Echocardiographic evaluation of left ventricular function in ischemic heart disease

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Chapter 12

Left ventricular resynchronization is mandatory for response to cardiac resynchronization therapy

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ABSTRACT

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

Methods and results: 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). Immediately after CRT implantation, LV dyssynchrony was reduced from 114 ± 36 ms to 40 ± 33 ms ($p<0.001$) which persisted at 6-month follow-up (35 ± 31 ms, $p<0.001$ versus baseline, $p=0.14$ versus immediately post-implantation). At 6-month 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 versus 79 ± 44 ms, $p=0.08$). If the extent of acute LV resynchronization was <20%, response to CRT at 6-month 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-month 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, a relatively high percentage of patients failed to respond to CRT (1,5-7). Approximately 30% of patients failed to improve in clinical symptoms and 40-50% of patients had no improvement in LV function on echocardiography (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). Indeed, patient selection based on echocardiographic detection of LV dyssynchrony resulted in a superior response rate compared to patient selection based on QRS duration alone (5-10). However, the presence of pre-implantation LV dyssynchrony may not be the only determinant of response to CRT, since some patients with pre-implantation LV dyssynchrony do still not respond to CRT. It is currently unclear, whether a reduction in LV dyssynchrony (LV resynchronization) after implantation of the CRT device is mandatory for a positive response. 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, and if so, which extent of LV resynchronization is the best predictor 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 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), decompensated heart failure or non-successful LV lead implantation were excluded. Before CRT implantation, clinical status was assessed and 2-dimensional (2D) 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-month follow-up. The clinical status and changes in LV ejection fraction and LV volumes were re-assessed at 6-month follow-up.

Clinical evaluation

Evaluation of clinical status included assessment of NYHA functional class, quality-of-life score (using the Minnesota living with Heart Failure questionnaire) and evaluation of exercise capacity using the 6-minute hall-walk test. All parameters were re-assessed at 6-month 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 2D 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-month follow-up were considered responders to CRT (12). In addition, patients who died from progressive heart failure before the 6-month follow-up assessment were classified as non-responders.

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%) (13). All echocardiographic measurements after CRT implantation were made with the device in active pacing mode.

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 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). The analysis of peak systolic velocities was limited to the LV ejection period and post-systolic peaks were excluded. To mark the LV ejection period 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 (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 2- and 4-chamber apical TDI views down to the left ventricle (i.e. excluding the right ventricle and atria). 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). Based on previous data, a cutoff value of 65 ms was used as a marker of LV dyssynchrony (7). Previously reported inter- and intra-observer agreement for assessment of LV dyssynchrony was 90% and 96%, respectively (14). The percentage of immediate LV resynchronization was defined as the difference (%) between pre-implantation LV dyssynchrony and LV dyssynchrony immediately after CRT implantation.

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.). After implantation the LV lead position was assessed from the frontal and lateral chest X-rays. CRT devices were programmed in DDD(R)-mode in patients in normal sinus rhythm and in VVIR-mode in patients in atrial fibrillation. 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 ± standard deviation (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. Univariable and multivariable linear regression as well as logistic regression analyses were performed to study the relationship between immediate post-CRT implantation variables and response to CRT at 6-month follow-up. For all tests, a p value <0.05 was considered statistically significant. All authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

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-month 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-month 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 ($p<0.001$).

Eighty-five patients (85%) showed a reduction >10% in LV end-systolic volume at 6-month 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-month 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 $p=0.14$ 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-month 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-month follow-up (n=67, 67%). In other patients however, CRT resulted in only a minimal reduction or even an increase in LV dyssynchrony, though this was <10% of all patients (Figure 2). The percentage of acute LV resynchronization was not different between the patients with sinus rhythm or atrial fibrillation (66 ± 30% versus 63 ± 30%, $p=0.74$) or between patients with ischemic versus non-ischemic cardiomyopathy (62 ± 29% versus 68 ± 30%, $p=0.46$).

