New insight into device therapy for chronic heart failure

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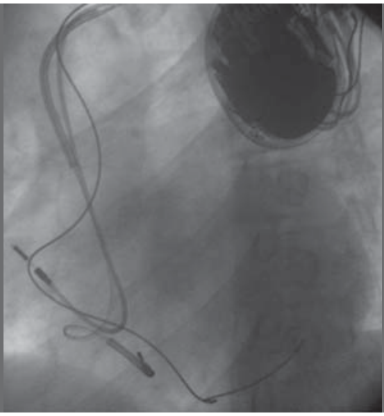
Chapter 3



Left ventricular resynchronization is mandatory for response to cardiac resynchronization therapy

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ABSTRACT

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

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

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

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

INTRODUCTION

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

METHODS

Study population and protocol

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

Clinical evaluation

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

Echocardiography

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

Images were obtained using a 3.5 MHz transducer, at a depth of 16 cm in the parasternal and apical views (standard long-axis, 2- and 4-chamber images). Standard 2-dimensional and color Doppler data, triggered to the QRS complex, were saved in cine-loop format. The LV volumes (end-systolic [ESV], end-diastolic [EDV]) and LVEF were calculated from the conventional apical 2- and 4-chamber images, using the biplane Simpson's technique (11).
Patients with a reduction of >10% in LVESV at 6 months follow-up were considered responders to CRT (12). In addition, patients who died from progressive heart failure before the 6 months follow-up assessment were classified as non-responders.

LV dyssynchrony assessment using color-coded TDI

In addition to the conventional echocardiographic examination, TDI was performed to assess LV dyssynchrony. For TDI, color Doppler frame rates were > 80 frames/s; pulse repetition frequencies were between 500 Hz and 1 KHz, resulting in aliasing velocities between 16 and 32 cm/s. TDI parameters were measured from color-coded images of 3 consecutive heart beats by offline analysis. To determine LV dyssynchrony, the sample volume (6 mm x 6 mm) was placed in the LV basal parts of the anterior, inferior, septal and lateral walls (using the 2-and 4-chamber apical views) and per region, the time interval between the onset of the QRS complex and the peak systolic velocity was derived (i.e. the electro-systolic delays). LV dyssynchrony was defined as the maximum delay between peak systolic velocities among the four walls within the left ventricle (most frequently observed between the inter-ventricular septum and the lateral wall) (7). The analysis of peak systolic velocities was limited to the LV ejection period and post-systolic peaks were excluded. To ensure highly interpretable and reproducible TDI curves (and minimize artefacts) high frame rates are crucial. The highest possible frame-rates were achieved by narrowing the 2- and 4-chamber apical TDI views down to the left ventricle (i.e. excluding the right ventricle and atria). Previously reported inter- and intra-observer agreement for assessment of LV dyssynchrony were 90% and 96%, respectively (13). Based on previous data, a cut-off value of 65 ms was used as a marker of LV dyssynchrony (7).
Data were analyzed using commercial software (Echopac version 5.0.1, General Electric – Vingmed). Echocardiographic data were analyzed by 2 independent observers, blinded to all other patient data.

Pacemaker implantation

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

Statistical analysis

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

RESULTS

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

Table 1. Baseline characteristics (n=100)

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

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

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

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

LV resynchronization after CRT

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

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

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

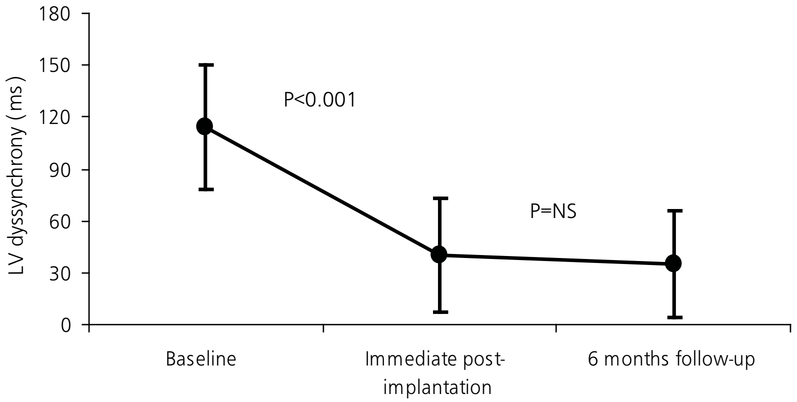
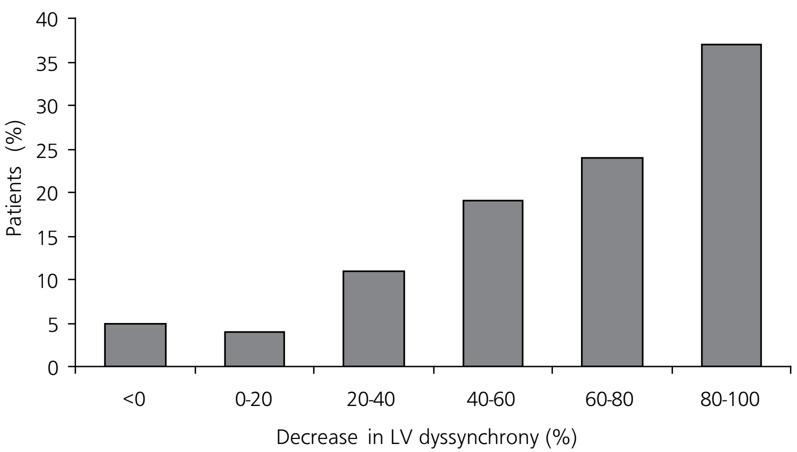


