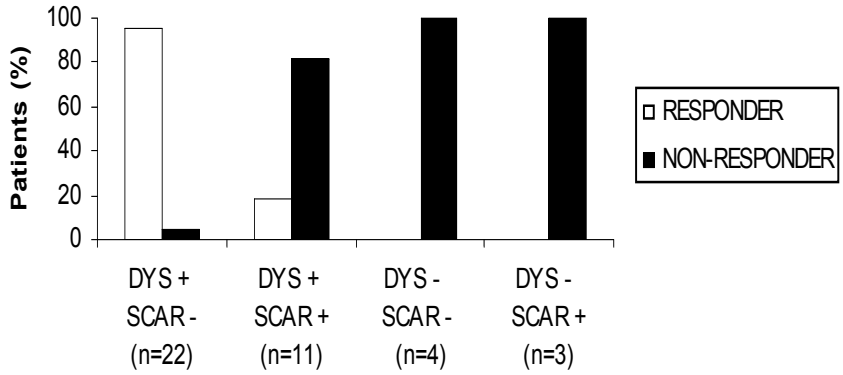

Figure 2. Percentages of responders to CRT for 4 different patient categories based on the presence/absence of transmural postero-lateral scar tissue (Scar+/Scar-) in combination with the presence/absence of baseline LV dyssynchrony ≥65 ms (Dys+/Dys).

P<0.05) and an excellent improvement in both clinical and echocardiographic parameters at 6 months follow-up.

The patients without baseline LV dyssynchrony and/or transmural postero-lateral scar tissue (n=18) failed to show a significant reduction in LV dyssynchrony (from 71±48 ms to 68±42 ms, ns), and there was no improvement in clinical and echocardiographic parameters.

Multivariable linear regression analysis (Table 5)

Table 5 demonstrates that the presence of postero-lateral scar tissue and LV dyssynchrony at baseline are independently associated with an improvement in clinical (quality-of life score and 6-minute walking distance) and echocardiographic variables (LVEF, LV end-diastolic and end-systolic volumes) at 6-month follow-up. In addition, a significant postero-lateral scar * LV dyssynchrony interaction was observed for improvement in quality-of-life, 6-minute walking distance and LVEF at 6 months follow-up. We found that in patients with postero-lateral scar tissue, LV dyssynchrony did not influence improvement in quality-of-life score (regression coefficient -31.0 + 31.9; table 5), 6-minute walking distance (regression coefficient 205 - 217) and LVEF (regression coefficient 11.1 - 10.8) at 6 months follow-up. This supports the finding that patients with postero-lateral scar tissue are unlikely to improve following CRT, irrespective of baseline LV dyssynchrony. No interaction was observed for improvement in LV end-diastolic and end-systolic volumes at 6 months follow-up.

Table 4. Patients with baseline LV dyssynchrony (≥65 ms) without postero-lateral scar tissue (n= 22) versus patients without baseline LV dyssynchrony and/or postero-lateral scar tissue (n=18); clinical and echocardiographic variables before and after 6 months CRT.

	Dyssynchrony No Scar(n=22)	Other (n=18)**	P-value
NYHA class (I/II/III/IV)			
baseline	0/0/19/3	0/0/17/1	ns
follow-up	3/18/0/1*	0/2/13/2	<0.05
6-MWT (m)			
baseline	277±97	309±104	ns
follow-up	432±118*	259±178	<0.05
QoL score			
baseline	38±13	40±18	ns
follow-up	12±10*	38±20	<0.05
LVEF (%)			
baseline	24±7	23±7	ns
follow-up	34±9*	22±9	<0.05
LVEDV (ml)			
baseline	253±80	235±92	ns
follow-up	211±67*	245±84	ns
LVESV (ml)			
baseline	197±75	183±82	ns
follow-up	138±32*	191±59	<0.05

LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; NYHA: New York Heart Association; 6-MWT: 6-minute walk test; QoL: quality-of-life score. * = P<0.05 follow-up vs. baseline; ** = 1 patient died before 6 months follow-up.

DISCUSSION

The findings in the current study demonstrate that patients with transmural scar tissue in the postero-lateral wall do not respond to CRT, even if extensive LV dyssynchrony exists. The combined assessment of scar tissue and LV dyssynchrony is needed to optimize prediction of response to CRT. Integration of these parameters resulted in a 95% response rate to CRT.

Cardiac resynchronization therapy was introduced in the early 1990s and is considered an important breakthrough in the treatment of patients with dilated cardiomyopathy and end-stage heart failure. Traditional patient selection for CRT include severe heart failure (NYHA class III or IV), depressed LVEF (≤35%) and a widened QRS complex (>120 ms) with left bundle branch block configuration [1-3,5]. Using these criteria, various studies have demonstrated the immediate benefit of CRT on hemodynamics and systolic performance of the left ventricle [18,19]. Moreover, large clinical trials have shown that these immediate effects were accompanied by an improvement in heart failure symptoms, exercise capacity and LV ejection fraction at mid-term follow-up [1-4]. However, simultaneously it has also become clear

Table 5. Multivariable linear regression models

		Model without interaction term *		Model with interaction term	
Independent variable	**Dependent variables**	**Coefficient**	**P-value**	**Coefficient**	**P-value**
Qol-post	Intercept	7.4		24.7	
	Qol-pre	0.75	<0.001	0.57	<0.001
	Postero-lateral scar tissue †	12.4	0.014	-13.5	0.2
	LV dyssynchrony †	-18.7	0.003	-31.0	<0.001
	Interaction	---		31.9	0.014
6-MWT-post (m)	Intercept	-44.3		-109.7	
	6-MWT-pre (m)	1.2	<0.001	1.16	<0.001
	Postero-lateral scar tissue †	-142	<0.001	33.2	0.7
	LV dyssynchrony †	117	0.014	205	<0.001
	Interaction	---		-217	0.016
LVEF- post (%)	Intercept	12.2		6.2	
	LVEF-pre (%)	0.58	<0.001	0.67	<0.001
	Postero-lateral scar tissue †	-9.6	<0.001	-0.78	0.9
	LV dyssynchrony †	6.6	0.009	11.1	<0.001
	Interaction	---		-10.8	0.031
LVEDV-post (ml)	Intercept	66.8		65.3	
	LVEDV-pre (ml)	0.69	<0.001	0.68	<0.001
	Postero-lateral scar tissue †	49.2	0.003	57.0	0.1
	LV dyssynchrony †	-32.1	0.093	-28.0	0.3
	Interaction	---		-9.6	0.8
LVESV-post (ml)	Intercept	56.0		57.3	
	LVESV-pre (ml)	0.64	<0.001	0.65	<0.001
	Postero-lateral scar tissue †	59.5	<0.001	54.1	0.1
	LV dyssynchrony †	-38.5	0.025	-41.3	0.077
	Interaction	---		6.6	0.8

* Interaction between postero-lateral scar tissue and LV dyssynchrony

† Postero-lateral scar tissue and LV dyssynchrony are coded as 0 (no) or 1 (yes)

LV: left ventricular; LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; 6-MWT: 6-minute walk test; QoL: quality-of-life score.

that 20-30% of patients do not respond to CRT [2,5,6]. Therefore, better understanding of the mechanism underlying response (and failure to respond) is needed, to allow better selection of patients who will benefit from CRT. Recent data have shown that baseline LV dyssynchrony is an important factor in the response to CRT. Indeed, patients with extensive LV dyssynchrony showed good response to CRT, whereas patients without dyssynchrony did not respond [6-8]. For example, Yu et al. [20] have evaluated 30 patients undergoing CRT and showed a significant improvement in clinical parameters (NYHA class, 6-minute walking distance) and echocardiographic variables (LV ejection fraction, LV reverse remodeling). The same authors have also demonstrated that TDI is the optimal approach to assess LV dyssynchrony [20,21].

In the current study, a mechanical delay ≥65 ms between the septum and the lateral wall on TDI was used as a marker of LV dyssynchrony. This cutoff value was recently demonstrated to be highly predictive for response to CRT [8]. Similar results were obtained in the current study; the patients with a delay ≥65 ms showed an immediate resynchronization after initiation of CRT, accompanied by an improvement in NYHA class, 6-minute walking distance and quality-of-life score at 6 months of CRT. In addition, an improvement in LVEF and reduction in LV volumes was observed after 6 months of CRT. In contrast, these beneficial effects were not observed in patients with a delay <65 ms. Still, on an individual basis, only 71% of the patients with LV dyssynchrony responded to CRT, indicating that other factors are important.

In the present study, only patients with ischemic cardiomyopathy were included. These patients frequently have a history of myocardial infarction and may have large areas of scar tissue. It is currently unclear whether LV pacing in a scarred region will be beneficial and was evaluated in the current study. The location and transmurality of scar tissue in the left ventricle was assessed using contrast-enhanced MRI, which currently has the highest spatial resolution and highest accuracy to assess scar tissue non-invasively [22]. It appeared that patients with transmural scar tissue in the postero-lateral wall, did not improve in clinical or echocardiographic parameters, not even in the patients with LV dyssynchrony at baseline. This observation suggests that transmural scar tissue in the target region (for LV pacing) prohibits response to CRT, and this hypothesis is further supported by the fact that patients with LV dyssynchrony did not exhibit resynchronization after CRT.

The patients with the highest likelihood of improvement after CRT (95% response rate) were the patients without transmural scar tissue in the postero-lateral wall with severe baseline LV dyssynchrony. This observation underscores that assessment of LV dyssynchrony in patients with ischemic cardiomyopathy should be combined with pre-implantation evaluation of scar tissue in order to verify whether the region that will be targeted for LV pacing does not contain transmural scar tissue.

Study limitations

In the current study, all patients had ischemic cardiomyopathy. In these patients extensive scar tissue can be present and may interfere with response to CRT. In patients with idiopathic dilated cardiomyopathy, localized scar tissue may be a lesser issue. Still, recent observations with contrast-enhanced MRI in patients with idiopathic dilated cardiomyopathy have also demonstrated areas of fibrosis. The effect of fibrosis in dilated cardiomyopathy on response to CRT needs further evaluation.

The postero-lateral region was the site of latest activation in all patients with LV dyssynchrony in the present study. It is anticipated that the negative impact of scar tissue will also apply to other regions with late activation, but this needs further study.

The presence of contractile reserve (using provocative tests such as dobutamine stress echocardiography or MRI) and its relation to response to CRT was not evaluated in the current

study and needs further study. Furthermore, the differentiation between passive myocardial movement or active contraction of scarred LV segments, as is possible with strain or strain rate imaging, needs further study.

In the current study, no adjustments were made to the V-V interval of the CRT device. However, V-V optimization may be of additional benefit in patients with postero-lateral scar tissue. By optimizing the V-V interval the negative effects of a delayed activation of the LV lateral wall through the scarred LV myocardium may be corrected, and this issue remains to be evaluated.

Conclusion

In the current study, CRT does not reduce LV dyssynchrony in patients with transmural scar tissue in the postero-lateral LV segments, resulting in clinical and echocardiographic non-response to CRT, irrespective of baseline LV dyssynchrony. Patients without transmural scar tissue in the postero-lateral LV segments ***and*** with severe baseline LV dyssynchrony (≥65 ms), on the other hand, have an excellent response rate of 95% following CRT implantation.

Despite the observation that CRT has a low success rate in patients with postero-lateral scar tissue, the number of patients in the current study is relatively small, and the results of the present study need to be confirmed in future larger studies.

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Part IV

Emerging indications

Chapter 14

Cardiac resynchronization therapy in patients with a narrow QRS complex

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ABSTRACT

Objective To evaluate the effects of cardiac resynchronization therapy (CRT) in heart failure patients with narrow QRS complex (<120 ms) and evidence of left ventricular (LV) dyssynchrony on tissue Doppler imaging (TDI).

Background CRT is beneficial in selected heart failure patients with wide QRS complex (≥120 ms). Patients with narrow QRS complex (<120 ms) are currently not eligible for CRT and the potential effects of CRT are not well studied.

Methods Thirty-three consecutive patients with narrow QRS complex and 33 consecutive patients with wide QRS complex (control group) were prospectively included. All patients needed to have LV dyssynchrony ≥65 ms on TDI, New York Heart Association (NYHA) class III/IV heart failure and LV ejection fraction ≤35%.

Results Baseline characteristics, particularly LV dyssynchrony, were comparable between patients with narrow and wide QRS complex (110±8 ms versus 175±22 ms, ns). No significant relationship was observed between baseline QRS duration and LV dyssynchrony (r=0.21, ns). The improvement in clinical symptoms and LV reverse remodeling was comparable between patients with narrow and wide QRS complex (mean NYHA class reduction 0.9±0.6 versus 1.1±0.6, ns and mean LV end-systolic volume reduction 39±34 ml versus 44±46 ml, ns).

Conclusion CRT appears to be beneficial in patients with narrow QRS complex (<120 ms) and severe LV dyssynchrony on TDI, with similar improvement in symptoms and comparable LV reverse remodeling to patients with wide QRS complex. The current results need confirmation in larger patient cohorts.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is a rapidly evolving treatment option for patients with drug-refractory heart failure. Large clinical trials have demonstrated the sustained benefit of CRT in patients with moderate-to-severe heart failure (New York Heart Association Class (NYHA) class III or IV), systolic dysfunction (left ventricular (LV) ejection fraction (EF) ≤35%) and a widened QRS complex (≥120 ms) [1-4]. Beneficial effects of CRT include the improvement in heart failure symptoms, exercise capacity and LV systolic performance, associated with a reduction in re-hospitalization for heart failure and improved long-term survival as compared to optimized medical therapy [1-5].

Previous studies demonstrated that the predominant mechanism of benefit from CRT appears related to the presence of LV dyssynchrony and subsequent resynchronization after CRT [6-10]. The presence of baseline LV dyssynchrony may thus be mandatory for response to CRT. Traditionally, the duration of the QRS complex on the surface ECG has been used as a marker of LV dyssynchrony [1-4,11,12]. However, recent studies demonstrated that QRS duration is only a weak marker of LV dyssynchrony [13-16]. It was observed that 20-30% of patients with QRS duration ≥120 ms did not have LV dyssynchrony, which may (partially) explain lack of response to CRT [13]. Conversely, it was demonstrated that 20% to 50% of heart failure patients with a narrow QRS complex (<120 ms) may also exhibit LV dyssynchrony, and these patients may benefit from CRT [13-15]. At present, minimal data are available regarding the effects of CRT in heart failure patients with a narrow QRS complex. Accordingly, the objective of the current study was to evaluate the effects of CRT in heart failure patients with a narrow QRS complex and LV dyssynchrony. In addition, these effects were compared to results obtained in a control group of heart failure patients with wide QRS complex and LV dyssynchrony.

METHODS

Patients and study protocol

Consecutive heart failure patients with evidence of LV dyssynchrony (≥65 ms) on tissue Doppler imaging (TDI) who were scheduled for implantation of a CRT device were prospectively screened for inclusion into 2 groups based on the baseline QRS duration. The target sample size for each group was 33 patients and enrollment was continued until the target sample for each group was met.

The first group consisted of 33 consecutive patients with a narrow QRS complex (<120 ms), LV dyssynchrony ≥65 ms, severe heart failure (NYHA class III-IV) and LVEF ≤35%. The number of consecutive heart failure patients with a narrow QRS complex who were screened with TDI for the presence of LV dyssynchrony ≥65 ms was 105. The second group served as a control

group and included 33 consecutive patients with a wide QRS complex (≥120 ms), LV dyssynchrony ≥65 ms, severe heart failure (NYHA class III-IV) and LVEF ≤35%.
Patients with a recent myocardial infarction (<3 months) or decompensated heart failure were excluded. Before CRT implantation, clinical status (including NYHA class, quality-of-life score and 6-minute walking distance) and QRS duration were assessed. Two-dimensional echocardiography at rest was performed to calculate LV volumes and LVEF. Next, TDI was performed to evaluate LV dyssynchrony. QRS duration was re-assessed on the day after implantation. The extent of LV dyssynchrony was re-assessed both on the day after implantation and at 6 months follow-up. Clinical status, LV volumes and LVEF were re-assessed at 6 months follow-up.

Clinical evaluation

Evaluation of clinical status included assessment of NYHA class, quality-of-life score (using the Minnesota quality-of-life questionnaire) and exercise capacity using the 6-minute hall-walk test. QRS duration was measured from the surface ECG using the widest QRS complex from the leads II, V1 and V6. QRS duration was scored by two independent observers who were blinded to all other patient data.

Echocardiography

Resting echocardiography was performed at baseline, on the day after implantation and at 6 months follow-up. LV dyssynchrony assessment using TDI was performed at baseline and repeated on the day after implantation. 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- and short-axis and two- and four chamber images). Standard two-dimensional and color Doppler data, triggered to the QRS complex were saved in cine-loop format. LV volumes (end-systolic, end-diastolic) were derived and LVEF was calculated from the conventional apical two- and four-chamber images, using the biplane Simpson's technique [17].

Tissue Doppler imaging to assess LV dyssynchrony. 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. Data were analyzed using commercial software (Echopac version 5.0.1, General Electric – Vingmed).
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 four- and two 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) [10]. The analysis of peak systolic velocities was limited to the LV ejection period and post-systolic peaks were excluded. The opening and closure of the aortic valve were measured from the pulsed-wave Doppler signals in the LV outflow tract and subsequently superimposed on the TDI curves to mark the LV ejection period (using the "event-timing" function on the Echopac echo analysis software). 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 four-and two 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 [10]. All echocardiographic measurements were obtained by two independent observers without knowledge of the clinical status of the patient.

Pacemaker implantation

The LV pacing lead was inserted transvenously via the subclavian route. First, a coronary sinus venogram was obtained during occlusion of the coronary sinus using a balloon catheter. Next, the LV pacing lead was inserted in the coronary sinus with the help of an 8Fr-guiding catheter, and positioned as far as possible in the venous system, preferably in the (postero-) lateral vein. The right atrial and right ventricular leads were positioned conventionally. When a conventional indication for an internal defibrillator existed, a combined device was implanted.

CRT device and lead implantation were completed 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.).

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. Comparison of proportions was performed using the Fisher's exact test. Linear regression analysis was performed to determine the relationship between QRS duration and LV dyssynchrony and LV dyssynchrony and percentage change in LV end-systolic volumes . For all tests a P-value <0.05 was considered statistically significant.

The data were analysed using the SPSS for Windows version 11.0.1 (SPSS Inc, Chicago, Illinois).

RESULTS

Patients with narrow QRS complex

Thirty-three patients with a narrow QRS complex and LV dyssynchrony ≥65 ms were included (28 men, mean age 63±11 years). Baseline patient characteristics are summarized in Table 1. Following CRT implantation, QRS duration showed a slight but significant increase from 110±8 ms to 129±21 ms (P<0.001). TDI demonstrated an immediate decrease in LV dyssynchrony from 102±32 ms to 35±29 ms (P<0.001), indicating acute LV resynchronization (Figure 1), which remained unchanged at 6 months follow-up (44±35 ms, P<0.001 vs. baseline and P=NS vs. immediate post-implant). Figure 2 shows an example of TDI recordings in a patient with a narrow (panel A) and a wide QRS complex (panel B).

Table 1. Baseline characteristics of the patients with QRS duration <120 ms (n=33) compared to patients with QRS duration ≥120 ms (n=33).

	QRS <120 ms	QRS ≥120 ms	P-value
Age (yrs)	63±11	67±9	ns
Gender			
male	28 (85%)	25 (76%)	ns
female	5 (15%)	8 (24%)	
Etiology			
ischemic	23 (70%)	21 (64%)	ns
non-ischemic	10 (30%)	12 (36%)	
QRS duration (ms)	110±8	175±22	<0.001
Rhythm			
sinus rhythm	27 (82%)	26 (79%)	ns
atrial fibrillation	6 (18%)	7 (21%)	
NYHA functional class			
III	29 (88%)	29 (88%)	ns
IV	4 (12%)	4 (12%)	
Medication			
Diuretics	27 (82%)	30 (91%)	ns
ACE inhibitors	29 (88%)	28 (85%)	ns
Beta-blockers	25 (76%)	26 (79%)	ns
Qol-score	39±18	42±15	ns
6-MWT (m)	274±133	253±124	ns
LVEF (%)	22±6	21±6	ns
LVEDV (ml)	216±78	238±72	ns
LVESV (ml)	174±75	189±60	ns
LV dyssynchrony (ms)	102±32	113±30	ns

6-MWT: 6-minute walking distance; LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; NYHA: New York Heart Association; Qol: quality-of-life score.

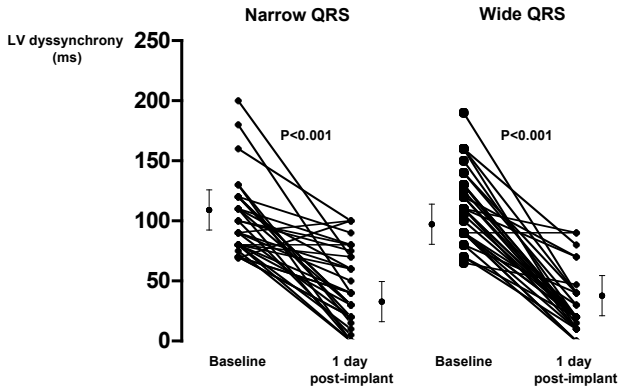

Figure 1. LV dyssynchrony before and 1 day post-CRT implantation in patients with narrow QRS complex (<120 ms, n=33) and in patients with wide QRS complex (≥120 ms, n=33).