LV resynchronization versus response to CRT

As indicated above, 85 patients (85%) showed a reduction >10% in LV end-systolic volume at 6-month follow-up and were therefore classified as responders to CRT. Fourteen patients (14%)

Table 1. Baseline characteristics (n=100)

Age (yrs)	67 ± 11
Gender	
Male	86 (86%)
Female	14 (14%)
Etiology	
Ischemic	59 (59%)
Non-ischemic	41 (41%)
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
LVESV (ml)	188 ± 71
LVEDV (ml)	243 ± 76
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.

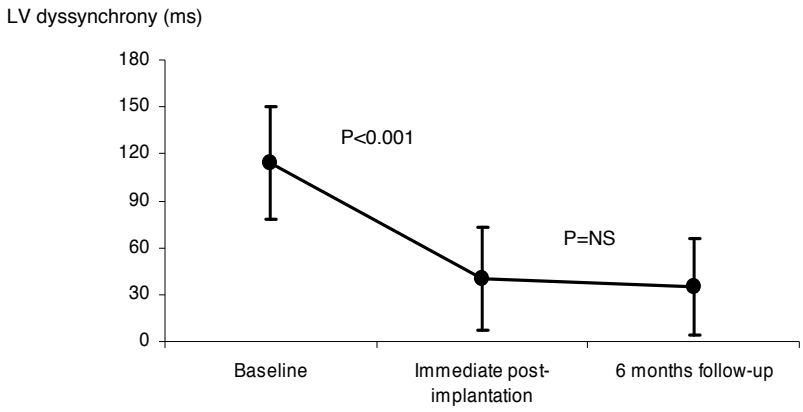

Figure 1. Time course of LV resynchronization following CRT implantation in all patients (n=100). CRT: cardiac resynchronization therapy.

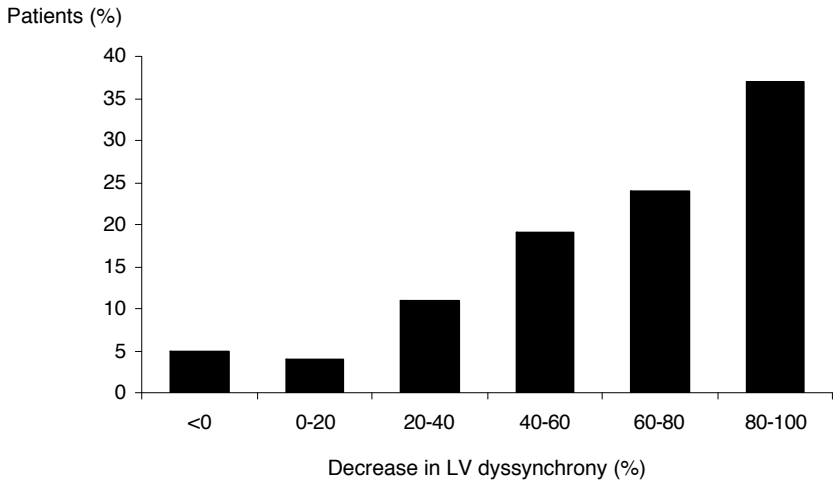

Figure 2. Extent of the decrease in LV dyssynchrony immediately following CRT implantation. CRT: cardiac resynchronization therapy; LV: left ventricular.

had a reduction ≤10% in LV end-systolic volume and 1 patient died from progressive heart failure before 6-month 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, p=0.49). The prevalence of ischemic cardiomyopathy was higher in the non-responders, although this difference was not statistically significant (80% versus 55%, p=0.13). There was a trend towards a lower percentage of reduction in LV end-systolic volume at 6-month follow-up between patients with ischemic versus non-ischemic cardiomyopathy (24 ± 21% reduction in LV end-systolic volume versus 30 ± 18%, respectively, p=0.13).

By definition, LV end-systolic volume did not decrease in the non-responders at 6-month follow-up (170 ± 79 ml at baseline versus 177 ± 73 ml at follow-up, p=0.19). 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=0.64), 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=0.08), whereas the responders demonstrated a significant reduction in LV dyssynchrony from 115 ± 37 ms to 32 ± 23 ms (p<0.001) (Figure 3).

