Chapter 2

Value of tissue Doppler echocardiography in predicting response to cardiac resynchronization therapy in patients with heart failure

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ABSTRACT

Background: Several studies demonstrated a relation between left ventricular (LV) dyssynchrony and response to cardiac resynchronization therapy (CRT). Many methods of determining LV dyssynchrony have been opposed, among which a value of 65 ms assessed with tissue Doppler imaging. Aim of this validation study was to prospectively test the predictive accuracy of the 65 ms cut-off for LV dyssynchrony in a large cohort of heart failure patients undergoing CRT.

Methods: The study comprised 361 patients undergoing CRT. Clinical and echocardiographic parameters were assessed at baseline and at 6 months follow-up. Clinical response was defined as an improvement ≥1 New York Heart Association (NYHA) class and echocardiographic response as a reduction in LV end-systolic volume (LVESV) ≥15%.

Results: At 6 months follow-up, 259 patients (72%) showed clinical response and 187 patients (52%) showed echocardiographic response. Responders had more LV dyssynchrony than non-responders (91±49 ms vs. 50±44 ms for clinical response and 101±46 ms vs. 55±45 ms for echocardiographic response). In multivariate analysis, LV dyssynchrony remained predictive for response, independent of other characteristics.

Conclusions: LV dyssynchrony ≥65 ms is an independent predictor of both clinical and echocardiographic response in patients with heart failure undergoing CRT in this validation study.

INTRODUCTION

PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) was the first large-scale, multicenter clinical trial that evaluated the capability of several echocardiographic measures of dyssynchrony to predict response to CRT.[1] Various measures of dyssynchrony were capable to predict clinical outcome and reverse remodeling at 6 months follow-up. However, the sensitivity and specificity of these markers were modest. One of the dyssynchrony measures with the highest predictive value in PROSPECT was the septal to lateral delay (Ts-[lateral-septal]), defined as the delay between time to peak systolic velocity at basal septal and basal lateral segments, measured with color-coded tissue Doppler imaging (TDI). This measure of dyssynchrony was proposed by this center and the extent of LV dyssynchrony needed to predict response to CRT was defined as 60 ms.[2] After that, a more sensitive marker of LV dyssynchrony ≥65 ms among 4 basal walls within the LV (most frequently observed between the interventricular septum and the lateral wall) was identified.[3] This cut-off value however was derived by receiver operating characteristic curve analysis, which thus needs validation. Consequently, that initial population should be considered as a "learning population", used to derive an optimal cut-off value for LV dyssynchrony, which then needs further prospective testing in a so-called "validation population". Accordingly, the aim of the current study was to prospectively test the predictive accuracy of the 65 ms cut-off value for LV dyssynchrony in a large cohort of heart failure patients undergoing CRT.

METHODS

Patient population

A total of 361 patients who were scheduled for CRT were included in the present study. Patients were selected according to the current inclusion criteria: NYHA class III-IV, LVEF ≤35% and QRS duration ≥120 ms. The study protocol was as follows: in all patients clinical status was assessed before implantation and two-dimensional (2D) echocardiography was performed to measure LVEF and LV volumes. Color-coded TDI was used to measure the extent of LV dyssynchrony. Clinical status and changes in LVEF and LV volumes were re-assessed at 6 months follow-up.

Clinical evaluation

Clinical status was assessed at baseline and at 6 months follow-up and included NYHA functional class, quality of life score (using the Minnesota Living with Heart Failure Questionnaire)[4] and distance covered in the 6-minute walking test.[5]