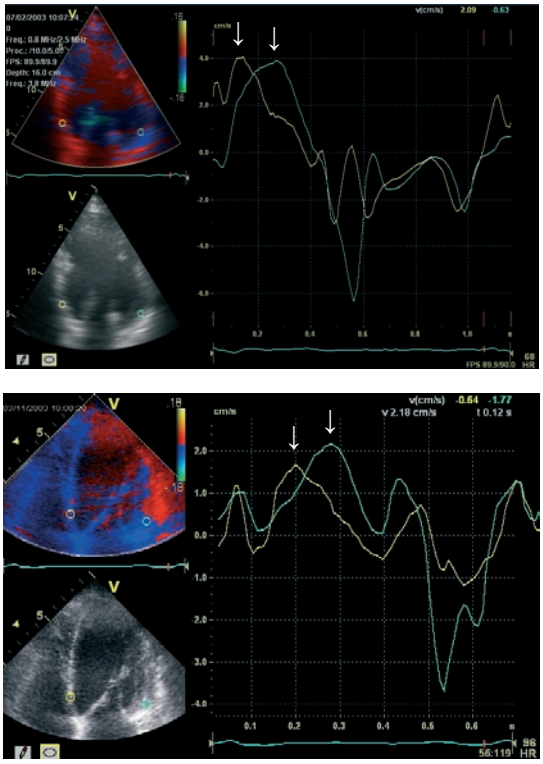

Figure 2. Panel A: Color-coded tissue Doppler recordings in a heart failure patient with narrow QRS complex (96 ms). The tissue Doppler tracings are obtained from samples placed in the basal part of the septum and the lateral wall, demonstrating a delay in peak systolic velocities of 85 ms (first arrow indicates peak systolic velocity of septum, second arrow indicates peak systolic velocity of the lateral wall). **Panel B:** Color-coded tissue Doppler recordings in a patient with wide QRS complex (170 ms) illustrating a delay of 140 ms.

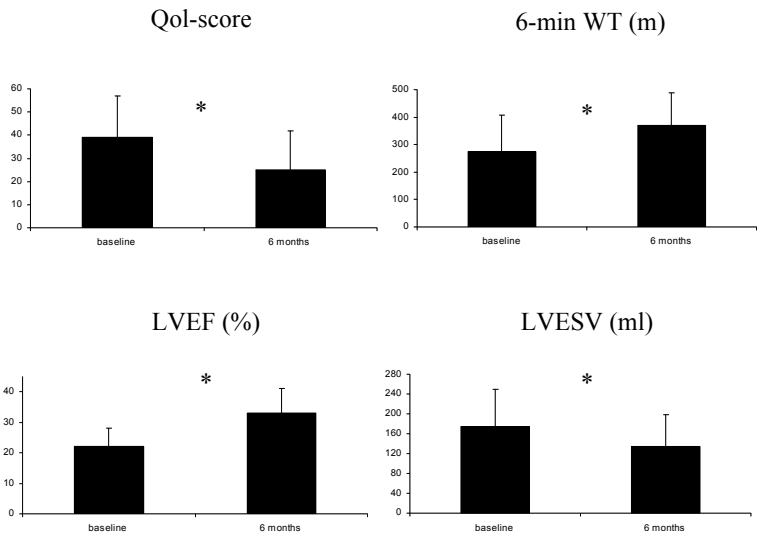

Figure 3. Improvements in clinical and echocardiographic parameters at 6 months follow-up in patients with a narrow QRS complex (<120 ms). (Qol = Quality-of-life; 6-min WT = 6-minute walking distance; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume, *=P<0.05).

Clinical and echocardiographic changes after 6 months of CRT. At 6 months follow-up, all clinical and echocardiographic parameters improved significantly (Figure 3). Mean NYHA class improved from 3.1±0.3 to 2.2±0.6 (P<0.001). The Minnesota quality-of life score improved from 39±18 to 25±17 (P<0.001) with a significant improvement in 6-minute walking distance (from 274±133 m to 370±119 m, P<0.001). Of note, on a patient basis, 88% of patients showed a clinical response to CRT (defined as an improvement ≥1 NYHA class).

Echocardiography at 6 months follow-up revealed a significant improvement in LVEF (from 22±6% to 30±8%, P<0.001) and significant LV reverse remodeling with a decrease in LV end-diastolic volume from 216 ± 78 ml to 189 ± 81 ml and a decrease in LV end-systolic volume from 174 ± 75 ml to 134 ± 64 ml (both P<0.001, Figure 3).

No correlation was observed between baseline LV dyssynchrony and percentage change in LV end-systolic volume at 6 months follow-up (y=-0,1x-9, n=33, r=0.22, ns).

Patients with wide QRS complex

Thirty-three consecutive patients with wide QRS complex and LV dyssynchrony ≥ 65 ms were also included in the current study and served as a control group (25 men, mean age 67±9 years). Baseline characteristics are summarized in Table 1. Following CRT implantation, QRS duration decreased from 175±22 ms to 150±22 ms (P<0.001). The day after pacemaker im-

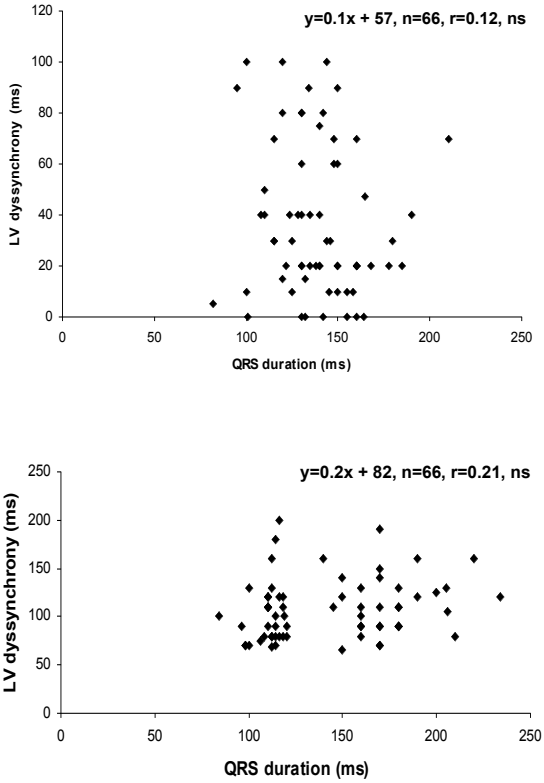

Figure 4. No significant relationship existed between LV dyssynchrony and QRS duration in the entire patient group (n =66), both before implantation (**Panel A**) and at 1 day after implantation of the CRT device (**Panel B**).

plantation, TDI demonstrated a reduction in LV dyssynchrony from 113±30 ms to 34±24 ms (P<0.001, Figure 1), indicating immediate LV resynchronization, which remained unchanged at 6 months follow-up (32±32 ms P<0.001 vs. baseline and P=NS vs. immediate post-implant). At 6 months follow-up 91% of patients showed a clinical response to CRT.

Clinical and echocardiographic changes after 6 months of CRT. At 6 months follow-up, clinical parameters had improved significantly. Mean NYHA class improved from 3.1±0.3 to 2.0±0.6 (P<0.001). The quality-of-life score improved significantly from 42±15 to 25±15 (P<0.001) and the 6-minute walking distance improved from 253±124 m to 385±119 m (P<0.001).
Using echocardiography, a significant improvement in LVEF (from 21±6% to 30±9%, P<0.001) and a significant decrease in LV volumes (LV end-systolic volume from 189±60 ml to 144±58 ml, and LV end-diastolic volume from 238±72 ml to 203±66 ml, both P<0.001) were observed. No correlation was observed between baseline LV dyssynchrony and percentage change in LV end-systolic volume at 6 months follow-up.(y=0,1x-35, n=33, r=0.14, ns).

Patients with narrow QRS versus wide QRS complex

Baseline characteristics. In Table 1 the baseline characteristics of the patients with narrow versus wide QRS complex are compared. Apart from the difference in baseline QRS duration, no significant differences were observed in baseline clinical and echocardiographic parameters. In particular, baseline LV dyssynchrony was similar between both groups (102±32 ms vs. 113±30 ms, ns).
No significant correlation was observed between baseline LV dyssynchrony and baseline QRS duration, neither in patients with narrow baseline QRS complex (y=0.7x + 21, n=33, r=0.18, ns) nor in patients with wide QRS complex (y=0.2x + 86, n=33, r=0.11, ns) (pooled data presented in Figure 4A).

Follow-up. In patients with narrow QRS complex at baseline, QRS duration showed a significant increase following CRT implantation, whereas QRS decreased in patients with baseline QRS duration ≥120 ms. The change in QRS duration was significantly different between both groups (Table 2). In contrast, the reduction in LV dyssynchrony (resynchronization) following CRT implantation was comparable between both patient groups (Table 2, Figure 1A/B).
Similar to the situation before CRT implantation, no significant relation between the QRS duration and LV dyssynchrony could be assessed at 1 day post-implantation (Figure 4B).
At 6 months follow-up, the magnitude of improvement in clinical parameters was not different between both patients groups. For example, NYHA class improved by 0.9±0.6 in patients with narrow QRS as compared to 1.1±0.6 in patients with wide QRS. Also, the magnitude of improvement in LVEF and the extent of LV reverse remodeling were comparable (Table 2).

DISCUSSION

The effects of CRT in this pilot study including heart failure patients with narrow QRS complex (<120 ms) and LV dyssynchrony can be summarized as follows. CRT resulted in an immediate reduction in LV dyssynchrony, which was followed at 6 months by an improvement in clinical symptoms and LVEF with LV reverse remodeling. Moreover, the extent of LV resynchronization and the magnitude of clinical and echocardiographic improvement were comparable in a control group of patients with wide QRS complex and LV dyssynchrony.

QRS complex versus LV dyssynchrony

Recent studies have indicated that the key mechanism of benefit from CRT is the resynchronization of LV contraction. It was demonstrated that patients with extensive LV dyssynchrony at baseline improved in clinical symptoms and LV function following CRT, whereas patients without baseline LV dyssynchrony did not improve [6-10].

Traditionally, the duration of the QRS complex on surface ECG has been used as a marker of LV dyssynchrony and consequently only patients with a wide QRS complex (>120-150 ms) were included in large trials [1-4,11,12]. However, recent data indicated that the QRS duration does not adequately reflect LV dyssynchrony [13-16, 18], as illustrated also in the current study (Figure 3). The lack of a relation between QRS duration and LV dyssynchrony has been reported not only in patients with wide QRS complex, but also in patients with narrow QRS complex. Moreover, various studies demonstrated that severe LV dyssynchrony may be present in 20% to 50% of patients with narrow QRS complex [13-15,18], suggesting that CRT may also be beneficial in heart failure patients with narrow QRS complex, provided the presence of severe LV dyssynchrony. This is an important issue, since the majority of heart failure patients may not show prolongation of the QRS complex and recent observations suggested that QRS widening >120 ms may only occur in 30% of heart failure patients [19-21]. Thus, the majority of the heart failure patients have a narrow QRS complex and are currently not eligible for CRT [19-21].

However, preliminary data from 2 small studies suggested that heart failure patients with narrow QRS complex may benefit from CRT [22,23]. Turner et al. [22] studied only the acute effects of CRT in a group of 20 heart failure patients with a QRS duration ≤120 ms. In these patients, CRT resulted in an acute hemodynamic improvement, in particular in patients with a pulmonary capillary wedge pressure >15 mmHg [22]. In addition, Achilli et al. studied the effects of CRT in a group of 14 heart failure patients with a QRS duration ≤120 ms and compared these effects to a control group of 38 heart failure patients with a QRS duration >120 ms [23]. All patients had evidence of LV dyssynchrony on M-mode echocardiography in combination with inter-ventricular dyssynchrony. The authors demonstrated that the clinical and functional benefit was similar in heart failure patients with wide and narrow QRS complex [23].

In the current study, both the immediate and mid-term effects of CRT were evaluated in a group of 33 consecutive heart failure patients with a narrow QRS complex (≤120 ms), with LV dyssynchrony as detected by TDI.

Effects of CRT in patients with narrow QRS complex

Immediately following CRT implantation, a significant reduction in LV dyssynchrony was observed, indicating LV resynchronization. This reduction in LV dyssynchrony was comparable between patients with narrow and wide QRS complex, which is an important observation since recent studies indicated that resynchronization of LV dyssynchrony is the predominant mechanism underlying benefit from CRT [6-10].

At 6 months follow-up, clinical status improved significantly as evidenced by improvement in NYHA class, quality-of life score and 6-minute walking distance. Importantly, the magnitude of benefit was comparable between patients with narrow and wide QRS complex. The clinical improvement was associated with an improvement in LV systolic function and a reverse

LV remodeling. These findings clearly indicate the beneficial effects of CRT in patients with narrow QRS complex.
Of note, the magnitude of beneficial effects was not different from patients with wide QRS complex.

Limitations

Various limitations need to be addressed. Patients with narrow QRS complex, but without LV dyssynchrony (<65 ms) on TDI were not included in the current study. However, recent studies in patients with QRS duration ≥120 ms have indicated that patients without LV dyssynchrony at baseline did not benefit from CRT [6,10]. In addition, a control group of narrow QRS patients without CRT was not included, and needs to be evaluated in future studies. In addition, the current findings need confirmation in larger studies. Moreover, whether CRT will improve survival in heart failure patients with narrow QRS complex remains to be determined.
In the present study, LV dyssynchrony was assessed from 4 basal LV segments [10], however evaluation of more segments may further improve accurate assessment of LV dyssynchrony.
Also, color-coded TDI measures the velocity of the myocardium, which may not always equal active myocardial contraction. Other echocardiographic techniques, e.g. strain and strain rate imaging, can discriminate between active and passive myocardial motion. Large, comparative studies are needed to define which technique is most accurate in assessment of LV dyssynchrony.
Finally, the importance of postero-lateral scar formation for response to CRT has recently been demonstrated [24]. The presence of postero-lateral scar tissue may be one of the explanations for the lack of improvement in patients, despite the presence of baseline LV dyssynchrony. In the current study, however, data on scar tissue were not systematically available.

Conclusion

CRT has comparable effects in heart failure patients with narrow QRS complex as compared to patients with wide QRS complex in terms of LV resynchronization, improvement in clinical symptoms, LVEF and LV reverse remodeling. These beneficial effects need confirmation in studies with larger populations.

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Chapter 15

Cardiac resynchronization therapy in patients with systolic left ventricular dysfunction and symptoms of mild heart failure secondary to ischemic or non-ischemic cardiomyopathy

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ABSTRACT

Cardiac resynchronization therapy (CRT) is beneficial in selected patients with moderate-to-severe heart failure (New York Heart Association (NYHA) class III-IV). Patients with mildly symptomatic heart failure (NYHA class II) are currently not eligible for CRT and potential beneficial effects in these patients are not well studied.

Fifty consecutive patients with NYHA class II heart failure and 50 consecutive NYHA class III-IV patients (control group) were prospectively included. All patients had left ventricular (LV) ejection fraction (EF) ≤35% and QRS duration >120 ms. The effects of CRT in NYHA class II patients were compared to results obtained in the control group.

The severity of baseline LV dyssynchrony (assessed with color-coded tissue Doppler imaging) was comparable between patients in NYHA class II vs NYHA class III-IV (83±49 ms vs 96±51 ms, ns), and resynchronization was achieved in both groups. NYHA class II patients showed a significant improvement in LVEF (from 25±7% to 33±10%, P<0.001) and reduction in LV end-systolic volume (from 168±55 ml to 132±51 ml, P<0.001) following CRT, similar to patients in NYHA class III-IV. In addition, only 8% of NYHA class II patients showed progression in heart failure symptoms.

In conclusion, CRT has comparable effects in patients with NYHA class II and NYHA class III-IV heart failure in terms of LV resynchronization, improvement in LVEF and LV reverse remodeling.

INTRODUCTION

Currently, patients presenting with mildly symptomatic heart failure (New York Heart Association (NYHA) class II) are not eligible for cardiac resynchronization therapy (CRT) [1,2]. Nonetheless, patients with heart failure NYHA class II may also exhibit reduced left ventricular (LV) ejection fraction (EF) and LV dilatation in combination with a widened QRS complex. In view of the recent observations showing that CRT halts the progression of heart failure and resulted in improvement of LVEF and reversal of LV dilatation [3-5], it seems plausible that CRT may also improve LV function and reverse LV dilatation in patients with mildly symptomatic heart failure and severely impaired LV function. In addition, CRT may also prevent the progression of heart failure towards NYHA class III-IV. At present, the effects of CRT in patients with NYHA class II and systolic LV dysfunction are not well studied and it is unknown whether the effects are comparable to the results of CRT in patients with NYHA class III or IV. Accordingly, the objective of the current study was to evaluate the effects of CRT in patients with mildly symptomatic heart failure (NYHA class II), LVEF ≤35% and a widened QRS complex (>120 ms) and to compare these effects to the benefits of CRT in a control group of patients in NYHA class III or IV with established selection criteria (LVEF ≤35%, and QRS duration >120 ms).

METHODS

Patients and study protocol

Patients who were scheduled for the implantation of a biventricular pacemaker were prospectively included into 2 groups based on baseline NYHA functional class.

The first group consisted of 50 consecutive patients with mildly symptomatic heart failure (NYHA class II), LVEF ≤35% and QRS duration >120 ms.

The second group served as a control group and included 50 consecutive patients in NYHA class III or IV with established selection criteria for CRT (LVEF ≤35% and QRS duration>120 ms).

Patients with a recent myocardial infarction (<3 months) or decompensated heart failure were excluded. Before pacemaker implantation, clinical status (including NYHA class, quality-of-life score and 6-minute walking distance) and QRS duration were assessed. Two-dimensional echocardiography at rest was performed to calculate LV volumes and LVEF. Next, color-coded tissue Doppler imaging (TDI) was performed to evaluate LV dyssynchrony. LV dyssynchrony and QRS duration were re-assessed on the day after implantation. Clinical status, LV volumes and LVEF were re-assessed at 6 months follow-up.

Clinical Evaluation

Evaluation of clinical status included assessment of NYHA class, quality-of-life score (using the Minnesota quality-of-life questionnaire) and assessment of exercise capacity using the

6-minute hall-walk test. NYHA class II was defined as shortness of breath during normal exercise, NYHA class III was defined as dyspnea during less minimal exercise (e.g. not able to climb 1 flight of stairs) and NYHA class IV was defined as shortness of breath at rest. The assessment of NYHA class and other clinical parameters was performed by an independent physician, who was blinded to all other patient data. In all patients, QRS duration was measured from the surface ECG using the widest QRS complex from the leads II, V1 and V6.

Echocardiography

Resting echocardiography and color-coded TDI were performed at baseline and on the day after implantation. 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- and short-axis and two- and four-chamber images). Standard two-dimensional and color Doppler data, triggered to the QRS complex were saved in cine loop format. LV volumes (end-systolic, end-diastolic) were derived and LVEF was calculated from the conventional apical two- and four-chamber images, using the biplane Simpson's technique [6].

In addition to the conventional echocardiographic examination, color-coded TDI was performed to assess LV dyssynchrony. For TDI, color Doppler frame rates varied between 80 and 115 frames/s depending on the sector width of the range of interest; pulse repetition frequencies were between 500 Hz and 1 KHz, resulting in aliasing velocities between 16 and 32 cm/s. Color-coded TDI parameters were measured from color images of 3 consecutive heart beats by offline analysis. Data were analyzed using commercial software (Echopac version 4.0.3., General Electric – Vingmed).

To determine LV dyssynchrony, the color-coded TDI sample volume was placed in the basal portions of the septum and the LV lateral wall; peak systolic velocities and time-to-peak systolic velocities were obtained and the delay in peak velocity between the septum and the LV lateral wall was calculated as an indicator of LV dyssynchrony (referred to as the septal-to-lateral delay) [7,8]. Inter- and intra-observer agreement for assessment of the septal-to-lateral delay were 90% and 96%, respectively [9].

The severity of mitral regurgitation was graded semi-quantitatively from color-flow Doppler images. For quantification of mitral regurgitation, the apical 4-chamber images were used. 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%) [10].

All echocardiographic measurements were obtained by 2 independent observers without knowledge of the clinical status of the patient.

Pacemaker Implantation

The LV pacing lead was inserted transvenously via the subclavian route. First, a coronary sinus venogram was obtained during occlusion of the coronary sinus using a balloon catheter. Next, the LV pacing lead was inserted in the coronary sinus with the help of an 8Fr-guiding catheter, and positioned as far as possible in the venous system, preferably in the (postero-) lateral vein. The right atrial and right ventricular leads were positioned conventionally. When a conventional indication for an internal defibrillator existed, a combined device was implanted. For each patient the atrio-ventricular interval was adjusted to maximize the mitral inflow duration using pulsed-wave Doppler echocardiography. No adjustments were made to the V-V interval during the first 6 months of CRT.

CRT-device and lead implantation was 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.).

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. Univariate analysis for categorical variables was performed using the chi-square test with Yates' correction. For all tests a P-value <0.05 was considered statistically significant.

RESULTS

NYHA class II patients

Fifty patients with mildly symptomatic heart failure (NYHA functional class II) were included in this study (47 male, mean age 65±10 years). Baseline patient characteristics are summarized in Table 1.

Following CRT implantation, QRS duration decreased from 160±30 ms to 148±20 ms ($P<0.01$). The day after pacemaker implantation, TDI demonstrated a reduction in LV dyssynchrony from 83±49 ms to 35±30 ms ($P<0.001$), indicating immediate LV resynchronization.

At 6 months follow-up, all clinical parameters showed a small, but significant improvement. Eighteen patients had improved to NYHA class I, whereas 28 patients remained in NYHA functional class II and only 4 patients had deteriorated to NYHA functional class III (Figure 1). A modest, but significant improvement in mean NYHA class was observed from 2±0 to 1.7±0.6 ($P<0.01$). The quality-of life score improved from 22±14 to 13±13 ($P<0.001$) and a small but significant improvement was observed in 6-minute walking distance (from 430±94 m to 469±118 m, $P<0.01$, Figure 2).

Table 1. Baseline characteristics of the patients in New York Heart Association class II (n=50) compared to the patients in New York Heart Association class III-IV (n=50).