Table 2. Clinical and echocardiographic variables for patients with versus without LV reverse remodeling at 6-month follow-up

	LV reverse remodeling present	LV reverse remodeling absent[#]	p value
Age (yrs)	67 ± 10	66 ± 15	0.65
Gender (M/F)	73/12	13/2	0.74
Etiology (isch/non-isch)	47/38	12/3	0.13
QRS duration (ms)	169 ± 28	158 ± 18	0.13
LV dyssynchrony (ms)			
Baseline	115 ± 37	106 ± 29	0.49
Follow-up (acute)	32 ± 23*	79 ± 44	<0.001
NYHA class			
Baseline	3.0 ± 0.2	3.1 ± 0.3	0.65
Follow-up	2.0 ± 0.5*	2.6 ± 0.5*	<0.001
6-MWT (m)			
Baseline	295 ± 110	264 ± 89	0.34
Follow-up	419 ± 85*	337 ± 151*	0.003
QoL score			
Baseline	37 ± 17	42 ± 13	0.42
Follow-up	18 ± 14*	28 ± 16*	0.01
LVESV (ml)			
Baseline	190 ± 69	170 ± 79	0.43
Follow-up	130 ± 59*	177 ± 73	0.007
LVEDV (ml)			
Baseline	245 ± 75	220 ± 84	0.42
Follow-up	200 ± 72*	231 ± 80	0.14
LVEF (%)			
Baseline	23 ± 7	24 ± 7	0.57
Follow-up	34 ± 9*	25 ± 7	<0.001

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 volume; NYHA: New York Heart Association; Qol: quality-of-life.
*p<0.05 follow-up versus baseline value; [#]1 patient died before 6-month follow-up.

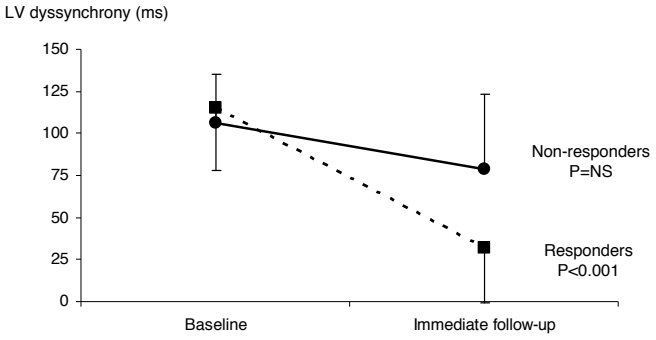

Figure 3. Immediate decrease in LV dyssynchrony in the patients with response to CRT (n=85, 85%, defined as >10% reduction in LV end-systolic volume) versus the patients without response (n=15, 15%). CRT: cardiac resynchronization therapy; LV: left ventricular.

In the multivariable regression analysis 3 variables were related to the absolute change in LV end-systolic volume at 6-month follow-up (r=0.59, p<0.001): the extent of immediate LV resynchronization (p<0.001), baseline LV end-diastolic volume (p<0.001) and baseline severity of mitral regurgitation (p=0.02). In the multivariable logistic analysis including all studied variables, immediate LV resynchronization was the only variable that was predictive of response to CRT at 6-month follow-up.

Linear regression analysis demonstrated a significant relationship between the immediate reduction in LV dyssynchrony and the reduction in LV end-systolic volume at 6-month 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. In the patient who died from progressive heart failure before the 6-month follow-up assessment, LV dyssynchrony showed an immediate increase from 140 to 160 ms. Conversely, 85 of 91 patients with ≥20% LV resynchronization immediately after CRT implantation, responded to CRT at 6-month follow-up. Applying this cutoff 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-month follow-up with an area under the curve of 0.84. Importantly, no differences were observed between the characteristics of the patients with and without immediate LV resynchronization, except that in patients without LV resynchronization the LV lead was more frequently located in the anterior LV segments (2% versus 33%, p<0.01, Table 3). An interesting observation was that all patients without LV resynchronization and a posterior or lateral LV lead position had ischemic cardiomyopathy (n=6), whereas in the 3 patients with non-ischemic cardiomyopathy the LV lead was located in the anterior LV segments.