Echocardiographic evaluation

All patients underwent echocardiography in the left lateral decubitus position before and 6 months after CRT device implantation. Studies were performed using a commercially available echocardiographic system (VIVID 7, General Electric Vingmed Ultrasound, Milwaukee, USA). Images were obtained using a 3.5 MHz transducer, at a depth of 16 cm in the parasternal (long- and short-axis) and apical (2- and 4-chamber) views. Standard 2D and color Doppler data, triggered to the QRS complex, were saved in cineloop format. A minimum of 3 consecutive beats were recorded from each view and the images were digitally stored for offline analysis (EchoPac 7.0.0, General Electric Vingmed Ultrasound, Milwaukee, USA). LVESV, LV end-diastolic volumes (LVEDV) and LVEF were measured from the apical 2- and 4-chamber images, using the modified biplane Simpson's rule.[6]

For TDI, color Doppler frame rates were >80 frames/s in all subjects, pulse repetition frequencies were between 500 Hz and 1 kHz, resulting in aliasing velocities between 16 and 32 cm/s. To assess LV dyssynchrony, time-to-peak systolic velocities were obtained by placing sample volumes in the basal portions of the septal and lateral walls. LV dyssynchrony was calculated as the maximum time delay between the peak systolic velocities of these opposing basal walls. Interobserver and intraobserver agreement for assessment of septal-to-lateral delay were 90% and 96%, respectively.[7] Based on previous work, a delay of ≥65 ms was prospectively defined as substantial LV dyssynchrony.[3]

Definition of response

Clinical response after 6 months CRT was defined as an improvement ≥1 in NYHA class score. Additionally, echocardiographic response at 6 months follow-up was defined as a decrease in LVESV of 15% or more. Patients who died before 6 months follow-up were defined as both clinical and echocardiographic non-responders.

Statistical analysis

Continuous data are presented as mean±SD, and dichotomous data are presented as numbers and percentages. Comparison of data between patient groups was performed using the independent-samples t test for continuous data. Fisher's exact tests or χ^2 tests were used as appropriate to compare dichotomous data. Comparison of data within patient groups (at baseline and at 6 months follow-up) was performed with the paired-samples t test. Univariate and multivariate logistic regression analyses were performed to evaluate LV dyssynchrony as a predicting factor for clinical and echocardiographic response at 6 months follow-up. Variables that showed a statistically significant effect at the 0.50 level in univariate analyses were entered in a multivariate model. Finally, linear regression analysis was performed to evaluate the relation between LV dyssynchrony at baseline and echocardiographic response at 6 months follow-up. All analyses were performed with SPSS for Windows, version 16.0 (SPSS, Chicago, IL). A p-value <0.05 was considered statistically significant. To find a significant difference as small as 25% of the group standard deviation between patient groups with a power >.90, the study required a minimum of 326 patients.

RESULTS

Patient characteristics

Three hundred and sixty-one consecutive patients were included in this study. Baseline characteristics of these patients are summarized in Table 1. Mean extent of LV dyssynchrony at baseline was 79±51 ms, with 229 patients (63%) having pre-defined substantial LV dyssynchrony (≥65 ms). Three hundred and twenty-one patients received a combined CRT-ICD device, while 40 patients received a CRT device only.

Table 1. Patient characteristics (n = 361)

Age (years)	67 ± 10
Men / Women	272 / 89
NYHA class	
III	319 (88%)
IV	42 (12%)
Cause of heart failure	
Ischemic	221 (61%)
Nonischemic	140 (39%)
QRS duration (ms)	169 ± 24
Left bundle branch block	275 (76%)
Paced QRS	54 (15%)
Other conduction disorder	32 (9%)
Rhythm	
Sinus rhythm	283 (78%)
Atrial fibrillation	58 (16%)
Paced	20 (6%)
Systolic blood pressure (mmHg)	120 ± 21
Diastolic blood pressure (mmHg)	72 ± 11
Serum creatinine (µmol/l)	131 ± 69
LV ejection fraction (%)	23 ± 7
LV end-diastolic volume (ml)	239 ± 85
LV end-systolic volume (ml)	187 ± 75
LV dyssynchrony (ms)	79 ± 51
LV dyssynchrony ≥65 ms (n)	229 (63%)
Medication	
Diuretics	329 (91%)
ACE-inhibitors	328 (91%)
B-blockers	224 (62%)
Spironolactone	188 (52%)
Digoxine	88 (24%)
Ca-antagonists	26 (7%)