	NYHA II	NYHA III-IV	P-value
Age (years)	65±10	66±11	ns
Gender			
male	47 (94%)	41 (82%)	ns
female	3 (6%)	9 (18%)	
Etiology			
ischemic	29 (58%)	28 (56%)	ns
non-ischemic	21 (42%)	22 (44%)	
QRS duration (ms)	160±30	168±27	ns
QRS complex configuration			
Left bundle branch block	33 (66%)	32 (64%)	ns
Intra-ventricular conduction disorder	9 (18%)	8 (16%)	
Right bundle branch block	4 (8%)	3 (6%)	
Right ventricular paced	4 (8%)	7 (14%)	
Rhythm			
sinus rhythm	42 (84%)	44 (88%)	ns
atrial fibrillation	8 (16%)	6 (12%)	
Medication			
Diuretics	38 (76%)	43 (86%)	ns
ACE inhibitors	48 (96%)	44 (88%)	ns
Beta-blockers	35 (70%)	31 (62%)	ns
Quality-of-life score	22±14	45±11	<0.05
6-minute walking distance (m)	430±94	243±103	<0.05
LV dyssynchrony ≥65 ms	32 (64%)	36 (72%)	ns
LV ejection fraction (%)	25±7	20±7	<0.05
LV end-diastolic volume (ml)	219±63	243±90	ns
LV end-systolic volume (ml)	168±55	195±82	ns
Severe mitral regurgitation (grade 3-4+)	3 (6%)	12 (24%)	<0.05
LV dyssynchrony (ms)	83±49	96±51	ns

Echocardiography at 6 months follow-up revealed a significant improvement in LVEF (from 25±7% to 33±10%, P<0.001) and significant LV reverse remodeling with a decrease in LV end-diastolic volume from 219± 63 ml to 191± 51 ml (P<0.001) and a decrease in LV end-systolic volume from 168± 55 ml to 132± 51 ml (P<0.001, Figure 2). A reduction in mitral regurgitation was observed from grade 1.2±0.8 to 1.0±0.8 (P=0.01).

The patients who improved by 1 NYHA class at 6 months follow-up (n=18) and the patients who remained in NYHA class II (n=28) showed a significant improvement in LVEF and LV volumes following CRT. The improvements in LVEF (7±11% versus 11±10%, respectively, ns) and reduction in LV end-systolic volume (48±42 ml versus 33±37 ml, respectively, ns) were slightly (but not significant), higher in the patients who also improved in NYHA class (n=18, see Figure 3).

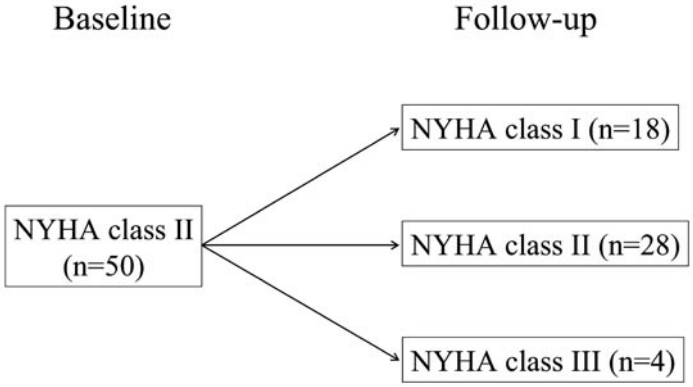

Figure 1. Change in NYHA functional class after 6 months of CRT in NYHA class II patients.

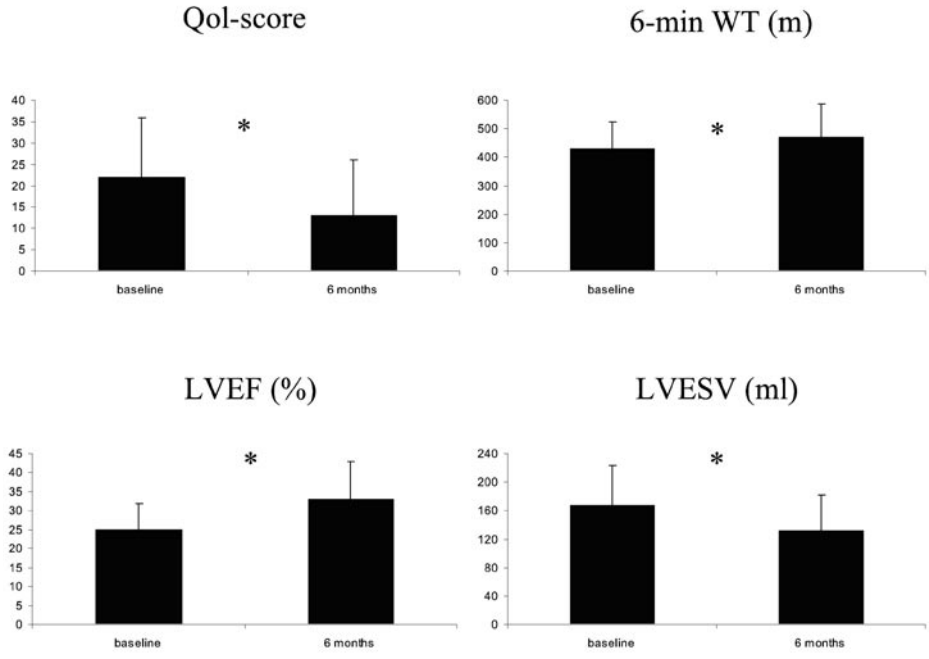

Figure 2. Improvements in clinical and echocardiographic parameters at 6 months follow-up in NYHA class II patients (QoI = Quality-of-life; 6-min WT = 6-minute walking distance; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume, *=P<0.05).

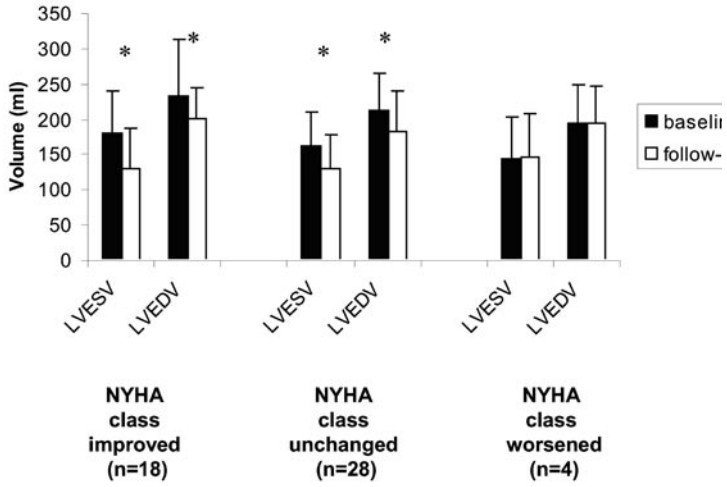

Figure 3. Magnitude of LV reverse remodeling at 6 months follow-up in NYHA class II patients with improvement in NYHA class (n=18) versus patients with unchanged NYHA class (n=28) or with deterioration in NYHA class (n=4, *=P<0.05).

In contrast, the 4 patients who deteriorated to NYHA functional class III did not show improvement in LVEF or LV volumes (Figure 3).

NYHA class III-IV patients (control group)

Fifty patients with moderate-to-severe heart failure (NYHA class III-IV) were included in the current study (41 male, mean age 66±11 years). At baseline 43 patients were in NYHA functional class III and 7 patients were in NYHA class IV. Other baseline patient characteristics are summarized in Table 1.

Following CRT implantation, QRS duration decreased from 168±27 ms to 150±25 ms (P<0.001). The day after pacemaker implantation, TDI demonstrated a reduction in LV dyssynchrony from 96±51 ms to 31±27 ms (P<0.001), indicating immediate LV resynchronization.

At 6 months follow-up, clinical parameters had improved significantly. Mean NYHA class improved from 3.1±0.4 to 2.1±0.7 (P<0.001). The quality-of-life score improved significantly from 45±11 to 29±15 (P<0.001) and the 6-minute walking distance improved from 243±103 m to 370±150 m (P<0.001).

Using echocardiography a significant improvement in LVEF (from 20±7% to 27±10%, P<0.001) and a significant decrease in LV volumes (LV end-systolic volume from 195±82 ml to 166±73 ml, and LV end-diastolic volume from 243±90 ml to 221±78 ml, both P<0.001) were observed. Mitral regurgitation showed a reduction from grade 1.6±0.9 to 1.2±0.7 (P<0.001).

NYHA class II patients versus NYHA class III-IV patients

In Table 1 the baseline characteristics of the NYHA class II patients are compared to the baseline characteristics of the NYHA class III-IV patients. No differences were observed in age, gender and etiology of heart failure. The quality-of-life score and the 6-minute walking distance were significantly lower in the NYHA class III-IV patients compared to the NYHA class II patients. The number of patients with LV dyssynchrony ≥65 ms was comparable in both groups (n=32 (64%) vs. n=36 (74%), P=ns). In addition, LVEF was significantly higher in patients with NYHA class II (25±7% vs. 20±7%, P<0.05). Moreover, severe mitral regurgitation was less frequently observed in patients with NYHA class II.

The immediate reduction in LV dyssynchrony following CRT implantation was comparable between the NYHA class II patients and the NYHA class III-IV patients, indicating a similar level of LV resynchronization in both groups (Table 2).

At 6 months follow-up, both the patients in NYHA class II (Figure 2) and the patients in NYHA class III-IV showed a significant improvement in clinical and echocardiographic characteristics. However, the magnitude of improvement in clinical parameters was significantly less in the NYHA class II patients. This difference was most outspoken for the reduction in NYHA class (0.3±0.6 versus 1.0±0.8, respectively, P<0.001) and the level of improvement in 6-minute walking distance (38±87 m versus 127±108 m, respectively, P<0.001).

Table 2. Magnitude of improvement in clinical and echocardiographic parameters following cardiac resynchronization therapy. Patients with baseline New York Heart Association class class II (n=50) are compared to patients with New York Heart Association class III-IV (n=50)

	NYHA II	NYHA III-IV	P-value
Immediate post-implant			
Shortening in QRS duration (ms)	11±26	18±30	ns
Reduction in LV dyssynchrony (ms)	48±50	65±53	ns
6 months follow-up			
Reduction in NYHA class	0.3±0.6	1.0±0.8	<0.001
Improvement in 6-minute walking distance (m)	38±87	127±108	<0.001
Reduction in Quality-of-life score	8±11	16±14	<0.001
Improvement in LV ejection fraction (%)	7±11	7±7	ns
Reduction in LV end-diastolic volume (ml)	28±38	22±43	ns
Reduction in LV end-systolic volume (ml)	36±41	29±42	ns

In contrast, the improvement in echocardiographic parameters was comparable between the NYHA class II patients and the patients in NYHA class III-IV. Both the increase in LVEF (7±11% versus 7±7%, respectively, ns) and the decrease in LV volumes were similar (Table 2).
In line with previous studies, only the patients with substantial LV dyssynchrony in both groups improved in LV function and showed a reduction in LV dyssynchrony (e.g. in the NYHA class II patients with LV dyssynchrony ≥65 ms (n=32) LVEF improved from 24±6% to 36±9% as compared to an improvement from 20±7% to 29± 9% in NYHA class III-IV patients, both P<0.001), whereas the patients without LV dyssynchrony at baseline showed no reduction in LV dyssynchrony and did not improve in LV function (e.g. in the NYHA class II patients with LV dyssynchrony < 65 ms (n=18) LVEF did not change (from 27±7% to 27±10%) and in the NYHA class III-IV patients with LV dyssynchrony <65 ms (n=14) LVEF changed from 21±8% to and 22± 12%, both P=ns)

DISCUSSION

The findings in the current study demonstrate that CRT induced significant LV reverse remodeling with an improvement in LVEF in patients with systolic LV dysfunction and NYHA class II heart failure. The improvement in LV function was not restricted to patients who improved in NYHA class, but was also observed in patients without improvement in NYHA class at 6 months follow-up. Only 4 patients (8%) showed a progression of heart failure towards NYHA class III and these patients failed to show an improvement in LVEF or LV reverse remodeling.
The magnitude of improvement in LVEF and LV volumes in the NYHA class II patients was comparable to that observed in patients in NYHA class III or IV, whereas the improvement in clinical parameters was significantly less compared to the patients in NYHA class III or IV.
In the present study the effects of CRT in patients with mildly symptomatic heart failure (NYHA class II) and systolic dysfunction were studied. These patients were less symptomatic as evidenced by a relatively low Minnesota score and long 6-minute walking distance. However, despite the presence of relatively mild symptoms of heart failure, all patients had severely impaired systolic LV function, severe LV dilatation and substantial LV dyssynchrony. Directly after CRT implantation, LV dyssynchrony decreased significantly, indicating resynchronization of LV contraction. This acute LV resynchronization was followed by a significant improvement in both clinical and echocardiographic parameters at 6 months follow-up. The magnitude of improvement in clinical parameters was limited, as evidenced by the fact that only 36% of patients improved to NYHA class I, and NYHA class remained unchanged in 56% of patients. This finding is not surprising in view of the minimal symptoms at baseline. Importantly, the percentage of patients with a progression of heart failure symptoms to NYHA class III was low (8%), suggesting that CRT may prevent the progression of heart failure symptoms in NYHA class II patients. Similar observations have been reported by Abraham et al. in NYHA

class II patients undergoing CRT [11]. In addition, CRT may also prevent the progression/or prevention of heart failure in patients with an impaired LV function and an indication for a conventional pacemaker [12,13].

In contrast to the minimal improvements in clinical symptoms, the improvements in LV function after 6 months of CRT were substantial, as evidenced by considerable LV reverse remodeling and markedly improved LVEF. Of note, LV reverse remodeling and improvement in LVEF were not restricted to patients who improved in NYHA class, but were also present in patients without improvement in NYHA class. The patients with deterioration to NYHA class III however, did not improve in LV function. This is in line with the study by Higgins et al. who showed that the NYHA class I-II patients did not improve in clinical symptoms compared to a placebo group, however these patients did show a significant reduction in LV volumes compared to the placebo group [14]. In a cohort of patients in NYHA class III or IV, Yu et al. have recently demonstrated that the positive effect of CRT on cardiac function, in particular the decrease in LV systolic volume, predicted improvement in survival following CRT whereas the improvement in clinical parameters did not predict long-term prognosis [15]. In view of these data, the substantial improvement in LV function (and particularly the LV reverse remodeling) observed in the NYHA class II patients is likely to be of clinical relevance [15]. Our results are in contrast to results reported by Kuhlkamp et al; these authors did not find an improvement in clinical and echocardiographic parameters in NYHA class II [16].

The percentage of NYHA class II patients exhibiting progression of symptoms to NYHA class III following CRT is very low (8%), suggesting that CRT may prevent progression of heart failure in these patients. To firmly draw this conclusion, a control group of NYHA class II patients without CRT should have been included. This was indeed shown by Abraham recently, demonstrating less progression of heart failure symptoms in NYHA class II patients undergoing CRT as compared to NYHA class II patients treated medically [11]. The strength however of the current study is the comparison with NYHA class III-IV patients showing comparable effect on improvement in LV function and LV reverse remodeling.

Follow-up after CRT was assessed at 6 months and sustained effect at longer follow-up needs to be confirmed in future studies.

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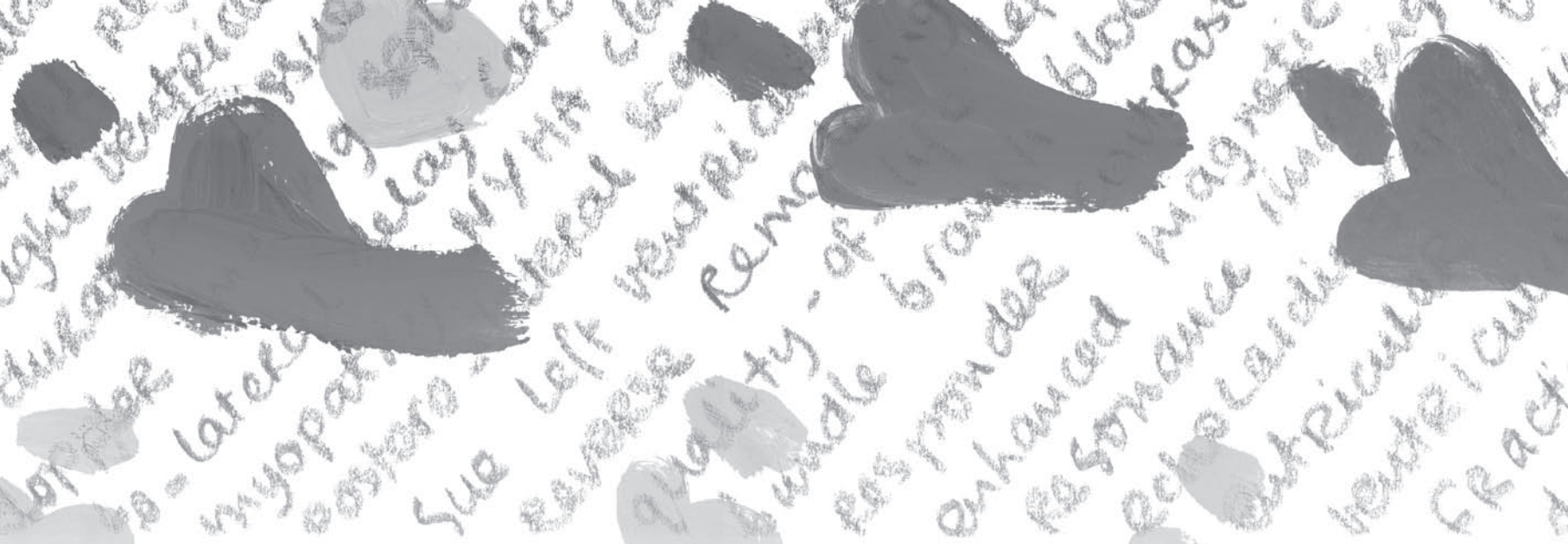

Optimal use of echocardiography in CRT

Part V

Chapter 16

Optimal use of echocardiography in cardiac resynchronization therapy

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Heart, in press

INTRODUCTION

At present, cardiac resynchronization therapy (CRT) is considered an important step forward in the treatment of patients with severe heart failure. To date, several large randomized trials have shown the sustained beneficial effects of CRT on heart failure symptoms and left ventricular (LV) function [1-3]. However, in parallel to the impressive results of CRT in these large trials, a consistent percentage of patients did not respond to CRT (non-responders) when the traditional patient selection criteria (New York Heart Association (NYHA) class III-IV, LV ejection fraction <35% and QRS duration >120 ms) were applied [1,4,5].

When response to CRT is defined using clinical parameters (e.g. improvement in NYHA class or quality-of life) the prevalence of non-responders is about 30% and when echocardiographic parameters (LV reverse remodeling, improvement in LV ejection fraction) are applied, the number of non-responders is usually around 40% [4,5].

The reduction of the number of non-responders is one of the main challenges in the field of CRT today. Recent studies have indicated that selection of patients with a high likelihood of response is possible with several (novel) echocardiographic techniques [6] (Table 1). In addition to patient selection, echocardiography is also useful to assess acute and long-term beneficial effects of CRT. Moreover, echocardiography is needed for the optimization of pacemaker settings [7-11]. These issues are discussed in the current review.

I. ECHOCARDIOGRAPHY TO PREDICT RESPONSE TO CRT

Recent studies, addressing the issue of non-response to CRT have indicated that none of the traditional selection criteria (NYHA class III-IV, LV ejection fraction ≤35% and QRS duration >120 ms) were able to predict a positive response to CRT, thereby highlighting the need for improvement of the selection criteria [5,12]. In search for better selection criteria, it has become clear that the key mechanism of benefit from CRT is the presence and subsequent reduction of LV dyssynchrony [4,5]. Traditionally, QRS duration has been used as an (indirect) marker of LV dyssynchrony. The duration of the QRS complex, however proved to be a poor marker of LV

Table 1: the most widely used techniques to assess LV dyssynchrony

M-mode echocardiography
Pulsed-wave tissue Doppler imaging
Color-coded tissue Doppler imaging
Tissue synchronization imaging
Strain imaging
Real time 3D echocardiography

dyssynchrony, thereby explaining its low predictive value for response to CRT [13,14]; indeed, QRS duration merely reflects inter (right versus left) ventricular dyssynchrony [15].
Various studies have recently demonstrated that patients with extensive baseline LV dyssynchrony had a high likelihood of response to CRT, whereas patients without baseline LV dyssynchrony did not respond to CRT. Of note, although inter-ventricular dyssynchrony (between the right and the left ventricle) tends to decrease after CRT, this parameter has limited value for the prediction of response to CRT [5,8].
Many different techniques have been tested for their ability to detect and quantify LV dyssynchrony in CRT patients. Since this observation, several cardiac imaging techniques have been tested for their ability to detect and quantify LV dyssynchrony. Among the different techniques, echocardiography proved particularly well suited for detection of LV dyssynchrony in the clinical setting.
The most important echocardiographic techniques to detect LV dyssynchrony in CRT patients will be discussed hereafter and are summarized in Table 1, ranging from simple M-mode echocardiography to more sophisticated echocardiographic techniques, such as tissue Doppler imaging (TDI), strain (rate) imaging and 3D-echocardiography.

A. M-mode echocardiography

A relatively simple and elegant echocardiographic technique for the detection of LV dyssynchrony has been developed by Pitzalis et al. who used M-mode echocardiography to measure the delay between the systolic excursion of the (antero-) septum and the posterior wall on the parasternal short-axis view, the so-called septal to posterior wall motion delay (SPWMD, Figure 1A) [16,17]. In an initial study, including 20 patients, responders to CRT had a significantly larger SPWMD as compared to non-responders. Using a cut-off value of 130 ms, SPWMD yielded an accuracy of 85% (sensitivity 100%, specificity 63%) to predict response after CRT [16]. In a subsequent study the same authors evaluated another 60 patients and demonstrated that the cut-off value of 130 ms was a strong predictor of patient prognosis following CRT implantation [17].
In contrast however, Marcus et al. recently revealed less favourable results with this technique. The SPWMD measurement was applied retrospectively in a large cohort (n=79 patients, 72% ischemic cardiomyopathy) of heart failure patients who were included in the CONTAK-CD trial [18]. The authors reported a sensitivity of 24% with a specificity of 66% to predict response to CRT, and the SPWMD could not be assessed in 50% of patients (Figure 1B). Recent data in 98 heart failure patients scheduled for CRT indicated that the poor interpretability of the SPWMD recordings was the result of the absence of a clear systolic motion on M-mode echocardiography due to akinesia of the inter-ventricular septum (53%), the posterior wall (12%) or both (3%) or a poor acoustic window in the parasternal view (32%). Of note, in the patients without an interpretable SPWMD, LV dyssynchrony assessment was still feasible in 90% of patients when color-coded TDI was applied [19].