Immediately after CRT implantation the patients without acute LV resynchronization did not demonstrate a reduction in QRS duration (from 157 ± 17 ms versus 152 ± 27 ms, p=0.69),

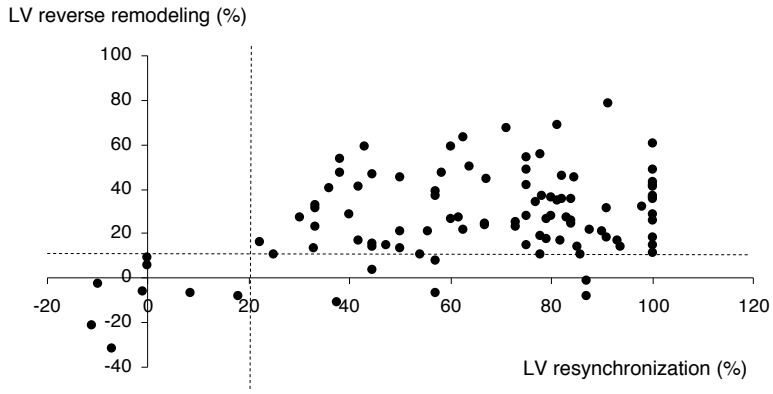

Figure 4. Relationship between immediate LV resynchronization and reduction in LV end-systolic volume at 6-month follow-up (y=0.29x+8, n=99, r=0.41, p<0.001). LV: left ventricular.

Table 3. Baseline characteristics for patients with versus without LV resynchronization

	Resynchronization present	Resynchronization absent[#]	p-value
Age (yrs)	67 ± 10	65 ± 17	0.64
Gender (M/F)	79/12	7/2	0.81
Etiology (isch/non-isch)	53/38	6/3	0.89
QRS duration (ms)	169 ± 28	157 ± 17	0.24
LV dyssynchrony (ms)	114 ± 37	112 ± 24	0.87
NYHA class	3.0 ± 0.2	3.1 ± 0.3	0.36
LVESV (ml)	187 ± 70	197 ± 79	0.70
LVEDV (ml)	241 ± 76	255 ± 84	0.60
LVEF (%)	23 ± 7	23 ± 7	0.87
LV lead position			
Anterior	2 (2%)	3 (33%)	<0.01
Posterior	42 (46%)	3 (33%)	
Lateral	44 (48%)	3 (33%)	
Not available	3 (3%)	0 (0%)	

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

whereas the patients with acute LV resynchronization had a significant reduction in QRS duration from 169 ± 28 ms to 151 ± 24 ms, p<0.001.

At 6-month follow-up, the patients with immediate LV resynchronization had a significant reduction in mitral regurgitation from grade 1.6 ± 1.0 to 1.1 ± 0.8 (p<0.001), whereas patients without acute LV resynchronization after CRT did not experience a reduction in mitral regurgitation grade at 6-month follow-up (from 1.8 ± 1.3 to 1.9 ± 1.0, p=0.83).

DISCUSSION

The main findings of the current study can be summarized as follows: 1) LV resynchronization following CRT occurs acutely and is sustained at 6-month 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-month 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, $p<0.05$) (15).

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-month 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% (5,6,16). 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 cutoff 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-month 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 cutoff value of 10% reduction in LV end-systolic volume was the optimal cutoff value for prediction of improved survival following CRT (12).

Time course and extent of LV resynchronization following CRT

Various studies have reported on LV resynchronization after CRT (6,7,17,18). 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 (18). 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 dyssyn-

chrony, 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 (7,15-17). 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%.