ACE = angiotensin-converting enzyme; LV = left ventricular; NYHA = New York Heart Association

Clinical and echocardiographic response after CRT

After 6 months follow-up, mean NYHA class had improved from 3.1±0.3 to 2.2±0.6 ($p<0.001$). In addition, quality of life score decreased from 42±16 to 27±18, while 6-minute walking distance increased from 268±106 m to 369±128 m (both $p<0.001$). Also, echocardiographic improvement was noted after 6 months, as demonstrated by a decrease in LV volumes (LVESV decreased from 187±75 ml to 150±71 ml and LVEDV decreased from 239±85 ml to 207±80 ml, both $p<0.001$). LV systolic function improved as evidenced by an increase in LVEF from 23±7% at baseline to 30±11% at follow-up ($p<0.001$). Twenty-two patients had died due to worsening heart failure before 6 months follow-up; these were considered as both clinical and echocardiographic non-responders.

Clinical responders vs. non-responders

After 6 months of CRT, 259 patients (72%) were classified as clinical responders. Both responders and non-responders had comparable baseline characteristics, except for more extensive LV dyssynchrony (91±49 ms vs. 50±44 ms, p<0.001) in the responders, see Table 2A. By definition, responders showed a decrease in NYHA class from 3.1±0.3 at baseline to 1.9±0.4 at follow-up. Similarly, an increase in 6-minute walking distance was observed from 275±104 m at baseline to 403±106 m at follow-up. Also, the quality of life score decreased in responders (from 41±16 at baseline to 21±14 at follow-up, p<0.001), but remained unchanged in clinical non-responders (46±16 at baseline vs. 46±17 at follow-up, p = NS). As demonstrated in Figure 1, clinical responders showed a significant increase in LVEF, with a significant reduction in LV volumes; these parameters did not improve in the clinical non-responders. Of note,

Table 2A. Patient characteristics in clinical responders and non-responders

Variable	Responders (n = 259)	Non-responders (n = 102)	p-value
Age (years)	66 ± 11	68 ± 10	0.164
Men / Women	196 / 63	76 / 26	0.892
NYHA class			0.364
III	226 (87%)	93 (91%)	
IV	33 (13%)	9 (9%)	
Cause of heart failure			0.404
Ischemic	155 (60%)	66 (65%)	
Nonischemic	104 (40%)	36 (35%)	
QRS duration (ms)	170 ± 25	165 ± 23	0.108
Rhythm			0.397
Sinus rhythm	205 (79%)	78 (76%)	
Atrial fibrillation	38 (15%)	20 (20%)	
Paced	16 (6%)	4 (4%)	
Systolic blood pressure (mmHg)	120 ± 21	119 ± 19	0.861
Diastolic blood pressure (mmHg)	72 ± 11	71 ± 12	0.494
Serum creatinine (µmol/l)	129 ± 76	136 ± 49	0.389
LV ejection fraction (%)	22 ± 7	23 ± 7	0.349
LV end-diastolic volume (ml)	242 ± 85	229 ± 85	0.183
LV end-systolic volume (ml)	190 ± 76	179 ± 74	0.186
LV dyssynchrony (ms)	91 ± 49	50 ± 44	**<0.001**
LV dyssynchrony ≥65 ms (n)	195 (75%)	34 (33%)	**<0.001**
Medication			
Diuretics	232 (90%)	97 (95%)	0.104
ACE-inhibitors	232 (90%)	96 (94%)	0.225
B-blockers	168 (65%)	56 (55%)	0.092
Spironolactone	135 (52%)	53 (52%)	1.000
Digoxine	62 (24%)	26 (25%)	0.786
Ca-antagonists	19 (7%)	7 (7%)	1.000

ACE = angiotensin-converting enzyme; LV = left ventricular; NYHA = New York Heart Association

percentage of biventricular pacing at follow-up was comparable between responders and non-responders (98±5% in responders vs. 98±3% in non-responders p = 0.415).