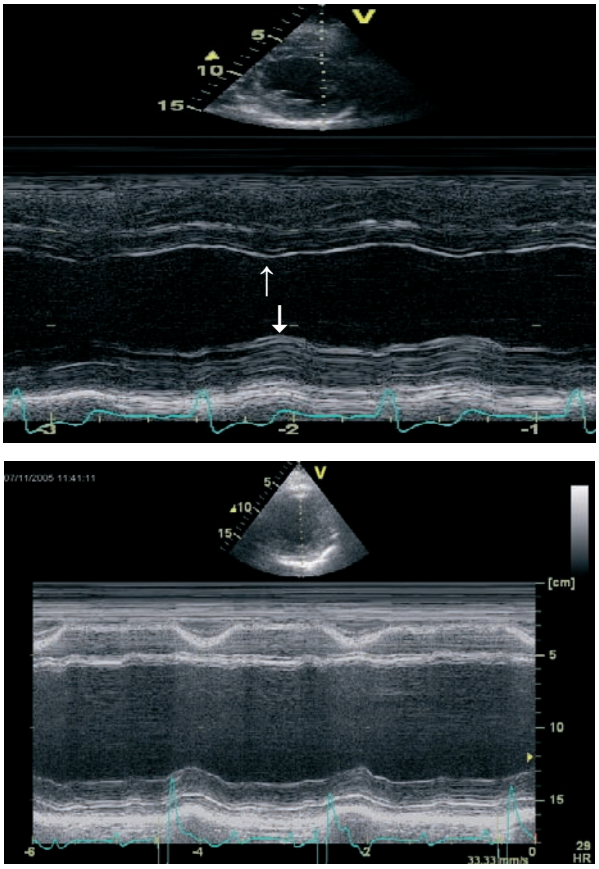

Figure 1: *Panel A:* Measurement of the septal to posterior wall motion delay (SPWMD) using M-mode echocardiography. An M-mode recording through the (antero-) septum and posterior LV wall is obtained in the parasternal short-axis view. LV dyssynchrony is defined as the shortest interval between the maximal systolic displacement of the septum and the maximum systolic displacement of the LV posterior wall. Arrows indicate maximal systolic displacement. *Panel B:* Patient example in which assessment of LV dyssynchrony was not feasible with M-mode echocardiography due to akinesia of the antero-septal wall.

B. Tissue Doppler imaging

One of the most widely studied techniques for the assessment of LV dyssynchrony in the selection of CRT patients is TDI. This technique allows the measurement of peak systolic velocities in different regions of the myocardium [4,5,20], and more importantly, the time-intervals between electrical activity (QRS) and the mechanical activity (segmental peak systolic velocity) (Figure 2).

The myocardial velocity curves can either be constructed on-line using pulsed-wave TDI (Figure 3), or reconstructed off-line from the 2D color-coded TDI images (Figure 2). The advantages of color-coded TDI over pulsed-wave TDI are the possibility for off-line analysis and the possibility to analyse multiple segments in one heart beat thereby avoiding potential errors

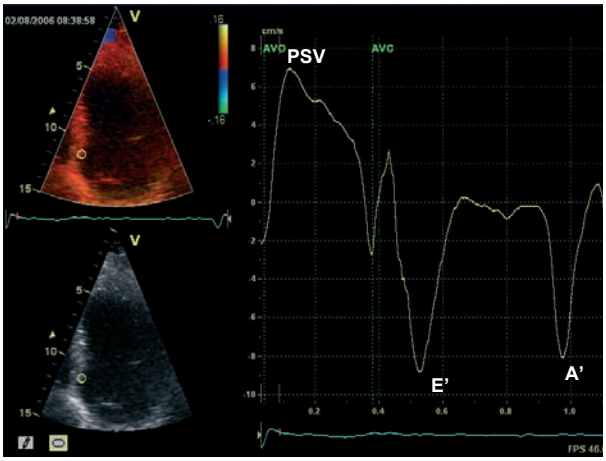

Figure 2: Color-coded tissue Doppler imaging in the apical 4-chamber view in a normal individual. The sample is placed **off-line** in the basal part of the septum, demonstrating peak systolic velocity (PSV), and diastolic parameters (E' and A'). (AVO en AVC indicate aortic valve opening and closure, respectively).

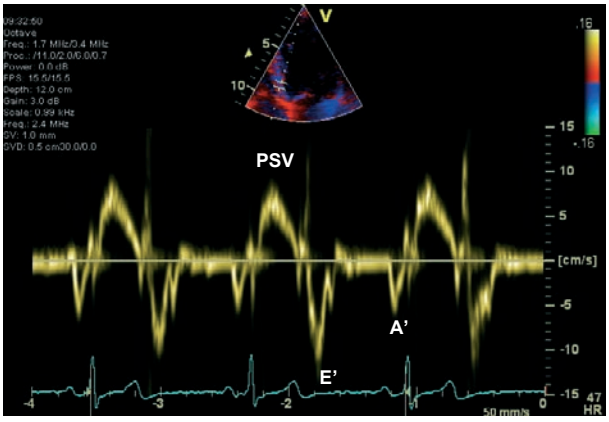

Figure 3: Pulsed-wave tissue Doppler imaging in the apical 4-chamber view in a normal individual. The pulsed-wave sample is placed **on-line** in the region of interest (basal part of the inter-ventricular septum) and the myocardial velocity curve is derived. (PSV = peak systolic velocity, E' and A' represent diastolic parameters).

from differences in cardiac frequency. In addition, the peak systolic velocity is displayed more accurate when color-coded TDI is applied.

In order to assess regional dyssynchrony, one commonly used method is to measure the time to peak systolic velocity of individual left ventricular (LV) segments with reference to the QRS complex [4,5]. Integration of this information allows accurate assessment of electromechanical coupling, estimation of severity of LV global delay, as well as evaluation of LV dyssynchrony (Figure 4).

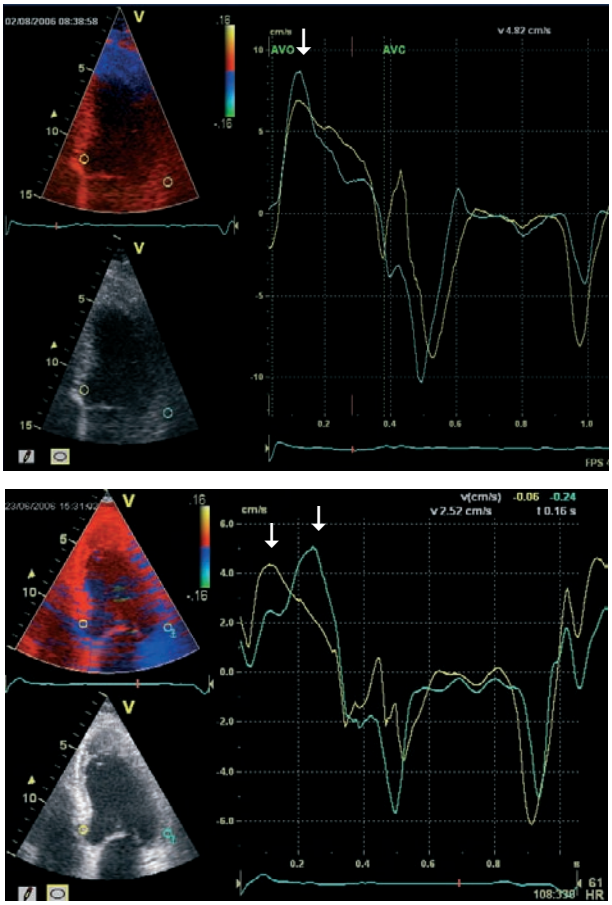

Figure 4: *Panel A*: 2-segment color-coded tissue Doppler imaging in the apical 4-chamber view in a normal individual without LV dyssynchrony. LV dyssynchrony is defined as the time delay in peak systolic volume between the basal septum and lateral wall. The arrow indicates peak systolic velocity of both the basal septum and lateral wall illustrating perfect synchrony.
Panel B: 2-segment color-coded tissue Doppler imaging in heart failure patient with LV dyssynchrony. The delay in peak systolic velocity between the basal septum and lateral wall is 130 ms indicating severe LV dyssynchrony. (Arrows indicate peak systolic velocities).

The number of segments used for evaluation of LV dyssynchrony varied among the different studies. Most frequently, 2 or 4 basal segments (septal, lateral, inferior, anterior) are evaluated. Bax et al. [5] evaluated 85 heart failure patients with follow-up data obtained up to 1 year. Receiver operating characteristic curve analysis was performed and revealed that LV dyssynchrony of 65 ms or more was highly predictive of both clinical response (sensitivity/specificity 80%) and LV reverse remodeling (sensitivity/specificity 92%).

Other studies have used a multiple segmental approach to create various models of LV dyssynchrony in order to predict a favourable response to CRT. Examples of these models include 6 basal LV segments, or a combination of 6-basal and 6-mid LV segments. Notobartolo

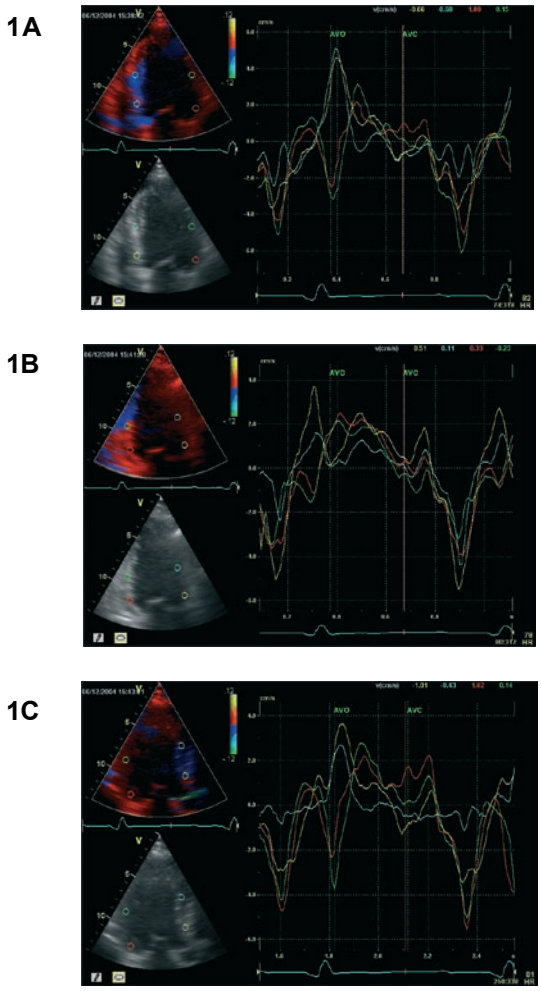

Figure 5: 12-segment color-coded tissue Doppler imaging in patient with LV dyssynchrony in multiple segments. Myocardial velocity curves were derived **off-line** at basal and mid levels of the left ventricle in the different walls. The time to peak systolic velocities during the ejection phase in each view are compared. The ejection phase is defined by the aortic valve opening (AVO) and aortic valve closure (AVC) markers. Panel A: Apical 4-chamber view showing delay in the lateral wall. Panel B: Apical 2-chamber view showing delay in the anterior wall. Panel C: Apical long-axis view showing delay in the posterior wall.

et al. used the 6-basal LV segmental model from the 3 apical views. The authors measured the time to the highest peak velocity in either ejection phase or post-systolic shortening, and calculated the maximal time difference to generate the "peak velocity difference" [20]. In 49 patients undergoing CRT, a peak velocity difference >110ms at baseline predicted LV reverse remodeling at 3 months follow-up with a sensitivity of 97% and a specificity of 55% [20]. Examination of ejection phase velocities appears to provide a better trade-off between sensitivity and specificity. Yu et al. proposed to measure the standard deviation of the time

to peak systolic velocity in ejection phase in the 6-basal/6-mid segmental model to compute the asynchrony index (or Ts-SD) (Figure 5). With a population-derived cut-off value of 32.6ms, the index was able to segregate responders from non-responders (defined as presence/absence of LV reverse remodeling) [12,21].

Another method to assess systolic dyssynchrony is to measure the time to onset of mechanical contraction in the ejection phase by pulsed-wave TDI (Figure 3). The work by Penicka et al. defined LV dyssynchrony as the maximal electromechanical delay among the 3 basal LV segments (septal, lateral and posterior wall) [22]. The authors reported a cut-off value of 102 ms, which yielded an accuracy of 88% to predict response to CRT (as defined by a relative increase in LV ejection fraction >25%).

C. Tissue Synchronization imaging

Another evolving technique to assess LV dyssynchrony is tissue synchronization imaging (TSI) (Vivid 7, General Electric-Vingmed, Milwaukee, Wisconsin, USA) [23]. This technique automatically calculates the peak systolic velocities from TDI and displays the timing of peak systolic velocities as a color-map, allowing for a quick visualization of the early activated segments (displayed in green) and identification of the latest activated segments (displayed in red), without the need for TDI curve analysis. In addition, quantitative assessment of regional delay is still possible (through construction of myocardial velocity curves, similar to TDI). Yu et al. studied this qualitative approach in 56 heart failure patients and reported a sensitivity of 82% with a specificity of 87% to predict response to CRT [23] (Figure 6).

Recently, a novel 3-dimensional probe (Vingmed Ultrasound, Horten, Norway) became commercially available allowing simultaneous acquisition of a triplane dataset and color-coded TDI of the left ventricle. During post-processing (Echopac), the TSI option can be applied to the TDI triplane dataset. The timing of the peak systolic velocities is presented as a color-map in the apical 4-, 2- and 3-chamber views during one single heartbeat. Additionally, by manually tracing the endocardial borders during post-processing (surface mapping) a 3-dimensional volume is generated semi-automatically, portraying the area of latest activation allowing quick visual identification of the delayed LV segment (Figure 7). If quantitative assessment of LV dyssynchrony is preferred than the regional myocardial velocity curves can be derived analogously to 2-dimensional TSI analysis.

D. Strain (rate) imaging

Strain (rate) imaging (SRI) is a potentially interesting derivation from color-coded TDI. In contrast to TDI, which only measures myocardial velocities, SRI examines the (rate of) myocardial deformation between 2 points in the region of interest. Accordingly, SRI has the potential advantage over TDI to differentiate between active and passive myocardial motion. Using SRI the extent of LV dyssynchrony can be quantified by measuring the time delays in time to peak systolic strain, comparable to TDI. Initial studies employing SRI to measure LV dyssynchrony

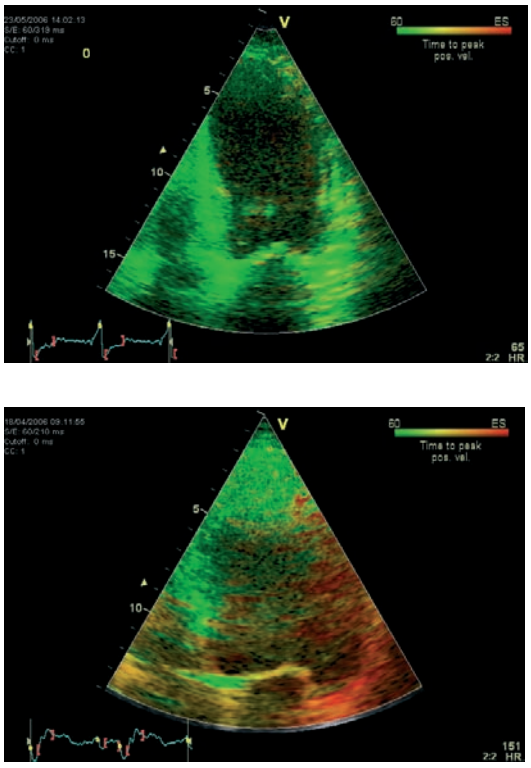

Figure 6: Tissue synchronization imaging: the colors represent time to peak systolic velocity. Green corresponds to early mechanical activation; yellow/orange/red indictes a delayed peak systolic velocity. Panel A shows a patient with a synchronous LV contraction (the entire left ventricle is colored green), Panel B shows delayed activation (indicated in orange/red) of the lateral wall.

from the apical views *(measuring longitudinal strain)* reported relatively low predictive values for response to CRT [21]. The low predictive values were due to the relatively high angle dependency of SRI which resulted in limited reproducibility of measurements.

Dohi et al. produced more promising results when strain imaging was used to calculate LV dyssynchrony from the short axis views *(measuring radial strain*) in 38 patients undergoing CRT. A ≥130 ms difference in septal versus posterior wall peak strain was strongly predictive of immediate improvement in stroke volume with CRT (sensitivity 95%, specificity 88%) (Figure 8) [24].

In addition, the same authors recently studied a novel echocardiographic technique, speckle tracking, which is able to calculate myocardial strain from conventional 2D echocardiography. The main advantage of this technique over TDI derived strain is its lack of angle dependency (Figure 9). In 48 patients undergoing CRT, a sensitivity of 91% with a specificity of 75% to predict acute response to CRT were obtained using a cut-off value ≥130 ms for LV dyssynchrony [25].

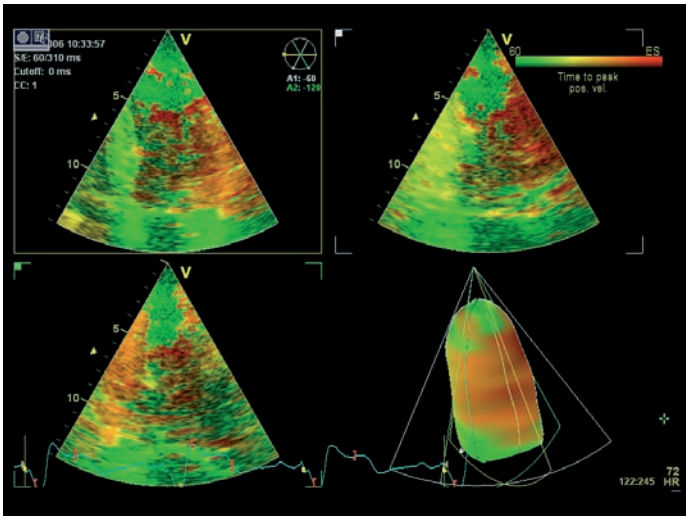

Figure 7: Example of tissue synchronization imaging applied to a triplane dataset. The areas of latest mechanical activation are indicated in orange/red in the apical 4-, 2- and 3-chamber views. The lower right panel shows a semi-automatically generated 3-dimensional LV volume portraying the area of latest mechanical activation.

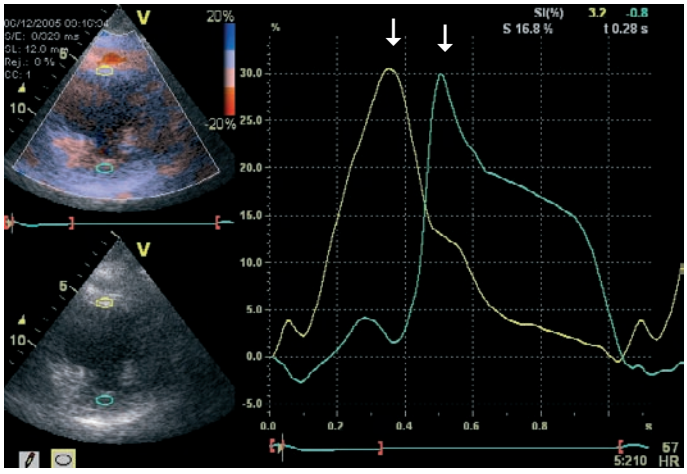

Figure 8: Example of tissue Doppler-derived radial strain imaging in the parasternal short axis view at the mid-LV level in a patient with severe LV dyssynchrony (160 ms). LV dyssynchrony is defined as the difference in peak strain between the antero-septum (yellow curve) and the posterior wall (green curve). (Arrows indicate peak strain)

E. 3D echocardiography

The main advantage of real-time 3D echocardiography (RT3DE, Philips Medical Systems, Andover, Massachusetts, USA) for the quantification of LV dyssynchrony compared to 2D echocardiographic techniques is that it provides simultaneous information on the timing of contraction of a large number of LV segments (Figure 10). With an excellent spatial resolution

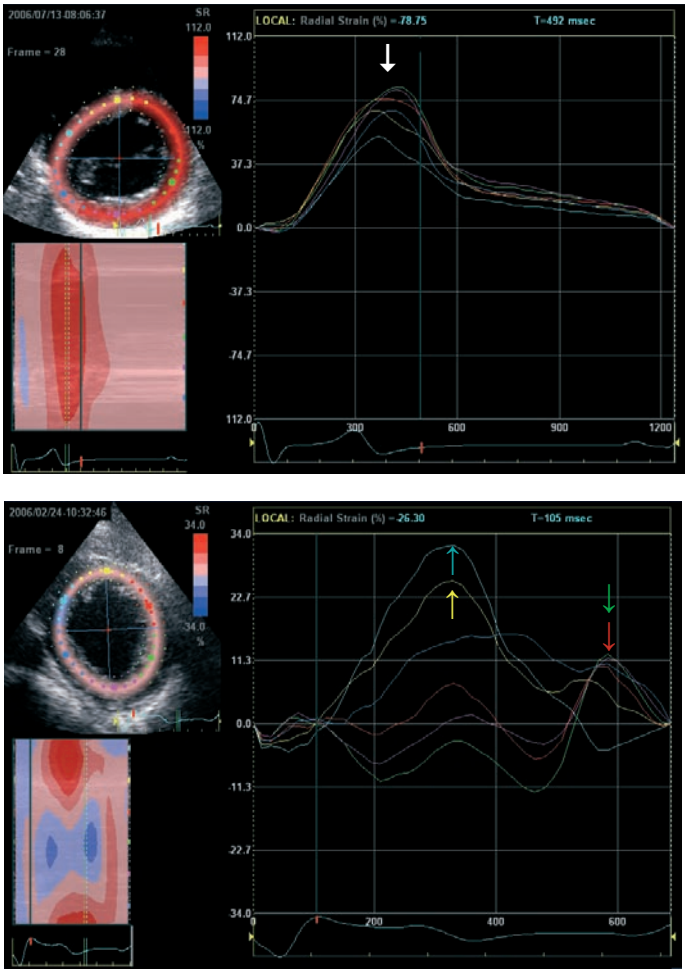

Figure 9: Panel A: Speckle tracking derived radial strain imaging in the parasternal short-axis view at the mid LV level. In this example peak radial strain (arrow) occurs simultaneously in all 6 segments, indicating a synchronous LV contraction (the curves are color-coded in accordance with the segments on the short-axis view). Panel B: Example of radial time-strain curves from speckle tracking in a heart failure 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).