Although the number of patients without LV resynchronization in the current study is low (n=9), a sub-optimal position of the LV pacing lead appears to be related the lack of LV resynchronization. Rossillo et al. recently demonstrated in 233 consecutive patients that placement of the LV pacing lead in the lateral or postero-lateral branches of the coronary sinus was associated with a superior improvement in LV function (LV ejection fraction from 19% to 27%, $p<0.05$) compared to patients with an anterior LV pacing lead location (LV ejection fraction from 18% to 20%, p=NS) (19).

Recent data have indicated that in heart failure patients the postero-lateral LV segments are usually the latest activated LV segments (20). Pacing the left ventricle outside the area of latest activation resulted in less improvement in LV ejection fraction and LV volumes compared to pacing in the area of latest activation. Murphy et al. demonstrated that pacing the LV in a remote area (e.g. the anterior LV segments) even resulted in a worsening of LV volumes with a 9% increase in LV end-systolic volume during follow-up (21). The current study demonstrated that minimal or absent LV resynchronization may be a potential mechanism for the lack of benefit from CRT in patients with suboptimal LV lead positioning.

A second potential explanation for a lack of LV resynchronization may be the presence of large areas of scar tissue throughout the left ventricle (total scar burden) or the presence of scar tissue in the area of the LV pacing lead. Bleeker et al. recently demonstrated in 40 patients that CRT is unable to reduce LV dyssynchrony (from 84 ± 46 ms to 78 ± 41 ms, p=NS) in the presence of scar tissue in the postero-lateral LV segments. As a result, the (clinical) response rate to CRT in patients with postero-lateral scar tissue was poor (11%), whereas patients with severe baseline LV dyssynchrony without postero-lateral scar tissue had an excellent (clinical) response rate of 95% (22). In addition, several studies have recently demonstrated that the amount of LV scar tissue is highly predictive for response to CRT irrespective of baseline LV dyssynchrony

(23,24). The presence of scar tissue most likely prevents a normal activation of the myocardium since the activation front is delayed or stopped by large areas of scar tissue resulting in lack of LV resynchronization. A potential beneficial treatment strategy in patients without initial LV resynchronization is V-V delay optimization (25,26). Previous studies have shown that optimization of the V-V pacing delay may result in a (further) reduction in LV dyssynchrony and may therefore be beneficial in patients without initial LV resynchronization (26). Interestingly, Leon et al. demonstrated that patients with a history of myocardial infarction more frequently benefit from LV pre-excitation during V-V optimization, which may be the additional activation delay caused by large amounts of scar tissue (26). In the current study, V-V optimization was not performed before the 6-month follow-up assessment which may be considered as a limitation.

In addition, whether repositioning of the LV lead to the area of latest activation or to an area without myocardial scar tissue will result in LV resynchronization in patients without an initial reduction in LV dyssynchrony will also need further study.

Study limitations

Although none of the patients with acute LV resynchronization <20% responded to CRT (in contrast to a response rate of 93% in patients with acute LV resynchronization ≥20%), the cutoff value of a 20% acute reduction in LV dyssynchrony needs further validation.

In recent years, a wide variety of echocardiographic techniques has been introduced for quantification of LV dyssynchrony ranging from simple M-mode echocardiography to more advanced techniques such as TDI and strain imaging. All techniques have only been evaluated in small, single center studies indicating the clear need for larger multi-center studies directly comparing the different techniques. Also, the cutoff value of 65 ms for LV dyssynchrony measurement was validated in a single study. Further studies are required to confirm the 65 ms as optimal cutoff value for LV dyssynchrony assessment. Furthermore, the differentiation between passive myocardial motion active contraction of LV segments is possible with strain or strain rate imaging but with TDI. Still, TDI is among the most widely studied techniques for LV dyssynchrony assessment with a high predictive value for response to CRT (10). The fact that the current study only included patients with echocardiographic evidence of LV dyssynchrony limits the generalizibility of the study since the effects of CRT on LV dyssynchrony in patients without pre-implantation LV dyssynchrony were not studied.

Conclusion

In the present study, 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-month follow-up, indicating that resynchronization is mandatory for response to CRT.

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