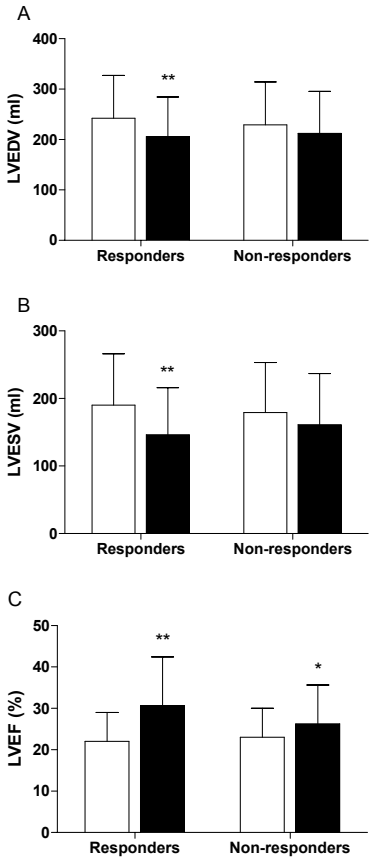

Figure 1. LV end-diastolic volume (LVEDV, panel A), LV end-systolic volume (LVESV, panel B) and LV ejection fraction (LVEF, panel C) at baseline (white bars) and after 6 months CRT (black bars) in clinical responders vs. non-responders (**p<0.001, *p<0.05, baseline vs. 6 months follow-up).

Echocardiographic responders vs. non-responders

Echocardiographic response (defined as a decrease in LVESV by 15% or more) after 6 months of CRT was noted in 187 patients (52%). Baseline characteristics for echocardiographic responders and non-responders are displayed in Table 2B. Echocardiographic responders had significantly more LV dyssynchrony at baseline (101±46 ms vs. 55±45 ms, p<0.001) and a wider QRS complex (172±24 ms vs. 166±24 ms, p<0.001) Furthermore, NYHA functional class IV, atrial fibrillation and ischemic heart failure, were more frequently observed in non-responders. Responders showed a significant decrease (by definition) in LVESV from 189±77 ml at baseline to 125±61 ml at 6 months follow-up. Additionally, LVEDV decreased from

Table 2B. Patient characteristics in echocardiographic responders and non-responders

Variable	Responders (n = 187)	Non-responders (n = 174)	p-value
Age (years)	66 ± 10	67 ± 11	0.496
Men / Women	134 / 53	138 / 36	0.112
NYHA class			**0.032**
III	172 (92%)	147 (84%)	
IV	15 (8%)	27 (16%)	
Cause of heart failure			**0.005**
Ischemic	101 (54%)	120 (69%)	
Nonischemic	86 (46%)	54 (31%)	
QRS duration (ms)	172 ± 24	166 ± 24	**0.041**
Rhythm			**0.025**
Sinus rhythm	151 (81%)	132 (76%)	
Atrial fibrillation	22 (12%)	36 (21%)	
Paced	14 (7%)	6 (3%)	
Systolic blood pressure (mmHg)	121 ± 21	118 ± 21	0.098
Diastolic blood pressure (mmHg)	72 ± 11	72 ± 12	0.609
Serum creatinine (µmol/l)	127 ± 81	134 ± 53	0.331
LV ejection fraction (%)	23 ± 7	23 ± 7	0.956
LV end-diastolic volume (ml)	242 ± 86	236 ± 85	0.512
LV end-systolic volume (ml)	189 ± 77	185 ± 74	0.588
LV dyssynchrony (ms)	101 ± 46	55 ± 45	**<0.001**
LV dyssynchrony ≥65 ms (n)	165 (88%)	64 (37%)	**<0.001**
Medication			
Diuretics	166 (89%)	163 (94%)	0.137
ACE-inhibitors	166 (89%)	162 (93%)	0.201
B-blockers	115 (61%)	109 (63%)	0.829
Spironolactone	89 (48%)	99 (57%)	0.092
Digoxine	42 (22%)	46 (26%)	0.393
Ca-antagonists	16 (9%)	10 (6%)	0.318