RT3DE is able to provide detailed information on both global and regional LV function. Using this technique regional volume-time curves can be derived for each of the LV segments; LV dyssynchrony is assessed by comparing the times to reach minimal regional volume for each LV segment. The systolic dyssynchrony index is used as a marker of global LV dyssynchrony and is defined as the standard deviation of the time taken to reach minimal regional volume for each of the LV segments. In addition, the regional time differences between different segments allow the identification of the area of latest LV activation, even when these areas are located in the most distal LV regions and/or the apex.

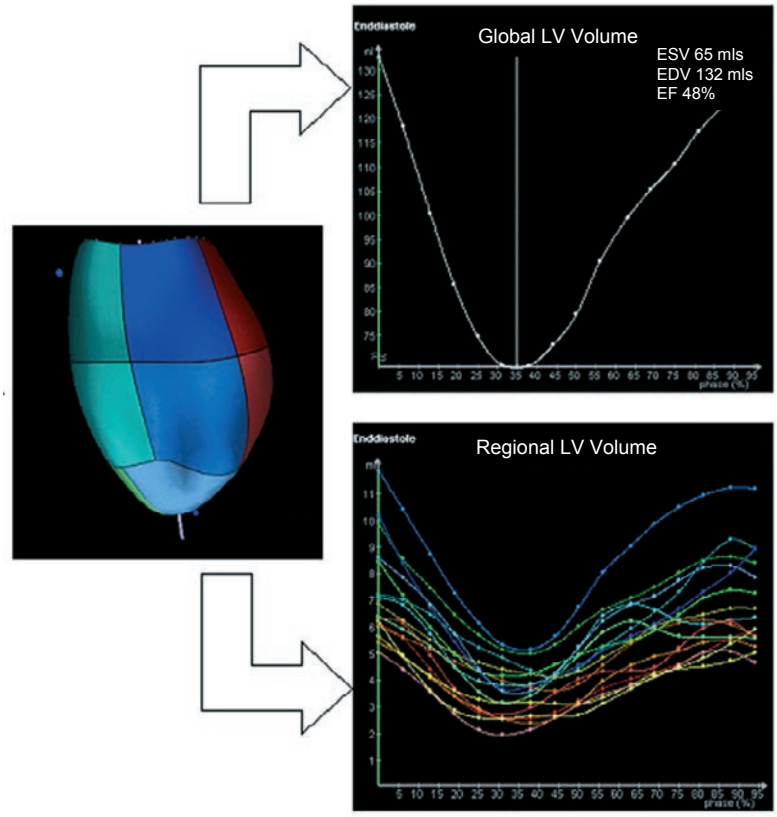

Figure 10: Global (top) and regional (bottom) LV volume curves derived from a 3D data set. The regional volume curves for each segment allow the calculation of the systolic dyssynchrony index which is defined as the standard deviation of the time taken to reach minimum regional volume for each segment.

Recently, Kapetanakis at al. demonstrated the feasibility of RT3DE to assess LV dyssynchrony in 174 unselected patients referred for routine echocardiography and concluded that RT3DE can rapidly quantify global LV dyssynchrony.

In addition, the authors used RT3DE to calculate global LV dyssynchrony in 26 additional patients undergoing CRT and demonstrated a significant difference in the systolic dyssynchrony index between responders and non-responders (16.6±1.1% vs 7.1±2%, P<0.001) [26]. An optimal cut-off value for prediction of response however was not reported and remains to be defined in future studies.

F. Which echo technique?

As discussed above, a large number of different echocardiographic techniques have been tested recently for quantification of the extent of (pre-implantation) LV dyssynchrony in heart failure patients, to select the patients with a high likelihood of response to CRT. The

echocardiographic techniques ranged from simple M-mode echocardiography (4 studies, 257 patients) [16-19], pulsed-wave TDI (4 studies , 123 patients) [8,22,27,28], to more sophisticated techniques including color-coded TDI (8 studies, 290 patients) [4,5,12,20,21,29-31], SRI (7 studies, 206 patients) [21,24,30-34], TSI (4 studies, 177 patients) [23,24,35,36] and 3D echocardiography studies, (2 studied, 39 patients) [26,37]. At present, no consensus exists on which technique is optimal to predict response to CRT, and the large number of different echocardiographic techniques that have been published (without direct comparisons between techniques) further contribute to the confusion on the optimal technique. Moreover, the different techniques employ varying numbers of segments to determine LV dyssynchrony (ranging from 2 to 16 segments) and different cut-off values to define substantial LV dyssynchrony (ranging from 65 ms to 130 ms). Consequently, larger multi-center studies, directly comparing different echocardiographic techniques, are needed to identify the optimal technique, with the optimal number of segments and the optimal extent of LV dyssynchrony to predict response to CRT. The prospective, multi-center PROSPECT trial is specifically designed to answer these questions. The study will include approximately 300 patients with a clinical follow-up of 6 months and the results are expected in 2007 [38].

II. IMMEDIATE FOLLOW-UP

Echocardiography can be used to assess the immediate benefits from CRT. In the acute setting, echocardiographic studies have demonstrated that CRT immediately improved LV systolic function (LV ejection fraction), with direct disappearance of this effect when CRT was switched off. The acute improvement in LV systolic function was reflected in a reduction in LV end-systolic volume, whereas LV end-diastolic volume remained unchanged (resulting in an increased LV ejection fraction [39]. In addition, echocardiographic studies demonstrated that some patients exhibit an immediate reduction in mitral regurgitation after CRT. Kanzaki et al. studied 26 patients and reported an acute reduction in regurgitant volume from 40±20 ml to 24±17 ml ($P<0.001$) acutely after CRT. The mechanism underlying the reduction in mitral regurgitation was evaluated using strain imaging. A significant mechanical delay was demonstrated between the posteromedial and anterolateral papillary muscles at baseline (106±74 ms) which was reduced immediately after CRT implantation (12±8 ms, $P<0.001$) [40,41], indicating that resynchronization of the dyssynchronous papillary muscles acutely restored valvular competency.

Thus, the beneficial effects of CRT appear related to an acute resynchronization of the left ventricle and papillary muscles. Echocardiography can be used to assess the LV resynchronization immediately after CRT. In Figure 11 an example of a patient without resynchronization after CRT is demonstrated. Indeed, recent data suggest that CRT may not always result in resynchronization (despite the presence of pre-implantation LV dyssynchrony) [42]. The

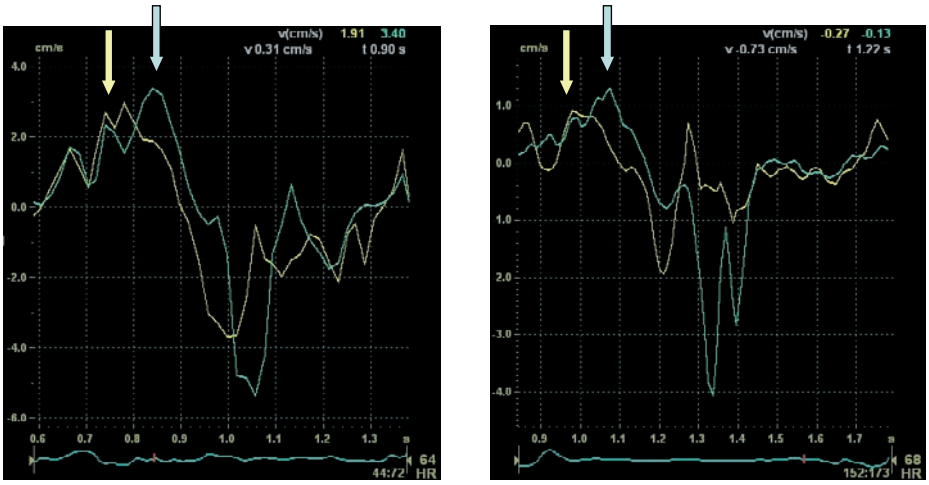

Figure 11: Example of a patient without LV resynchronization. Despite the presence of severe baseline LV dyssynchrony (120 ms) between the basal septum (yellow curve) and the basal lateral wall (green curve), CRT was unable to reduce LV dyssynchrony (post-implantation 110 ms). As a result, no LV reverse remodeling was observed at 6 months follow-up (LV end-systolic volume from 245 ml to 250 ml) and LV ejection fraction remained unchanged (from 23% to 20%). In addition, the patient showed no change in clinical parameters.

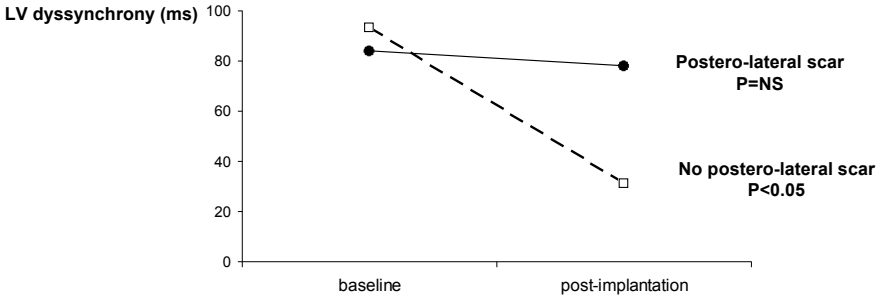

Figure 12: In patients with postero-lateral scar tissue (usually the location of the LV pacing lead), CRT is unable to restore LV synchrony. In patients without scar tissue, LV dyssynchrony reduced from 93±41 ms to 31±27 ms ($P<0.05$) whereas in patients with scar tissue LV dyssynchrony remained unchanged (84±46 ms at baseline versus 78±41 ms after CRT, P=NS, Adapted from reference 33).

mechanisms underlying failure to restore LV synchrony are not entirely clear, but recent data demonstrated that patients with scar tissue in the postero-lateral LV segments (usually the area where the LV lead is located) failed to resynchronize after CRT, associated with clinical and echocardiographic non-response (Figure 12). In particular, the response rate to CRT was excellent (95%) in patients with severe baseline LV dyssynchrony without postero-lateral scar tissue; in patients with postero-lateral scar tissue however, the response rate was low (11%) [42]. Not only the location but also the extent of scar tissue is important for the response to

CRT. Hummel et al. showed that the extent of scar tissue was inversely related to the response to CRT [43].

Failure to resynchronize can also be located to a mismatch between the site of latest activation and the position of the LV lead. Using color-coded TDI, Ansalone et al. demonstrated that the response to CRT was minimal when the LV lead was not located near the area of latest activation [27]. Similarly, Suffoletto et al. recently reported that patients with the LV lead positioned outside the area of latest activation had a significantly lesser response to CRT [25].

TSI may be the ideal technique to visualize the area of latest activation and thus guide LV lead positioning. This principle was applied recently by Murphy et al. who used TSI to evaluate the interaction between the LV lead position and the area of latest activation on the one hand, and LV reverse remodeling after CRT on the other hand [36]. The authors observed a larger reduction in LV end-systolic volume in patients with the LV lead positioned in the area of latest activation (23% reduction in LV end-systolic volume) as compared to patients with the lead positioned in an adjacent (15% reduction) or a remote region (9% increase). Although the area of latest activation is most often located in the postero-lateral LV segments, a wide variation between individuals has been reported [44]. Accordingly, echocardiography (in particular TSI) may provide a patient tailored approach for LV lead positioning, which targets the area of latest LV activation. In the past this approach has been hampered by the lack of (echocardiographic) techniques that were able to provide an accurate 3D representation of regional LV dyssynchrony.

One needs to realize however that not all areas of the left ventricle are suitable for endocardial (via the coronary sinus) LV lead placement due to the absence of suitable veins in the targeted area. It has recently been shown that multi-slice CT scanning can be helpful in assessing the venous anatomy before CRT implantation [45]. Information about the venous anatomy can then be combined with information about the area of latest LV activation and if suitable branches of the coronary sinus are absent, epicardial (surgical) LV lead placement should be considered.

III. LATE FOLLOW-UP

Echocardiography is the technique of choice to evaluate improvement in LV ejection fraction after CRT. In 125 heart failure patients, a significant improvement in LV ejection fraction from 23±8% to 32±9% was demonstrated after 6 months of CRT [46].

Yu et al. demonstrated that the improvement in LV ejection fraction is a gradual process with further improvements occurring over time (Figure 13) [4]. St John Sutton et al. recently evaluated a cohort of 228 patients included in the MIRACLE trial and demonstrated that the gradual improvement in LV ejection fraction was (in part) related to the etiology of heart failure. Patients with non-ischemic cardiomyopathy exhibit an immediate improvement in LV

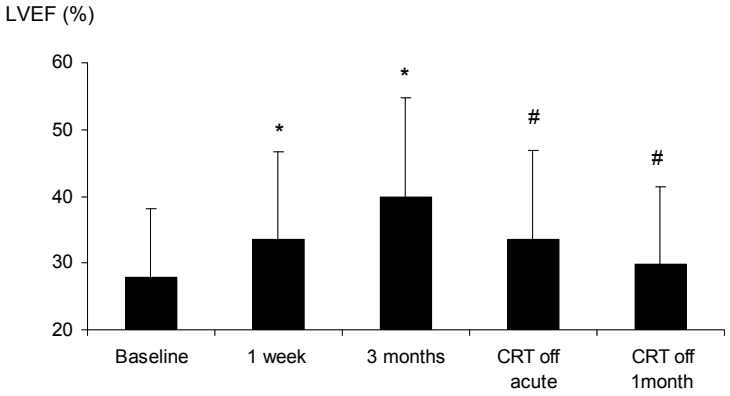

Figure 13: Changes in LV ejection fraction following CRT in 25 patients studied by Yu et al. A gradual increase in LV ejection fraction was observed (*: P<0.05 versus baseline). Interestingly after cessation of CRT at 3 months follow-up a gradual decline in LV ejection fraction was observed (#: P<0.05 versus 3 months of CRT , Adapted form reference 4).

ejection fraction, whereas the improvement occurs more gradually in patients with ischemic cardiomyopathy [47].

In addition to improvement in LV ejection fraction, echocardiography permits measurement of LV reverse remodeling, with a reduction in both LV end-systolic and end-diastolic volumes. Reverse remodeling is clinically relevant, as reported recently by Yu et al. who demonstrated in 141patients that a reduction >10% in LV end-systolic volume after 3-6 months of CRT was the most important predictor of event-free survival at 12 months follow-up [10]. This important observation underscores that LV reverse remodeling as measured by echocardiography provides the most clinically meaningful definition of response to CRT (Figure 14).

In combination with the LV reverse remodeling a reduction in mitral regurgitation may be observed as well (Figure 15), which can be explained by a further reduction in annular dimensions resulting in a smaller regurgitant orifice.

In addition to the effects of CRT on the left ventricle, CRT may also affect right ventricular size and function. Bleeker et al. demonstrated the beneficial effects of CRT at 6-months follow-up including right ventricular reverse remodeling, a reduction in tricuspid regurgitation and a decrease in pulmonary artery pressure [48].

IV. OPTIMIZATION OF PACEMAKER SETTINGS

A. AV optimization

The aim of AV optimization is to select an "optimal" AV delay that results in an increase in diastolic filling time and a reduction of presystolic mitral regurgitation. This may lead to an

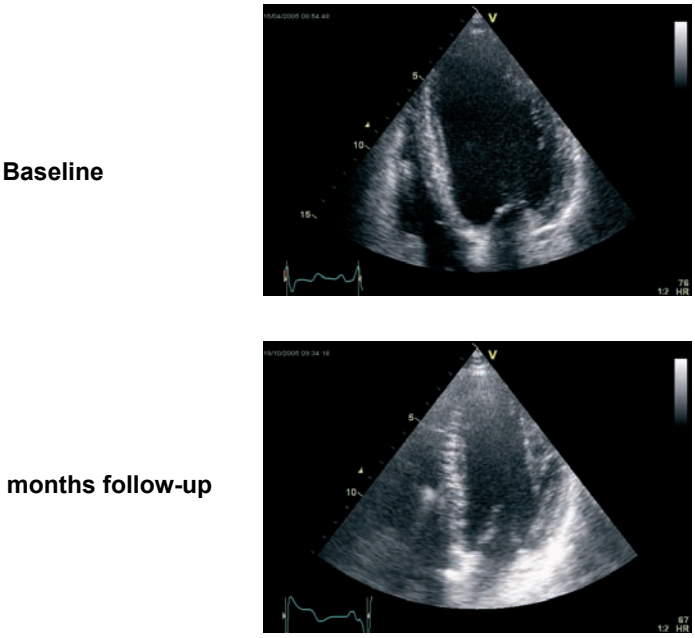

Figure 14: Echocardiographic demonstration of LV reverse remodeling after 6 months of CRT; the LV end-diastolic volume decreased from 237 ml to 118 ml.

improvement of stroke volume, symptoms and LV reverse remodeling. Several acute invasive studies have shown that LV dP/dt can be increased with 13%-34% during AV optimization [49-52]. Similar acute improvements have been documented in stroke volume during echocardiography-guided AV delay optimization [53]. However, the effect on exercise performance is unclear [54] and the effects on heart failure morbidity, hospitalizations and mortality have not been studied.

AV delay optimization can be performed by measuring LV diastolic filling time intervals and/or indices of LV systolic function.

The most frequently used echocardiographic method is the iterative method, which uses both transmitral pulsed-wave Doppler (to assess A wave truncation and the diastolic filling time) and aortic continuous wave Doppler (to assess the velocity time integral, VTI, as index of LV stroke volume). A long sensed AV delay (shorter than the intrinsic PR to ensure capture) is programmed (usually between 160 and 200 ms). This AV delay is shortened in steps of 20 ms until the A wave begins to truncate (visualized on the transmitral Doppler flow registration). Once A-wave truncation is noted, the AV delay is lengthened in steps of 20 ms until truncation no longer occurs. The optimal AV delay is characterized by the longest diastolic filling time or the highest aortic VTI. To obtain an optimal aortic VTI it is advised to use a fast sweep speed, a large velocity scale and a low filter. An example of the effect of changing the

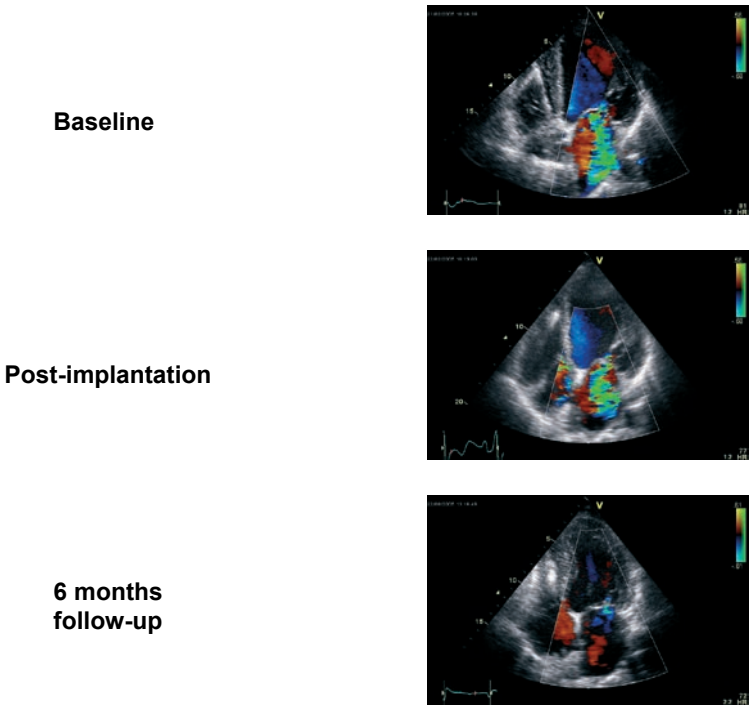

Figure 15: Patient with severe mitral regurgitation before CRT implantation. No significant change in severity of mitral regurgitation was observed immediately after CRT implantation. At 6 months follow-up however, a significant reduction in mitral regurgitation was observed, secondary to the LV reverse remodeling

AV delay on aortic VTI in a patient after CRT implantation is provided in (Figure 16). Since several measurements are needed and one has to wait at least 10 beats before recording the different flows during the different programmed AV delays, this method is time consuming.
A faster technique that only requires the mitral inflow has also been proposed. This mitral inflow technique was initially developed by Ritter for patients with complete heart block treated with dual chamber pacing [55,56]. It requires recordings of the mitral inflow by pulsed-wave Doppler at a long and a short AV delay. A long AV delay (AV long, for example 200 ms) results in premature mitral valve closure, prior to the paced QRS. The time interval "a" is measured from the termination of the mitral A wave to the onset of the paced QRS. A short AV delay (for example 60 ms) results in closure of the mitral valve due to onset of LV systolic contraction. The electromechanical delay, time interval "b", is measured from the onset of the paced QRS to the termination of the mitral A wave. The optimal AV delay is then calculated by the equation *AVlong – (b-a)*. Although attractive, this method has to be used cautiously in patients treated with CRT since loading conditions may significantly alter LV filling pressures. Also, in patients with elevated filling pressures (such as CRT patients), the mitral A wave may be severely attenuated or abbreviated which limits visualization of mitral A wave truncation.

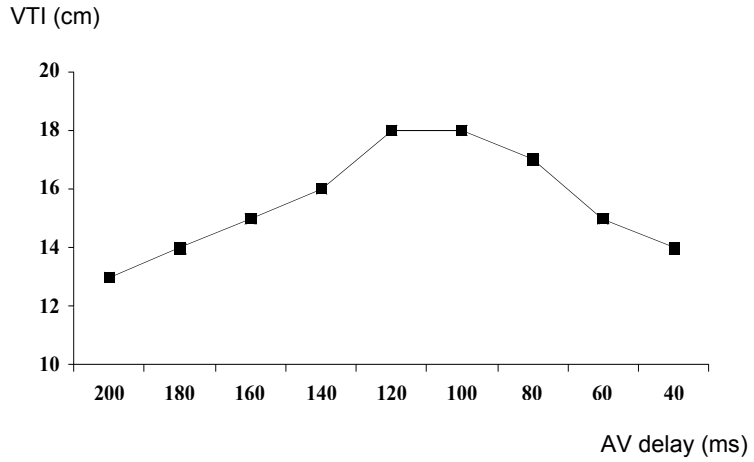

Figure 16: Example of the effect of changing the AV delay on aortic VTI in a patient after CRT implantation. The optimal AV delay is derived at 100-120 ms yielding the highest aortic VTI.