Figure 2. Extent of the decrease in LV dyssynchrony immediately following CRT implantation



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

LV resynchronization versus response to CRT

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

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

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

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

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

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

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

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

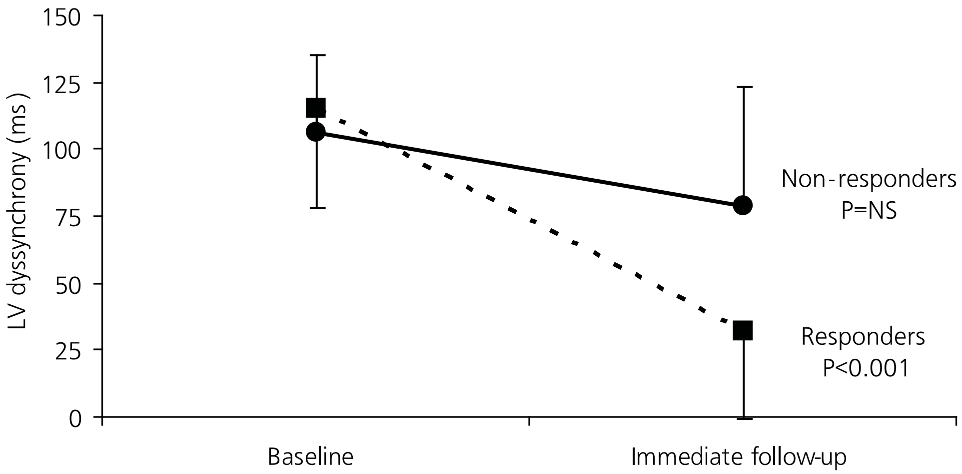
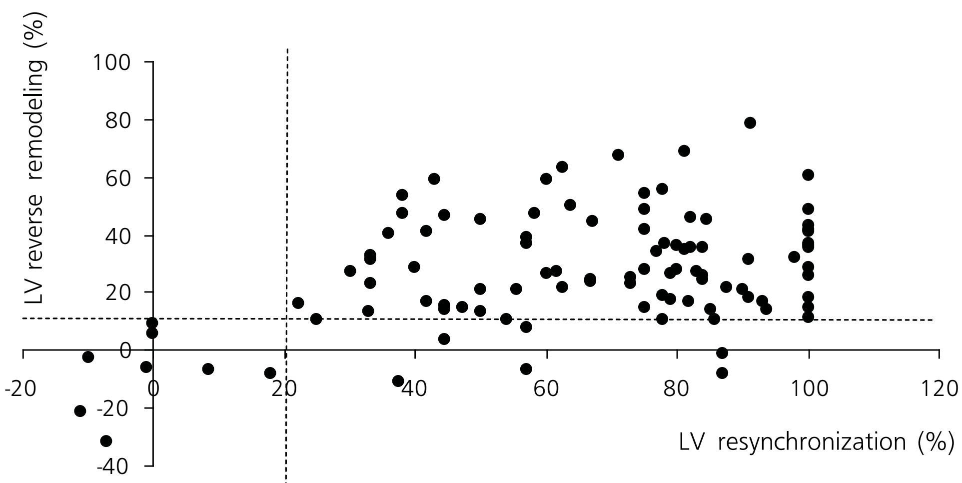


Figure 4. Relationship between immediate LV resynchronization and reduction in LV end-systolic volume at 6 months follow-up (y=0.29x+8, n=99, r=0.41, P<0.001)



An interesting observation was the difference in immediate LV resynchronization between the responders and the non-responders. The patients without response showed no significant reduction in LV dyssynchrony (from 106±29 ms to 79±44 ms, NS), whereas the responders demonstrated a significant reduction in LV dyssynchrony from 115±37 ms to 32±23 ms ($P<0.001$) (Figure 3).

Linear regression demonstrated a modest but significant relationship between the immediate reduction in LV dyssynchrony and the reduction in LV end-systolic volume at 6 months follow-up ($y=0.29x+8$, $r=0.41$, $n=99$, $P<0.001$) (Figure 4).

Of interest, when patients showed less than 20% LV resynchronization (n=9) immediately after CRT, response to CRT never occurred. Conversely, 85 of 91 patients with ≥20% LV resynchronization immediately after CRT implantation responded to CRT at 6 months follow-up. Applying this cut-off value of 20% immediate LV resynchronization, resulted in a positive and negative predictive value of 100% and 93% respectively, for prediction of response to CRT at 6 months follow-up. Importantly, no differences were observed in baseline characteristics between the patients with and without immediate LV resynchronization (Table 3).

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

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

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

DISCUSSION

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

Mechanism of response to CRT

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

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

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

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

Time course and extent of LV resynchronization following CRT

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

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

Lack of LV resynchronization

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

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

CONCLUSION

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

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