Because of the time-efforts and lack of proven clinical benefit, AV optimization is not routinely performed. Instead, a short AV delay (usually in the range of 100-120 ms) is often programmed and AV optimization is only performed in patients who do not respond to CRT. In addition, many questions are unresolved regarding AV optimization at the present time. For example the effect of body position (supine versus sitting) on the optimal AV delay is unknown. More importantly, it is largely unknown whether the AV delay should be shortened, kept constant or prolonged as heart rate increases during exercise in CRT patients. In previous multicenter trials the AV delay was programmed fixed or with dynamic shortening. However, Scharf et al [54] reported that the relatively short baseline AV delay should be prolonged and not shortened at increased heart rates to maintain stroke volume in CRT patients. If confirmed in future studies, this would imply that dynamic AV lengthening should become available in new CRT devices.

B. VV optimization

The aim of VV optimization is to select an "optimal" interventricular (VV) interval that further improves inter- and intraventricular dyssynchrony and thus mechanical efficiency or stroke volume. Acute invasive studies have shown that VV optimization resulted in a further improvement of dP/dt [51,52]. Sogaard et al. [31] showed in 20 patients that sequential VV activation resulted in a further reduction of delayed longitudinal contraction with a further increase of diastolic filling time, as compared to simultaneous biventricular activation. Accordingly Vanderheyden et al. [57] reported in 20 patients that VV optimization resulted in prolongation of LV filling time, reduction of inter- and in intra LV dyssynchrony, with an increase in stroke volume. Although these small studies appear to support VV optimization, larger studies on

the effects on exercise performance, heart failure morbidity/hospitalizations and mortality are not available yet.

Currently, consensus is lacking on which echocardiographic parameters should be measured during VV optimization. It seems logical however that both parameters of inter- and intra LV dyssynchrony as well as stroke volume should be evaluated.

Vanderheyden et al. [57] and Parreira et al. [58] used pulsed-wave TDI to assess inter- and intra LV dyssynchrony as well as the aortic VTI to assess stroke volume. In these studies VV optimization was performed by advancing the LV stimulus (left ventricle first) or the RV stimulus (right ventricle first) by 20 ms intervals up to 60 ms.

Leon et al. [59] evaluated the hemodynamic effects of VV optimization in 376 patients undergoing CRT implantation by measuring the aortic VTI for each VV interval. In 81% of patients optimization of the VV timing interval resulted in an increase in stroke volume, with a median increase of 8.6%. Of interest, in the majority of patients the highest aortic VTI was derived when the left ventricle was paced first [59], (Figure 17).

As with AV optimization, many questions are unresolved regarding VV optimization. There are virtually no published data on the effect of body position, exercise or outcome. Also, it is unclear whether AV optimization should proceed VV optimization or vice versa.

SUMMARY

The role of echocardiography in patients with CRT can be defined as follows.

First, echocardiography can optimize selection of CRT candidates by demonstration of LV dyssynchrony, and many echocardiographic techniques have been proposed. The extent of

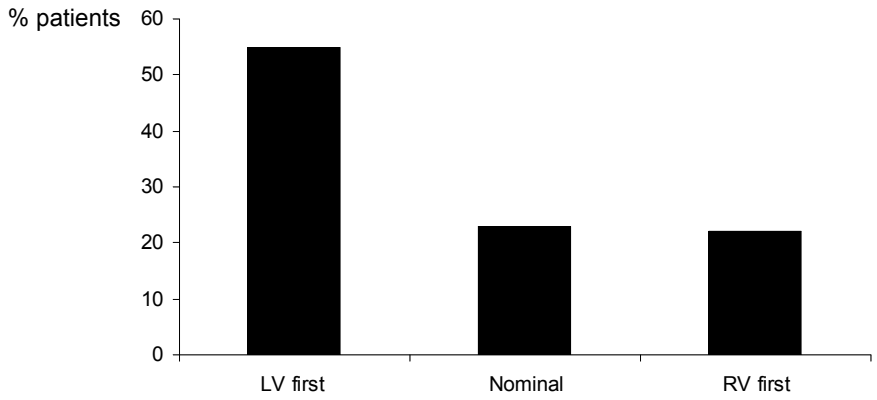

Figure 17: Optimal VV timing settings at pre-hospital discharge. In the majority of patients (55%) the aortic VTI was highest when the left ventricle was paced before the right ventricle. (Adapted from reference 59).

LV dyssynchrony that is mandatory for response to CRT is not yet defined, but may be derived from the PROSPECT trial [38].

Moreover, echocardiography can be used to assess immediate response to CRT including detection of acute LV resynchronization. Also, echocardiography is useful to evaluate long-term benefit from CRT (i.e. LV reverse remodeling).

Finally, echocardiography is important in optimization of pacemaker settings, including AV and VV optimization.

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Summary, Conclusions and Future perspectives

SUMMARY

The general introduction (**Chapter 1)** of this thesis provides a description of the rationale behind cardiac resynchronization therapy (CRT) and a general overview of the clinical results using CRT in patients with chronic heart failure. After the initial promising results in patients with drug-refractory heart failure in the late 1990's, the beneficial effects of CRT have now been clearly confirmed in large randomized trials which have currently included >4000 patients. The beneficial effects of CRT included an improvement in clinical symptoms (New York Heart Association (NYHA) class, quality-of-life and 6 minute walking distance) as well as an improvement in echocardiographic parameters (left ventricular (LV) ejection fraction, LV volumes and mitral regurgitation). In addition, the number of hospitalizations for decompensated heart failure and all-cause mortality were reduced after CRT in comparison to optimal medical therapy.

Based on these excellent results the use of CRT in patients with chronic heart failure is now considered a class I indication in both the ESC and the ACC/AHA/HRS guidelines. According to the guidelines, CRT is recommended in patients with moderate-to severe heart failure (NYHA class III-IV), impaired LV ejection fraction (<35%) and a widened QRS complex (>120 ms). However, in parallel to these impressive results, a consistent number of patients do not respond to CRT when the current selection criteria are applied. When response to CRT is defined using clinical parameters (e.g. improvement in NYHA class or quality-of life) the prevalence of non-responders is approximately 30% and when echocardiographic parameters (LV reverse remodeling, improvement in LV ejection fraction) are applied, the number of non-responders is usually around 40%.

The aim of the current thesis was improve the current selection criteria for CRT in order to reduce the number of non-responders. To achieve this goal the pathophysiological mechanisms underlying (non-) response to CRT were studied **(Parts I and II)** in order to develop more optimal CRT selection criteria **(Part III)**. In addition, introduction of new selection criteria may lead to the application of CRT in patient groups that are not eligible for CRT according to the established selection criteria **(Part IV)**.

Part I: Beneficial effects of CRT

In **Chapter 2** the response rate to CRT was evaluated in elderly patients (defined as ≥70 years of age) and compared to the results of CRT observed in younger patients (<70 years). A total of 170 consecutive patients was included based on established selection criteria for CRT (NYHA class III-IV, LV ejection fraction <35% and QRS duration >120 ms with LBBB). Mean patient age was 66±11 years and the study population comprised of 102 (60%) patients <70 years and 68 patients (40%) ≥70 years. Patients ≥70 years were more likely to have an ischemic cardiomyopathy (48% vs. 66%, P<0.05); all other baseline characteristics were comparable. In all patients, clinical and echocardiographic parameters improved significantly at 6 months fol-

low-up (e.g. NYHA class decreased from 3.2±0.4 to 2.2±0.7, P<0.001, and LV ejection fraction increased from 21±8% to 28±9%, P<0.001), associated with LV reverse remodeling. Improvements in clinical and echocardiographic parameters were comparable between patients <70 years and ≥70 years. The percentage of responders was also similar in both groups (75% versus 78%, ns). In addition, survival at 1 year after implantation was comparable in the patients <70 years and patients ≥70 years. CRT is thus equally effective in elderly patients in terms of improvement in clinical and echocardiographic parameters and 1-year mortality. Also, the percentage of individual responders to CRT is not different in elderly patients.
This study indicates that age does not influence response to CRT and demonstrates that CRT should also be considered in patients ≥70 years

The aim of **Chapter 3** was to evaluate whether a gender difference exists in the response rate to CRT. One-hundred seventy-three patients consecutive patients (NYHA class III-IV, LV ejection fraction ≤35%, QRS duration >120 ms with LBBB) were included. No differences in baseline characteristics were observed between men (n=137) and women (n=36) except that non-ischemic cardiomyopathy was more frequent in women (67% vs. 38%, P<0.05). At 6 months follow-up the magnitude of improvement in clinical and echocardiographic parameters was similar between women and men; e.g. the improvement in NYHA class was 0.9±0.6 in women and 1.0±0.7 in men (P=NS) and the increase in LV ejection fraction was 8±8% in women as compared to 7±9% in men (P=NS). The percentage of individual responders was not different between women and men (76% vs. 80%, P=NS) and 2-year survival was comparable for women and men (84% vs. 80%, P=NS).
In conclusion, no gender differences were observed in response to CRT and long-term survival after CRT.

In **Chapter 4** the precise relationship between improvement in clinical and echocardiographic parameters was evaluated. In recent studies a clear definition of response to CRT is lacking and both clinical and echocardiographic end-points are currently used. It is also unclear whether patients with clinical response also improve in echocardiographic end-points (and vice versa). One hundred forty-four consecutive patients (NYHA class III/IV, LV ejection fraction ≤35% and QRS duration ≥120 ms with LBBB) were included. At 3-6 months after CRT implantation clinical response (defined as improvement ≥1 NYHA class) and echocardiographic response (defined as a decrease >15% in LV end-systolic volume) occurred in 101 (70%) and 81 (56%) patients respectively. Clinical improvement without echocardiographic response was observed in 27 (19%) patients, whereas 7 (5%) patients showed no clinical response, in the presence of echocardiographic response. Accordingly, the disagreement between the 2 end-points was mainly related to patients who responded clinically without showing LV reverse remodeling. This observation may be explained by the presence of a placebo effect with respect to improvement in clinical symptoms following CRT, as already reported in double-blind randomized trials.

Thus, a good agreement (76%) between clinical and echocardiographic response from CRT was observed. Still, the echocardiographic response rate (56%) is somewhat lower than the clinical response rate (70%).

Part II: Mechanism of benefit from CRT

In **Chapter 5** the beneficial effects of CRT on the size of the right ventricle and on the severity of tricuspid regurgitation were evaluated. Both right ventricular (RV) size and function are known to be strong and independent predictors of prognosis in patients with heart failure and beneficial effects of CRT on the right ventricle may further explain the mechanism of benefit from CRT. Fifty-six consecutive patients (NYHA class III-IV, LV ejection fraction ≤35% and QRS duration >120 ms with LBBB) were included. At 6 months follow-up LV ejection fraction improved significantly from 19±6% to 26±8% (P<0.001) and LV end-diastolic volume decreased from 257±98 ml to 227±86 ml (P<0.001). In addition, RV annulus decreased significantly from 37±9 mm to 32±10 mm, RV short-axis from 29±11 mm to 26±7 mm, and RV long-axis from 89±11 mm to 82±10 mm (all P<0.001) with the largest decrease in the patients with the largest right ventricles at baseline. Interestingly, LV and RV reverse remodeling were only observed in patients with substantial LV dyssynchrony at baseline. Finally, significant reductions in severity of tricuspid regurgitation and pulmonary artery pressure were observed.
Thus, CRT results in significant reverse LV and RV remodeling after 6 months of CRT in patients with LV dyssynchrony. Moreover, CRT leads to a reduction of the severity of tricuspid regurgitation and a decrease in pulmonary artery pressure. Both findings may contribute to a better understanding of the beneficial mechanism of CRT.

In recent CRT studies a clear definition of response to CRT is lacking and both clinical and echocardiographic end-points (with arbitrary cut-off values) are currently used. The echocardiographic response rate is usually somewhat lower (60%) than the clinical response rate (70-80%) and in 24% there is a disagreement between clinical and echocardiographic response rate (see ***chapter 4***). The goal of **chapter 6** was to define the most clinically relevant definition of response to CRT. One hundred forty-one patients (NYHA class III-IV, LV ejection fraction <40% and QRS duration >120 ms) who received CRT were included and were followed for a mean period of 695±491 days. During the follow-up period there were 22 (15.6%) deaths, mostly due to heart failure or sudden cardiac death. ROC curve analysis revealed that a reduction in LV end-systolic volume ≥9.5% has a sensitivity of 70% and specificity of 70% in predicting all-cause mortality, and 87% and 69% respectively for cardiovascular mortality. With this cut-off value, there were 87 (61.7%) responders of reverse remodeling. In Kaplan-Meier survival analysis, responders has significantly lower all-cause morality (6.9% Vs 30.6%, Log-rank χ^2=13.26, p=0.0003), cardiovascular mortality (2.3% Vs 24.1%, Log-rank χ^2=17.1, p<0.0001), and heart failure events (11.5% Vs 33.3%, Log-rank χ^2=8.71, p=0.0032) than non-responders. Interestingly, improvements in clinical parameters were unable to predict any outcome event.

In conclusion, the strongest predictor of improved survival and reduction in heart failure events following CRT is a reduction of LV end-systolic volume >10% at 3-6 months follow-up and may thus be considered the most clinically relevant definition of response to CRT.

In **Chapter 7** a detailed invasive analysis of the hemodynamic consequences of CRT at mid-term follow-up was performed using pressure-volume loop analysis. Twenty-two patients scheduled for implantation of a CRT device (NYHA class III-IV, LV ejection fraction <35% and QRS duration >120ms with LBBB) were included. During diagnostic catheterization prior to CRT and at 6 months follow-up pressure-volume loop analysis during right atrial pacing at 80, 100, 120 and 140 beats/min was performed by conductance catheter. Using the pressure-volume loops it was demonstrated that previously reported acute improvements in LV function remain present at 6 months follow-up: dP/dt_{MAX} (+18%, $p<0.01$), dP/dt_{MIN} (+13%, $p<0.05$), SW (+34%, $p<0.05$). Effects of increased pacing rate were improved towards more physiological responses for LV ejection fraction, cardiac output and dP/dt_{MAX}. Moreover, the study shows improved ventricular-arterial coupling (+69%, $p<0.01$) and improved mechanical efficiency (+44%, $p<0.005$). Thus, acute hemodynamic improvements following CRT are maintained at mid-term-follow-up. In addition, ventricular-arterial coupling, mechanical efficiency, and chronotropic responses are improved after 6 months of CRT. These findings may help to explain the improved functional status and exercise tolerance in heart failure patients treated with CRT.

In **Chapter 8** the time course and the extent of LV resynchronization after CRT implantation and their relation with response to CRT were evaluated in 100 consecutive patients (NYHA class III-IV, LV ejection fraction ≤35% and QRS duration >120 ms) with evidence of pre-implantation LV dyssynchrony (≥65 ms, see ***chapter 12***) on color-coded tissue Doppler imaging (TDI). 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 ($P<0.001$ versus baseline and P=NS versus immediate post-implantation). At 6 months follow-up 85 patients were classified as responders to CRT (defined as >10% reduction in LV end-systolic volume (see ***chapter 6***). Thus, patient selection based on pre-implantation detection of LV dyssynchrony using TDI results in a superior echocardiographic response rate compared to selection based on the traditional CRT selection criteria (echocardiographic response rate around 60%). 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 failed to show a significant reduction in LV dyssynchrony (from 106±29 ms to 79±44 ms, P=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.
In conclusion, LV resynchronization following CRT is an acute phenomenon, and predicts response to CRT at 6 months follow-up.

Part III: Prediction of response to CRT

The presence of pre-implantation LV dyssynchrony seems mandatory for a positive response to CRT (see *chapters 8,12*). In the current selection criteria, QRS duration is used as a marker of LV dyssynchrony. However, recent studies indicate that QRS duration does not predict response to CRT. This issue is addressed in **chapter 9** in which the precise relationship between QRS duration and LV dyssynchrony on TDI was studied in 90 consecutive heart failure patients (NYHA class III-IV and LV ejection fraction <35%). Based on the QRS duration, 30 consecutive patients with a narrow QRS complex were included (QRS duration ≤120 ms), 30 patients with an intermediate QRS duration (120-150 ms), and 30 patients with a wide QRS complex (>150 ms). Severe LV dyssynchrony (>60 ms) was observed in 27% of patients with narrow QRS complex, in 60% of patients with intermediate QRS duration and in 70% of patients with wide QRS complex. No significant correlation existed between QRS duration and LV dyssynchrony (r=0.26, P=NS). In conclusion, 30-40% of heart failure patients with QRS duration >120 ms do not exhibit LV dyssynchrony, which may explain non-response to CRT. Alternatively, 27% of patients with heart failure and a narrow QRS complex has a significant LV dyssynchrony and may be candidates for CRT.

In **chapter 10** the prevalence of LV dyssynchrony was studied in 64 heart failure patients (NYHA class III-IV, LV ejection fraction <35%) with a narrow QRS complex (≤120 ms).Substantial LV dyssynchrony (defined as LV dyssynchrony >60 ms) was observed in 33% of these patients. No significant correlation was found between QRS duration and LV dyssynchrony (r=0.12, P=NS). No baseline clinical parameters were able to predict the presence of LV dyssynchrony in this patient group. Substantial inter-ventricular (LV- RV) dyssynchrony (>50 ms) was present in only 5% of the patients, suggesting that QRS duration is a marker of interventricular dyssynchrony rather than LV dyssynchrony.
In conclusion, substantial LV dyssynchrony is present in 33% of patients with heart failure and a narrow QRS complex which implies that CRT should also be considered in these patients.

The presence of pre-implantation LV dyssynchrony and consequent LV resynchronization by CRT are considered as the key mechanism of response to CRT (see *chapters 8,12*). Both M-mode echocardiography (using the septal-to-posterior wall motion delay, SPWMD) and color-coded TDI have been proposed for assessment of LV dyssynchrony and prediction of response to CRT. In **chapter 11** a head-to-head comparison between M-mode echocardiography and color-coded TDI was performed for assessment of LV dyssynchrony and prediction of response to CRT in 98 consecutive heart failure patients (NYHA class III-IV, LV ejection fraction ≤35% and QRS duration >120 ms) undergoing CRT implantation. Pre-implantation LV dyssynchrony assessment using M-mode echocardiography was not feasible in 41% of patients due to akinesia of the septal and/or posterior walls or poor acoustic windows. Conversely, with LV dyssynchrony could be assessed in 96% of patients using TDI. At 6 months follow-up, 75

patients (77%) were classified as responders to CRT (defined as improvement ≥1 NYHA class). The sensitivity and specificity of M-mode echocardiography to predict response to CRT were substantially lower as compared to TDI assessment of LV dyssynchrony (66% vs. 90%, P<0.05 and 50% vs. 82%, P= NS respectively).
Thus, LV dyssynchrony assessment was only feasible in 59% of patients with M-mode echocardiography as compared to 96% (P< 0.05) when color-coded TDI was used. In addition, color-coded TDI was superior over M-mode echocardiography for prediction of response to CRT.

In **chapter 12** response to CRT was predicted by the presence of LV dyssynchrony assessed by color-coded TDI. Moreover, the prognostic value of LV dyssynchrony in patients undergoing CRT was assessed. Eighty-five consecutive heart failure patients (NYHA class III-IV, LV ejection fraction ≤35% and QRS duration ≥120 ms with LBBB) were evaluated by TDI before CRT. None of the baseline characteristics (including all current selection criteria; NYHA class, LV ejection fraction and QRS duration) were different between clinical responders (74%) and clinical non-responders (26%), except for a larger LV dyssynchrony on TDI in responders (87±49 ms versus 35±20 ms, P<0.01). Patients with no or minimal dyssynchrony (<40 ms) had a low likelihood of improvement in clinical parameters and reverse remodeling, whereas patients with extensive dyssynchrony (≥80 ms) had a high likelihood of response. Using a cutoff value of 65 ms for LV dyssynchrony, a sensitivity of 81% and specificity of 81% to predict response to CRT, were obtained. Patients with dyssynchrony ≥65 ms had an excellent prognosis (6% event-rate) after CRT, as compared to a 50% event-rate in patients with dyssynchrony <65 ms (P<0.001).
Thus, none of baseline characteristics (including the current selection criteria) are able to predict response to CRT. In contrast, LV dyssynchrony ≥65 ms on TDI is highly predictive for response to CRT. In addition, patients with LV dyssynchrony ≥65 ms have an excellent prognosis after CRT.

In **Chapter 13** the effects of scar tissue in the postero-lateral LV segments (the area were the LV pacing lead is usually located) were evaluated in 40 consecutive heart failure patients (NYHA class III-IV, LV ejection fraction ≤35%, QRS duration >120 ms and LBBB) with an ischemic cardiomyopathy undergoing CRT implantation. The localization and transmurality of scar tissue was evaluated with contrast-enhanced MRI. Fourteen patients (35%) had a transmural (>50% of LV wall thickness) postero-lateral scar. In contrast to patients without postero-lateral scar tissue, these patients showed a low response rate (14% vs. 81%, P<0.05) and did not improve in clinical or echocardiographic parameters. In addition, LV dyssynchrony remained unchanged after CRT implantation (84±46 ms vs. 78±41 ms, P=NS). In contrast, patients without postero-lateral scar tissue ***and*** severe baseline dyssynchrony (≥65 ms) showed an excellent response rate of 95%, compared to patients with a postero-lateral scar and/or absent LV dyssynchrony (11%).

In conclusion, CRT is unable to reduce LV dyssynchrony in patients with transmural scar tissue in the postero-lateral LV segments, resulting in clinical and echocardiographic non-response to CRT.

Part IV: Emerging indications

In ***chapters 9 and 10*** it was demonstrated that approximately one third of heart failure patients with a narrow QRS complex (who are currently not eligible for CRT) exhibits substantial LV dyssynchrony thereby suggesting that these patients may also benefit from CRT. Accordingly, in **chapter 14** the effects of CRT were evaluated in heart failure patients with narrow QRS complex (<120 ms) and evidence of left ventricular (LV) dyssynchrony on TDI. Thirty-three consecutive patients with narrow QRS complex and 33 consecutive patients with wide QRS complex (control group) were prospectively included. All patients needed to have LV dyssynchrony ≥65 ms on TDI, New York Heart Association (NYHA) class III-IV heart failure and LV ejection fraction ≤35%. Baseline characteristics, particularly LV dyssynchrony, were comparable between patients with narrow and wide QRS complex (mean QRS duration 110±8 ms versus 175±22 ms). No significant relationship was observed between baseline QRS duration and LV dyssynchrony in all patients (r=0.21, P=NS). The improvement in clinical symptoms and the extent of LV reverse remodeling was comparable between patients with narrow and wide QRS complex (mean NYHA class reduction 0.9±0.6 versus 1.1±0.6, P=NS and mean LV end-systolic volume reduction 39±34 ml versus 44±46 ml, P=NS).
Thus, CRT appears to be beneficial in patients with narrow QRS complex (<120 ms) and severe LV dyssynchrony on TDI, with similar improvement in symptoms and comparable LV reverse remodeling to patients with wide QRS complex.

In **Chapter 15** the effects of CRT were evaluated in patients with mildly symptomatic heart failure (NYHA class II), who are also not eligible for CRT according to the current CRT selection criteria. Fifty consecutive patients with NYHA class II heart failure and 50 consecutive NYHA class III/IV patients (control group) were prospectively included. All patients had LV ejection fraction ≤35% and QRS duration >120 ms. The severity of baseline LV dyssynchrony was not different between patients in NYHA class II as compared to NYHA class III/IV patients and CRT resulted in a similar degree of LV resynchronization. The magnitude of improvement in clinical parameters was significantly less in the NYHA class II patients (e.g. NYHA class improved by 0.3±0.6 vs. 1.0±0.8, respectively, P<0.05), however patients without change in NYHA class (56%) still improved significantly in LV ejection fraction and LV volumes. The overall improvement in LV ejection fraction (7±11% vs. 7±7%, respectively, P=NS) and the decrease in LV volumes was comparable between NYHA class II patients and the control group.
In conclusion, CRT has comparable effects in patients with NYHA class II and NYHA class III/IV heart failure in terms of LV resynchronization, improvement in LV ejection fraction and LV reverse remodeling.

Part V: Optimal use of echocardiography in cardiac resynchronization therapy

Chapter 16 provides an integration of the data from *Chapters 2-15* and gives an overview of the optimal use of echocardiography in the care of patients undergoing CRT implantation, both before implantation (LV dyssynchrony detection), as well as after implantation (follow-up, optimization of pacemaker settings). A summary of **chapter 16** will be given in the following section "conclusions and future perspectives".

CONCLUSIONS AND FUTURE PERSPECTIVES

Despite the impressive results of CRT in large randomized trials, a consistent number of patients fails to improve following CRT when the established selection criteria (NYHA class III-IV, LV ejection fraction <35% and QRS duration >120 ms) are applied. A reduction in end-systolic volume >10% after 3-6 months of CRT recently proved to be the best predictor of improved long-term survival following CRT and therefore provides the most clinical meaningful definition of response to CRT. According to this definition 40% of patients do not respond to CRT. When response to CRT is defined using clinical parameters (e.g. improvement in NYHA class or quality-of life) the prevalence of non-responders usually around 30%.

Recent studies, addressing the issue of non-response to CRT have indicated that none of the baseline patient characteristics, (including the current selection criteria: QRS duration, NYHA class and LV ejection fraction) are able to predict a positive response to CRT, thereby highlighting the need for improvement of the current selection criteria. In the search for better selection criteria it has now been clearly demonstrated that the key mechanism of benefit from CRT is the presence of baseline LV dyssynchrony and its subsequent reduction following CRT implantation. In contrast, the presence inter-ventricular dyssynchrony appears of less importance.

Detection of LV dyssynchrony

Traditionally, QRS duration has been used as an (indirect) marker of LV dyssynchrony, but this parameter recently proved to be a poor marker of LV dyssynchrony, thereby explaining its low predictive value for response to CRT.

Since these observations, several cardiac imaging techniques have been tested for their ability to detect and quantify LV dyssynchrony. Among the different techniques, echocardiography proved particularly well suited for detection of LV dyssynchrony in the clinical setting. Most experience has been obtained with color-coded TDI, which proved highly predictive for both clinical response and prognosis after CRT implantation. In addition, various other echocardiographic techniques have been introduced ranging from simple M-mode echocardiography to more sophisticated echocardiographic techniques, such as strain (rate) imaging and recently 3D-echocardiography. At present, no consensus exists on which technique is optimal

for prediction of response to CRT, and the large number of different echocardiographic techniques that have been published (without direct comparisons between techniques) further contribute to the confusion on the optimal technique. Moreover, the different techniques employ varying numbers of segments to determine LV dyssynchrony (ranging from 2 to 16 segments) and different cut-off values to define substantial LV dyssynchrony (ranging from 65 ms to 130 ms). Consequently, larger multi-center studies, directly comparing different echocardiographic techniques, are needed to identify the optimal technique, with the optimal number of segments and the optimal extent of LV dyssynchrony to predict response to CRT. The prospective, multi-center PROSPECT-trial is specifically designed to answer some of these questions and the results are expected in 2007. However, although the relative merits and the precise cut-off values of all these different techniques for prediction of response to CRT remain to be defined, it has now been convincingly proven that patient selection based on echocardiographic detection of LV dyssynchrony is superior compared to patient selection based on the current selection criteria. It is therefore anticipated that echocardiographic detection of LV dyssynchrony will be included in future ACC/AHA/ESC guidelines.

Novel indications

Despite the fact that current guidelines only recommend the use of CRT in patients with NYHA class III-IV, LV ejection fraction <35% and QRS duration >120 ms it is expected that novel indications for CRT will be validated in the near future. In particular, recent small studies have demonstrated that CRT may be effective in the following three patient categories that are outside the established selection criteria; 1] heart failure patients with narrow QRS complex (<120 ms) and echocardiographic evidence of LV dyssynchrony (main goal: improvement of clinical symptoms / LV function and LV reverse remodeling), 2] patients with mildly symptomatic heart failure (NYHA class I-II) and impaired LV function (main goal: improvement in LV function, LV reverse remodeling and prevention of heart failure progression) and 3] patients with RV pacing induced LV dyssynchrony and (minimally) impaired LV function (main goal: prevention of heart failure progression) .

Scar tissue and LV lead positioning

Finally, recent data highlighted the importance of other issues related to response to CRT. In particular, the localization of the LV pacing lead in the area of latest LV activation appears to result in the highest benefit from CRT. Various echocardiographic techniques are currently available to assess the area of latest LV activation (including triplane tissue synchronization imaging and real-time 3D echocardiography), but more evidence is needed before recommendations can be made. In addition, assessment of scar tissue in the LV pacing area is important; large areas of scar tissue in the left ventricle appear to reduce benefit of CRT. In addition, it was recently demonstrated that CRT is unable to reduce LV dyssynchrony in the presence of scar tissue in the postero-lateral LV segments, resulting in non-response to CRT.

It may thus be considered to include pre-implantation assessment of scar tissue by contrast-enhanced MRI.

Conclusion

In conclusion, in the current field of CRT research there is clear need for large multi-center (randomized) trials to confirm the findings of recent small single-center studies in particular addressing the following topics; 1] The definition of the optimal echocardiographic method to detect LV dyssynchrony 2] Validation of novel CRT indications (narrow QRS complex, NYHA class I-II and RV pacing induced LV dyssynchrony) and 3] Evaluation of the influence of LV scar tissue and LV lead positioning.

Awaiting the results of these trials it is anticipated that in the near future the current patient selection criteria will be extended with the presence of substantial LV dyssynchrony (spontaneous or RV pacing induced and irrespective of QRS duration).

Samenvatting, Conclusies en Toekomstperspectief

SAMENVATTING

De introductie van dit proefschrift (**Hoofdstuk 1)** geeft een overzicht van het werkingsmechanisme van cardiale resynchronisatie therapie (CRT) en beschrijft de klinische resultaten van CRT die zijn beschreven bij patiënten met chronisch hartfalen.
Na de veelbelovende eerste resultaten in de tweede helft van de 90'er jaren van de vorige eeuw, zijn de positieve effecten van CRT nu ook overtuigend bewezen in grote gerandomiseerde studies die inmiddels meer dan 4000 patiënten hebben geïncludeerd. De positieve effecten van CRT zijn onder meer een verbetering in klinische symptomen (zoals NYHA functionele klasse, kwaliteit van leven en 6-minutenloopafstand) en een verbetering in echocardiographische parameters (Linker ventrikel (LV) ejectiefractie, LV volumina en mitralisklep insufficiëntie). Bovendien leidde CRT tot een afname van het aantal opnames voor gedecompenseerd hartfalen en een afname van de mortaliteit in vergelijking met patiënten die alleen werden behandeld met optimale farmacologische therapie.
Naar aanleiding van deze indrukwekkende resultaten wordt CRT op dit moment, zowel in de Europese (ESC) als in Amerikaanse richtlijnen (ACC/AHA/HRS) beschouwd als een klasse I indicatie in patiënten met chronisch hartfalen.
In deze richtlijnen wordt CRT aanbevolen bij patiënten met (matig-) ernstig hartfalen (NYHA klasse III-IV), een verminderde LV ejectie fractie (<35%) en een verbreed QRS complex (>120 ms). Echter, naast deze indrukwekkende resultaten bleek er ook een groep patiënten te zijn die niet verbeterde na CRT, ondanks selectie volgens de huidige richtlijnen (de zogenaamde non-responders).
Wanneer non-response na CRT wordt gedefinieerd als de afwezigheid van een verbetering in klinische symptomen (bijv. verbetering in NYHA klasse of kwaliteit van leven) dan is het percentage non-responders ongeveer 30% en wanneer non-response wordt gedefinieerd met behulp van echocardiographische parameters (LV reverse remodeling of verbetering in LV ejectiefractie) dan ligt het percentage non-responders rond de 40%.
Het doel van dit proefschrift was om de huidige CRT selectiecriteria zo te verbeteren dat het aantal non-responders na CRT vermindert. Om dit doel te bereiken werd het pathophysiologische mechanisme van (non-) response na CRT bestudeerd **(Deel I en II)** om zo meer optimale selectiecriteria te ontwikkelen **(Deel III)**. Bovendien werd naar aanleiding van de nieuw ontwikkelde selectiecriteria het gebruik van CRT ook getest in patiënten die volgens de huidige criteria geen indicatie voor CRT hebben **(Deel IV).**

Deel I: Positieve effecten van CRT

In **Hoofdstuk 2** werd het percentage responders na CRT vergeleken tussen oudere (gedefinieerd als ≥70 jaar) en jongere patiënten (<70 jaar). 170 opeenvolgende patiënten werden geïncludeerd op basis van de huidige CRT selectiecriteria (NYHA klasse III-IV, LV ejectiefractie <35% en een QRS duur van >120 ms (met linker bundeltakblok patroon)). De gemiddelde

leeftijd van de patiënten was 66±11 jaar, waarbij 102 (60%) patiënten < 70 jaar oud was. Patiënten ≥70 jaar hadden vaker een ischemische cardiomyopathie als oorzaak van hartfalen (48% vs. 66%, P<0.05); alle andere patiënten karakteristieken voor implantatie waren gelijk. Na 6 maanden follow-up werd er in de gehele patiëntengroep een significante verbetering gezien in zowel de klinische als de echocardiographische parameters (bijv. de NYHA klasse nam af van 3.2±0.4 naar 2.2±0.7, P<0.001, de LV ejectiefractie nam toe van 21±8% naar 28±9%, P<0.001, en er was sprake van een significante LV reverse remodeling). De mate van verbetering in klinische en echocardiographische parameters was vergelijkbaar in de patiënten < 70 jaar en ≥70 jaar. Tevens was het percentage responders gelijk in beide groepen (75% vs. 78%, P=NS). Verder was de 1-jaarsoverleving vergelijkbaar in de patiënten < 70 jaar en ≥70 jaar. CRT heeft dus vergelijkbare positieve effecten in oudere patiënten en jongere patiënten wat betreft verbetering in klinische en echocardiographische parameters en 1-jaarsoverleving. Ook is het percentage responders in oudere patiënten niet verschillend van het percentage in jongere patiënten.
Deze studie geeft aan dat de leeftijd van de patiënt geen invloed heeft op de mate van response na CRT en dat CRT dus ook overwogen dient te worden in oudere patiënten.
Het doel van **Hoofdstuk 3** was om het effect van het geslacht van de patiënt op de mate van response na CRT te evalueren. 173 opeenvolgende patiënten (NYHA klasse III-IV, LV ejectiefractie ≤35% en een QRS duur >120 ms (met linkerbundeltakblok patroon) werden geïncludeerd. Er waren geen verschillen in de pre-implantatie patiënten karakteristieken tussen mannen (n=137) en vrouwen (n=36), behalve dat vrouwen meer frequent een non-ischemische oorzaak van het hartfalen hadden (67% vs. 38%, P<0.05). Na 6 maanden follow-up was de mate van verbetering in klinische en echocardiographische parameters vergelijkbaar tussen beide groepen; bijv. de verbetering in NYHA klasse was 0.9±0.6 in vrouwen en 1.0±0.7 in mannen (P=NS) en de toename in LV ejectiefractie was 8±8% in vrouwen vergeleken met een toename van 7±9% in mannen (P=NS). Het percentage van individuele responders was niet verschillend tussen mannen en vrouwen (76% vs. 80%, P=NS) en de 2-jaars overleving was vergelijkbaar in beide groepen (84% vs. 80%, P=NS).
Concluderend, laat deze studie zien dat er geen verschillen zijn in het percentage responders en de overleving na CRT tussen mannen en vrouwen.

In **Hoofdstuk 4** werd de precieze relatie tussen de verbetering in klinische en echocardiographische parameters onderzocht. In recente studies werd er geen vaste definitie van response gehanteerd en zowel klinische als echocardiographische eindpunten worden op dit moment gebruikt. Het is onduidelijk of patiënten met een klinische verbetering na CRT ook verbeteren in echocardiographische eindpunten (en vice versa). 144 opeenvolgende patiënten (NYHA klasse III-IV, LV ejectie fractie ≤35% en een QRS duur van ≥120 ms (met linkerbundeltakblok patroon) werden geïncludeerd. 3-6 maanden na CRT implantatie werd een klinische response (verbetering ≥1 NYHA klasse) waargenomen in 101 (70%) patiënten en een echocardiographi-

sche response (afname van het eind-systolische volume >15%) vond plaats in 81 (56%) patiënten. Klinische response zonder echo response vond plaats in 27 (19%) patiënten, terwijl 7 (5%) patiënten verbeterden in echocardiographische parameters zonder verbetering in klinische symptomen. De afwezigheid van overeenstemming tussen beide eindpunten in 24% van de patiënten werd dus voornamelijk veroorzaakt door patiënten met een verbetering in klinische symptomen, zonder een verbetering in echocardiographische parameters. Deze observatie kan worden verklaard door de aanwezigheid van een placebo effect in relatie tot de klinische verbetering na CRT, iets wat in eerdere gerandomiseerde studies reeds beschreven is.
Samenvattend, is er een goede relatie (76%) tussen klinische en echocardiographische response na CRT. Toch wordt echocardiographische response na CRT (56%) minder frequent gezien dan klinische response (70%).

Deel II: Werkingsmechanisme van CRT

In **Hoofdstuk 5** werden de effecten van CRT op de grootte van de rechter ventrikel en de ernst van de tricuspidalisklep insufficiëntie bestudeerd. Het is bekend dat zowel de grootte als de functie van de rechter ventrikel belangrijke en onafhankelijke voorspellers zijn van prognose in patiënten met hartfalen. Eventuele positieve effecten van CRT op de rechterventrikel kunnen daarom een verdere verklaring geven van het werkingsmechanisme van CRT. 56 opeenvolgende patiënten (NYHA klasse III-IV, LV ejectiefractie ≤35% en een QRS duur > 120 ms (met linkerbundeltakblok patroon) werden geïncludeerd. Na 6 maanden van CRT verbeterde de LV ejectiefractie van 19±6% naar 26±8% (P<0.001) en het LV eind-diastolische volume nam af van 257±98 ml naar 227±86 ml (P<0.001). Verder nam de diameter van de tricuspidalisklep-annulus significant af van 37±9 mm naar 32±10 mm, de korte-as diameter van de rechter ventrikel nam af van 29±11 mm tot 26±7 mm, en de lange-as diameter van de rechter ventrikel nam af van 89±11 mm naar 82±10 mm (alle metingen P<0.001), waarbij de grootste afname werd gezien in patiënten met de grootste rechter ventrikels voor implantatie. Een interessante observatie was het feit dat de afname van de linker-en rechter ventrikelgrootte alleen werd gezien in patiënten met een substantiële LV dyssynchronie voor de implantatie. Tenslotte was er een significante afname in de ernst van de tricuspidalisinsufficentie en in de pulmonaaldrukken.
Concluderend, leidt CRT tot een significante afname van de linker-en rechter ventrikelgrootte. Bovendien leidt CRT tot een afname van de ernst van de tricuspidalisinsufficentie en de druk in de pulmonaal arterie. Deze bevindingen kunnen een bijdrage leveren aan de verdere ontrafeling van het werkingsmechanisme van CRT.

In recente CRT studies ontbreekt een duidelijk omschreven definitie van response en zowel klinische als echocardiographische eindpunten (met arbitraire afkapwaarden) worden gebruikt. Het aantal echocardiographische responders is normaalgesproken lager (rond de 60%) dan het aantal klinische responders (70-80%) en bij 24% van de patiënten is er geen over-

eenstemming tussen klinische en echocardiographische response. (zie ***Hoofdstuk 4***) Het doel van **Hoofdstuk 6** was om de klinisch meest relevante definitie van response te definiëren. 144 patiënten (NYHA klasse III-IV, LV ejectiefractie <40% en QRS duur >120 ms) die een CRT implantatie ondergingen werden geïncludeerd en werden gevolgd voor een gemiddelde periode van 695±491 dagen. Gedurende deze periode overleden er 22 (15.6%) patiënten, voornamelijk als gevolg van progressief hartfalen en plotse hartdood. ROC curve analyse toonde aan dat een afname van ≥9.5% in het LV eind-systolische volume een sensitiviteit van 70% en een specificiteit van 70% had voor het voorspellen van de totale mortaliteit, en 87% en 69% respectievelijk voor het voorspellen van cardiovasculaire mortaliteit. Met deze afkapwaarde werd response gezien in 87 (61.7%) patiënten. In de Kaplan-Meier overlevings analyse hadden de responders een significant lagere totale mortaliteit (6.9% versus 30.6%, Log-rank χ^2=13.26, p=0.0003), cardiovasculaire mortaliteit (2.3% versus 24.1%, Log-rank χ^2=17.1, p<0.0001), and hartfalen "events" (11.5% versus 33.3%, Log-rank χ^2=8.71, p=0.0032) vergeleken met de non-responders. In tegenstelling tot verbeteringen in LV volumina waren verbeteringen in klinische parameters als gevolg van CRT niet in staat om de prognose na CRT te voorspellen.
Samenvattend, bleek een afname van 10% in het LV eind-systolische volume na 3-6 maanden van CRT de beste voorspeller voor een verbeterde overleving te zijn. Deze parameter kan daardoor als de klinisch meest relevante definitie van response na CRT worden beschouwd.

In **Hoofdstuk 7** is een gedetailleerde invasieve studie uitgevoerd naar de hemodynamische effecten van CRT met behulp van druk-volume curve analyse. 22 patiënten (NYHA klasse III-IV, LV ejectiefractie <35% en QRS duur >120 ms (met linkerbundeltakblok patroon) werden geïncludeerd. Voor CRT implantatie en na 6 maanden follow-up werd tijdens diagnostische hartcatherisatie een druk-volume curve analyse (d.m.v. een conductie-cathether) verricht tijdens rechts atriaal pacen met frequenties van 80, 100, 120 en 140 slagen/minuut. Met behulp van de druk-volume curves werd aangetoond dat eerder beschreven acute verbeteringen in LV functie ook na 6 maanden nog aanwezig zijn: dP/dt_{MAX} (+18%, p<0.01), dP/dt_{MIN} (+13%, p<0.05), SW (+34%, p<0.05). De effecten van een CRT leidden tot een meer fysiologische reactie op de verhoging van de hartfrequentie, wat betreft LV ejectiefractie, cardiac output en dP/dt_{MAX}. Bovendien liet deze studie een verbeterde ventriculaire-arteriële koppeling zien (+69%, p<0.01) en een verbeterde mechanische efficiëntie (+44%, p<0.005).
Samenvattend, blijven de acute hemodynamische effecten van CRT behouden na 6 maanden follow-up. Tevens is er een verbetering in de ventriculaire arteriële koppeling, mechanische efficiëntie en chronotrope response na 6 maanden van CRT. Deze bevindingen kunnen de positieve effecten van CRT verder verklaren.

In **Hoofdstuk 8** werden het tijdsbeloop en de mate van LV resynchronisatie na CRT implantatie en hun relatie met response na CRT bestudeerd in 100 opeenvolgende patiënten (NYHA klasse III-IV, LV ejectiefractie ≤35% QRS duur >120 ms). Alleen patiënten met echocardio-

graphisch bewijs van LV dyssynchronie (≥65 ms, zie ***Hoofdstuk 12***) op color-coded tissue Doppler imaging (TDI) werden geïncludeerd. Meteen na CRT implantatie was er een afname van LV dyssynchronie van 114±36 ms naar 40±33 ms (P<0.001), welke onveranderd bleef na 6 maanden (35±31 ms (P<0.001 vs. voor implantatie en P=NS vs. meteen na implantatie). Na 6 maanden follow-up werden 85 patiënten geclassificeerd als responders (gedefinieerd als een >10% afname in LV eind-systolisch volume (zie ***Hoofdstuk 6***). Patiëntenselectie gebaseerd op de aanwezigheid van echocardiographische LV dyssynchronie m.b.v. TDI voor CRT implantatie is dus superieur vergeleken met selectie volgens de traditionele selectie criteria (met een echocardiographische response rond de 60%). Meteen na implantatie vertoonden de responders een significante afname van de LV dyssynchronie van 115±37 ms naar 32±23 ms (P<0.001). De non-responders, aan de andere kant, lieten geen significante afname van de LV dyssynchronie na implantatie zien (van 106±29 ms naar 79±44 ms, P=NS). Onder de patiënten met <20% acute reductie in LV dyssynchronie waren er geen patiënten met een echocardiographische response na 6 maanden. Patiënten met een ≥20% acute reductie in LV dyssynchronie daarentegen hadden een 93% response percentage.
Concluderend, is LV resynchronisatie na CRT een acuut fenomeen, en de aan/afwezigheid van acute LV resynchronisatie is een voorspeller van response na 6 maanden van CRT.

Deel III: Voorspellen van response na CRT

De aanwezigheid van LV dyssynchronie voor implantatie lijkt noodzakelijk voor een positief effect van CRT (zie ***Hoofdstukken 8,12***).
In de huidige selectiecriteria wordt de duur van het QRS complex gebruikt als maat voor de mate van LV dyssynchronie. Recente studies hebben echter laten zien dat de duur van het QRS complex niet voorspeld wie er gaat verbeteren na CRT implantatie. Dit onderwerp wordt behandeld in **Hoofdstuk 9**, waarin de relatie tussen de duur van het QRS complex en de mate van LV dyssynchronie worden onderzocht in 90 opeenvolgende patiënten met hartfalen, (NYHA klasse III-IV en LV ejectiefractie <35%). Patiënten werden geïncludeerd in 3 groepen gebaseerd op de duur van het QRS complex: 30 patiënten met een smal QRS complex (≤120 ms), 30 patiënten met een matig-ernstige QRS complex verbreding (120-150 ms) en 30 patiënten met een sterk verbreed QRS complex (>150). LV dyssynchronie werd gezien in 27% van de patiënten met een smal QRS complex, in 60% van de patiënten met een matig-ernstige QRS verbreding en in 70% van de patiënten met een sterk verbreed QRS complex. Er was geen significante correlatie tussen de duur van het QRS complex en de mate van LV dyssynchronie. (r=0.26, P=NS).
Samenvattend, was er bij 30-40% van de patiënten met hartfalen en een QRS complex van >120 ms geen sprake van LV dyssynchronie, hetgeen non-response na CRT in deze patiëntengroep kan verklaren. Verder, vertoont 27% van de patiënten met een smal QRS complex LV dyssynchronie, hetgeen aangeeft dat deze patiënten ook baat zouden kunnen hebben bij CRT.

In **Hoofdstuk 10** werd de prevalentie van LV dyssynchronie bestudeerd in 64 patiënten met hartfalen (NYHA klasse III-IV, LV ejectiefractie <35%) en een smal QRS complex (≤120 ms). Substantiële LV dyssynchronie (gedefinieerd als LV dyssynchronie >60 ms) was Aanwezig in 33% van de patiënten. Geen significante correlatie werd gezien tussen de duur van het QRS complex en de mate van LV dyssynchronie (r=0.12, P=NS). Geen van de patiënten karakteristieken voor implantatie was in staat om de aanwezigheid van LV dyssynchronie te voorspellen. Substantiële inter-ventriculaire dyssynchronie (tussen linker-en rechter ventrikel, >50 ms) was aanwezig in slechts 5% van de patiënten, hetgeen suggereert dat de duur van het QRS complex meer een afspiegeling is van inter-ventriculaire dyssynchronie dan van LV dyssynchronie.
Concluderend, is LV dyssynchronie aanwezig in 33% van de patiënten met hartfalen en een smal QRS complex. Deze bevinding geeft aan dat CRT ook zou kunnen worden overwogen in patiënten met een smal QRS complex.

De aanwezigheid van LV dyssynchronie voor implantatie en de daaropvolgende afname na CRT implantatie wordt beschouwd als het sleutelmechanisme van verbetering na CRT (zie ***Hoofdstukken 8,12***). Zowel M-mode echocardiographie (met behulp van de septal-to-posterior wall motion delay, SPWMD) en color-coded TDI worden op dit moment gebruikt voor de bepaling van LV dyssynchronie om zo patiënten met een hoge kans op response te selecteren. In **Hoofdstuk 11** wordt een directe vergelijking uitgevoerd tussen M-mode echocardiographie en color-coded TDI. Beide technieken worden vergeleken voor hun vermogen om LV dyssynchronie te detecteren en response na CRT te voorspellen in 98 opeenvolgende patiënten met hartfalen (NYHA klasse III-IV, LV ejectiefractie ≤35% en QRS duur >120 ms). Het bepalen van LV dyssynchronie voor implantatie met behulp van M-mode echocardiographie was niet mogelijk in 41% als gevolg van akinesie van het septum of de posterior wand of door een slecht acoustisch venster. LV dyssynchronie detectie met behulp van TDI daarentegen was mogelijk in 96% van de patiënten. Na 6 maanden follow-up werden 75 patienten (77%) geclassificeerd als responders (gedefinieerd als een verbetering ≥1 NYHA klasse). De sensitiviteit en specificiteit van M-mode echocardiographie om response na CRT te voorspellen waren substantieel lager vergeleken met TDI. (66% versus 90%, P<0.05 en 50% versus 82%, P= NS, respectievelijk).
Samenvattend, was LV dyssynchronie detectie met behulp van M-mode echocardiographie slechts mogelijk in 59% van de patiënten, terwijl met TDI dit percentage 96% was (P< 0.05). Bovendien was de voorspellende waarde van TDI voor response na CRT superieur vergeleken met M-mode echocardiographie.

In **Hoofdstuk 12** werd color-coded TDI gebruikt om LV dyssynchronie te detecteren met als doel om patiënten met een hoge kans op verbetering na CRT te identificeren. Bovendien werd de prognostische waarde van LV dyssynchronie in patiënten die een CRT implantatie

ondergingen bestudeerd. 85 opeenvolgende patiënten met hartfalen (NYHA klasse III-IV, LV ejectiefractie ≤35% en een QRS duur ≥120 ms (met linkerbundeltakblok patroon) werden onderzocht met TDI voor CRT implantatie. Geen van de patiënten karakteristieken voor de implantatie (inclusief alle huidige CRT selectiecriteria: NYHA klasse, LV ejectiefractie en QRS duur) waren verschillend tussen de klinische responders (74%) en klinische non-responders (26%). De enige pre-implantatie parameter die de responders van de non-responders onderscheidde was de mate van LV dyssynchronie op TDI (87±49 ms vs. 35±20 ms, P<0.01). Patiënten zonder of met minimale LV dyssynchronie (<40 ms) hadden een lage kans op verbetering in klinische parameters en LV reverse remodeling, terwijl patiënten met een forse LV dyssynchronie (≥80 ms) een hoge kans op response hadden. Met een afkapwaarde van 65 ms had de LV dyssynchronie een sensitiviteit van 81% en een specificiteit of 81% om response te voorspellen. Patiënten met een LV dyssynchronie van ≥65 ms hadden bovendien een uitstekende prognose (6% "events") na CRT implantatie vergeleken met een 50% "events" in patiënten met een LV dyssynchronie <65 ms (P<0.001).
Samenvattend, was geen van de pre-implantatie patiënten karakteristieken in staat om response na CRT te voorspellen (inclusief de huidige CRT selectiecriteria). Een LV dyssynchronie op TDI ≥65 ms had daarentegen een goede voorspellende waarde voor response na CRT implantatie. Bovendien hadden patiënten met een LV dyssynchronie ≥65 ms een uitstekende prognose na CRT implantatie.

In **Hoofdstuk 13** worden de effecten van littekenweefsel in de postero-laterale LV segmenten (dit is de regio waar de LV pacing lead meestal ligt) bestudeerd in 40 patiënten (NYHA klasse III-IV, LV ejectiefractie ≤35%, en QRS duur >120 ms (met linkerbundeltakblok patroon)) met een ischemische cardiomyopathie die een CRT implantatie ondergingen. De localisatie en de transmuraliteit van het littekenweefsel werd bepaald met behulp van contrast-enhanced MRI. Bij 14 patiënten (35%) was er sprake van een transmuraal litteken (>50% van de wanddikte) in de postero-laterale LV segmenten. In tegenstelling tot patiënten zonder postero-lateraal littekenweefsel liet deze patiëntengroep een laag percentage responders zien (14% versus 81%, P<0.05) en verbeterden zij niet in klinische of echocardiographische parameters. Bovendien, bleef de LV dyssynchronie onveranderd na CRT implantatie (84±46 ms versus 78±41 ms, P=NS). Daarentegen hadden patiënten zonder postero-lateraal littekenweefsel in combinatie met pre-implantatie LV dyssynchronie ≥65 ms een hoge kans op response (95%) vergeleken met patiënten met postero-lateraal littekenweefsel en/of afwezigheid van pre-implantatie LV dyssynchrony (11%).
Samenvattend, is CRT niet in staat om LV dyssynchronie te reduceren in de aanwezigheid van postero-lateraal littekenweefsel, hetgeen resulteert in klinische en echocardiographische non-response na CRT.

Deel IV: Nieuwe indicaties

In de ***Hoofdstukken 9 en 10*** werd gezien dat er bij ongeveer een derde van de patiënten met hartfalen en een smal QRS complex (deze patiënten hebben op dit moment geen indicatie voor CRT) sprake is van substantiële LV dyssynchronie, wat suggereert dat deze patiënten ook baat kunnen hebben bij CRT.

Naar aanleiding van deze bevindingen werden in **Hoofdstuk 14** de effecten van CRT in patiënten met hartfalen, een smal QRS complex (<120 ms) en LV dyssynchronie op TDI geevalueerd. 33 patiënten met een smal QRS complex en 33 patiënten met een verbreed QRS complex (controlegroep) werden prospectief geïncludeerd. Patiënten werden geïncludeerd op basis van de volgende criteria: LV dyssynchronie ≥65 ms op TDI, NYHA klasse III-IV en LV ejectiefractie ≤35%. De pre-implantatie patiënten karakteristieken, in het bijzonder de mate van LV dyssynchronie waren vergelijkbaar tussen de patiënten met een smal en een verbreed QRS complex (gemiddelde QRS duur 110±8 ms vs. 175±22 ms). Geen significante relatie was aanwezig tussen QRS duur en LV dyssynchronie (r=0.21, P=NS). De mate van verbetering in klinische symptomen en LV functie was vergelijkbaar tussen patiënten met een smal en een verbreed QRS complex (gemiddelde reductie in NYHA klasse 0.9±0.6 vs. 1.1±0.6, P=NS en een gemiddelde reductie in LV eind-systolisch volume 39±34 ml vs. 44±46 ml, P=NS).

Concluderend, resulteert CRT in positieve effecten in patiënten met een smal QRS complex en LV dyssynchronie op TDI, met klinische en echocardiographische verbeteringen die vergelijkbaar zijn met de verbeteringen in patiënten met een verbreed QRS complex.

In **Hoofdstuk 15** werden de effecten van CRT in patiënten met milde symptomen van hartfalen (NYHA klasse II) onderzocht. Deze patiënten hebben op dit moment geen indicatie voor CRT. Vijftig opeenvolgende patiënten met NYHA klasse II hartfalen en 50 patiënten met NYHA klasse III-IV hartfalen (controlegroep) werden prospectief geïncludeerd. Alle patiënten hadden een LV ejectiefractie ≤35% en een QRS duur >120 ms. De mate van LV dyssynchronie was niet verschillend tussen patiënten in NYHA klasse II en de patiënten in NYHA klasse III/IV en CRT resulteerde in een vergelijkbare mate van LV resynchronisatie.

De mate van verbetering in klinische parameters was significant lager in de NYHA klasse II patiënten (bijv. NYHA klasse verbeterde met 0.3±0.6 vs. 1.0±0.8, respectievelijk, P<0.05), opvallend was echter dat de patiënten zonder verbetering in NYHA klasse (56%) wel een verbetering lieten zien in LV ejectiefractie en LV volumina. Bovendien was de verbetering in LV ejectiefractie en de afname in LV volumina niet verschillend tussen de NYHA klasse II en de NYHA klasse III/IV patiënten (bijv. verbetering in LV ejectiefractie 7±11% vs. 7±7%, respectievelijk, P=NS).

Concluderend, zijn de effecten van CRT in NYHA klasse II patiënten vergelijkbaar met de effecten in NYHA klasse III-IV patiënten wat betreft de mate van LV resynchronisatie, de verbetering in LV ejectiefractie en de mate van LV reverse remodeling.

Deel V: Optimaal gebruik van echocardiografie bij cardiale resynchronisatie therapie.

Hoofdstuk 16 geeft een integratie van de informatie die is beschreven in de ***Hoofdstukken 2-15*** en geeft een handleiding voor het optimale gebruik van echocardiographie in de zorg voor patiënten die een CRT implantatie ondergaan, zowel voor de implantatie (LV dyssynchronie detectie), als ook na de implantatie (follow-up en optimalisatie van de pacemaker settings). Een samenvatting van **Hoofdstuk 16** is verwerkt in de volgende sectie "conclusies en toekomstperspectief".

CONCLUSIES EN TOEKOMSTPERSPECTIEF

Ondanks de indrukwekkende resultaten van CRT in grote gerandomiseerde studies, blijkt een consistent aantal patiënten niet te verbeteren wanneer zij volgens de huidige CRT selectiecriteria (NYHA klasse III-IV, LV ejectiefractie <35% en QRS duur >120 ms) worden geselecteerd. Recent bleek dat een afname van het eind-systolische volume van >10% na 3-6 maanden CRT de beste voorspeller van een verbeterde lange-termijn overleving na CRT was en dus de meest klinisch relevante definitie van response na CRT verschaft. Volgens deze definitie van response heeft ongeveer 40% van de patiënten geen verbetering na CRT. Wanneer response na CRT gedefinieerd wordt met behulp van klinische parameters (bijv. verbetering in NYHA klasse of kwaliteit van leven) dan is het aantal non-responders rond de 30%.
Recente studies hebben aangegeven dat geen van de pre-implantatie patiënten karakteristieken (inclusief de huidige selectie criteria: QRS duur, NYHA klasse en LV ejectiefractie) in staat zijn om een positieve response na CRT te voorspellen. Deze bevindingen benadrukken de noodzaak voor de verbetering van huidige selectie criteria. Tijdens de zoektocht naar betere selectiecriteria is het nu duidelijk aangetoond dat het sleutelmechanisme van CRT de reductie van pre-implantatie LV dyssynchronie is. De aanwezigheid van inter-ventriculaire dyssynchronie daarentegen bleek minder van belang.

Detectie van LV dyssynchronie

Van oudsher werd de duur van het QRS complex gebruikt als een (indirecte) maat voor LV dyssynchronie, echter recent bleek deze parameter een slechte afspiegeling te geven van de mate van LV dyssynchronie, waarmee de lage voorspellende waarde van QRS duur voor response na CRT werd verklaard.
Na deze observatie, zijn verschillende cardiale beeldvormingstechnieken geëvalueerd voor hun vermogen om LV dyssynchronie te detecteren en te kwantificeren.
Van deze technieken bleek vooral echocardiographie uitermate geschikt om LV dyssynchronie te detecteren in de klinische praktijk.

Op dit moment is de meeste ervaring opgedaan met color-coded TDI en deze techniek bleek een goede voorspeller van zowel klinische response als ook van prognose na CRT implantatie. Naast TDI zijn er verschillende andere echocardiographische technieken geïntroduceerd variërend van M-mode echocardiographie tot strain rate imaging en 3D echocardiographie. Op dit moment is er geen consensus over welke techniek het meest geschikt is om response na CRT te voorspellen en het grote aantal echocardiographische technieken dat voor dit doel is geïntroduceerd (zonder deze technieken onderling te vergelijken) draagt verder bij aan de verwarring over de optimale techniek. Bovendien maakt iedere techniek gebruik van een verschillend aantal cardiale segmenten (van 2 tot 16 segmenten) en worden er verschillende afkapwaardes gebruikt (van 65 tot 130 ms).

Om te komen tot de keuze voor een optimale techniek (met een optimaal aantal segmenten en een optimale afkapwaarde) voor de voorspelling van response na CRT is er een dringende behoefte aan grotere multi-center studies die de verschillende technieken vergelijken. De prospectieve multi-center PROSPECT-studie is specifiek ontworpen om een aantal van deze vragen te beantwoorden en de resultaten worden verwacht in 2007.

Echter, ondanks het feit dat er op dit moment onduidelijkheid bestaat over de meest optimale echocardiographische techniek is in de laatste jaren overduidelijk bewezen dat patiëntenselectie gebaseerd op echocardiographische detectie van LV dyssynchronie superieur is vergeleken met selectie gebaseerd op de huidige criteria. Het ligt daarom in de lijn der verwachting dat de echocardiographische detectie van LV dyssynchronie zal worden geïncludeerd in toekomstige Europese en Amerikaanse richtlijnen.

Nieuwe indicaties

Ondanks het feit dat de huidige richtlijnen het gebruik van CRT alleen adviseren in patiënten met NYHA klasse III-IV hartfalen, LV ejectiefractie ≤35% en een QRS duur ≥120 ms is het te verwachten dat in de toekomst enkele nieuwe indicaties voor CRT zullen worden gevalideerd. Recente studies hebben namelijk aangetoond dat CRT ook van nut kan zijn in de volgende drie patiëntencategorieën (die op dit moment geen indicatie voor CRT hebben); 1] patiënten met hartfalen en een smal QRS complex (<120 ms) in combinatie met echocardiographische bewijs van LV dyssynchronie (doel: verbetering van klinische symptomen / LV functie en LV reverse remodeling), 2] patiënten met milde symptomen van hartfalen (NYHA klasse II) en verminderde LV functie (doel: verbetering van LV functie, LV reverse remodeling en preventie van progressie van hartfalen) en 3] patiënten met een LV dyssynchronie als gevolg van rechts ventriculair pacen in combinatie met een verminderde LV functie (doel: preventie van progressie van hartfalen).

Littekenweefsel en LV lead positie

Tenslotte, zijn er nog een aantal andere factoren die van invloed kunnen zijn op de mate van response na CRT. In het bijzonder de positie van de LV pacing lead in het gebied van laatste LV activatie lijkt te resulteren in de grootste mate van verbetering na CRT.
Verschillende echocardiographische technieken zijn op dit moment beschikbaar om dit gebied van laatste LV activatie te identificeren (zoals triplane tissue synchronization imaging and real-time 3D echocardiographie). Echter, voordat er aanbevelingen kunnen worden gedaan wat betreft LV lead positie zal er meer onderzoek moeten worden gedaan. Een tweede factor die mogelijk is gerelateerd aan non-response is de aanwezigheid van littekenweefsel in de linker ventrikel; grote gebieden van littekenweefsel lijken het effect van CRT te verminderen. Bovendien is recent aangetoond dat CRT niet in staat is om LV dyssynchronie te verminderen in de aanwezigheid van littekenweefsel in de postero-laterale segmenten van de linker ventrikel, resulterend in non-response na CRT. Het kan daarom overwogen worden om littekenweefsel in de linker ventrikel te identificeren voor CRT implantatie (bijv. met contrast enhanced MRI).

Conclusie

Concluderend is er op dit moment op het gebied van CRT-research een dringende behoefte aan multi-center studies om recente bevindingen uit kleinere single-center studies te bevestigen. Deze studies zouden zich op de volgende onderwerpen moeten richten: 1] Het definieren van de optimale echocardiographische methode om LV dyssynchronie te detecteren 2] Validatie van nieuwe CRT indicaties (smal QRS complex, NYHA klasse I-II en rechts ventriculair pacing geïnduceerde LV dyssynchronie) en 3] evaluatie van de invloed van LV littekenweefsel en LV lead positie
In afwachting van deze resultaten is het te verwachten dat de huidige richtlijnen voor CRT patiëntenselectie in de toekomst zullen worden uitgebreid met de aanwezigheid van LV dyssynchronie (spontaan of geïnduceerd (rechts-ventricular pacen) en onafhankelijk van QRS duur).

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Abstracts

The author of this thesis has (co-) authored around 50 abstracts at international cardiology meetings and has reached the highlight sessions of the three major cardiology meetings with the following abstracts:

- Bleeker GB et al. QRS duration is an insensitive marker of left ventricular dyssynchrony in patients with end-stage heart failure. (Highlight session, European Society of Cardiology congress 2004, München).
- Bleeker GB et al. Incidence of left ventricular dyssynchrony in patients with systolic heart failure and a narrow QRS complex. *2004* (Best of Sessions, American Heart Association congress 2004, New Orleans).

- Bleeker GB et al. Effect of postero-lateral scar tissue on clinical and echocardiographic improvement following cardiac resynchronization therapy. (Highlight session, American College of Cardiology annual meeting, 2006, Atlanta).

In addition, the author had several invited lectures at international cardiology meetings, including the Euroecho-meeting 2005 (Florence) and the American College of Cardiology annual meeting 2007 (New Orleans).

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CURRICULUM VITAE

De auteur van dit proefschrift werd geboren op 2 maart 1978 te Groningen. In 1996 behaalde hij het eindexamen aan het Stedelijk Gymnasium te Haarlem. In datzelfde jaar startte hij met de studie Geneeskunde aan de Rijksuniversiteit Leiden. In 2001 behaalde hij het doctoraalexamen en in 2003 werd het artsexamen (cum laude) afgelegd.

Tijdens de doctoraalfase was hij werkzaam als student-assistent bij de vakgroep Anatomie en Embryologie (prof dr. G.J. Maat en dr. H.K. Feirabend).
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Na het behalen van het artsexamen heeft hij enkele maanden gewerkt als arts-assistent op de afdeling Cardiologie van het Leids Universitair Medisch Centrum te Leiden (hoofd: prof. dr. E.E. van der Wall). In april 2003 is hij begonnen met klinisch wetenschappelijk onderzoek onder begeleiding van prof.dr.J.J. Bax. Dit project werd gefinancierd door de Nederlandse Hartstichting en het ICIN en heeft geleid tot dit proefschrift.
Per 1 april 2007 zal hij beginnen met de opleiding Cardiologie vanuit het Leids Universitair Medisch Centrum (Opleider prof.dr. E.E. van der Wall), welke zal aanvangen met de vooropleiding Interne Geneeskunde in het Rijnland Ziekenhuis te Leiderdorp (Opleider dr. F.H.M. Cluitmans).

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