ACE = angiotensin-converting enzyme; LV = left ventricular; NYHA = New York Heart Association

242±86 ml to 185±72 ml, p<0.001, and LVEF increased from 23±7% to 34±9%, p<0.001. No changes in LV volumes and LVEF were observed in non-responders. Also for echocardiographic response, there was no difference in percentage of biventricular pacing at follow-up (98±6% in responders vs. 98±4% in non-responders p = 0.377).

Characteristics associated with response to CRT

When clinical response was used to evaluate benefit from CRT, univariate analysis demonstrated that only extent of LV dyssynchrony was associated with response to CRT, see Table 3A. On multivariate analysis, LV dyssynchrony remained predictive for response with an Odds Ratio (OR) of 1.02 per ms (95% CI 1.01 - 1.03, p<0.001), see Table 4A. The pre-defined cut-off value of 65 ms for LV dyssynchrony predicted clinical response at 6 months follow-up with a sensitivity of 75% and a specificity of 67%, see Figure 2.

When echocardiographic response (defined as a reduction in LVESV by 15% or more) was used to evaluate benefit from CRT, univariate analysis demonstrated that LV dyssynchrony, QRS duration and etiology of heart failure were predictive characteristics, see Table 3B. On multivariate analysis, LV dyssynchrony and underlying cause of heart failure remained as independent predictors for echocardiographic response to CRT, see Table 4B. The pre-defined cut-off value of 65 ms for LV dyssynchrony predicted echocardiographic response to CRT at 6 months follow-up with a sensitivity of 88% and a specificity of 63%, see Figure 2. Moreover, a significant relation was observed between the extent of LV dyssynchrony at baseline and the relative reduction in LVESV (y = -3.9 – 0.2x, n = 360, r = 0.379, p<0.001), see Figure 3.

Table 3A. Univariates predicting clinical response to cardiac resynchronization therapy

Variable	Odds ratio	95% Confidence interval	p-value
LV dyssynchrony (per ms)	1.02	1.01 – 1.03	**<0.001**
QRS duration (per ms)	1.01	1.00 – 1.02	0.109
Age (per year)	0.98	0.96 – 1.01	0.165
LV end-diastolic volume (per ml)	1.00	1.00 – 1.01	0.183
LV end-systolic volume (per ml)	1.00	1.00 – 1.01	0.186
LV ejection fraction (per %)	0.98	0.95 – 1.02	0.348
Ischemic cardiomyopathy	0.81	0.51 – 1.31	0.394
Male gender	1.06	0.63 – 1.81	0.817

LV = left ventricular

Table 3B. Univariates predicting echocardiographic response to cardiac resynchronization therapy

Variable	Odds ratio	95% Confidence interval	p-value
LV dyssynchrony (per ms)	1.02	1.02 – 1.03	**<0.001**
Ischemic cardiomyopathy	0.53	0.34 – 0.81	**0.004**
QRS duration (per ms)	1.01	1.00 – 1.02	**0.042**
Male gender	0.66	0.41 – 1.07	0.093
Age (per year)	0.99	0.97 – 1.01	0.496
LV end-diastolic volume (per ml)	1.00	1.00 – 1.00	0.511
LV end-systolic volume (per ml)	1.00	1.00 – 1.00	0.587
LV ejection fraction (per %)	1.00	0.97 – 1.03	0.956

LV = left ventricular

Table 4A. Multivariate predicting clinical response to cardiac resynchronization therapy

Variable	Odds ratio	95% Confidence interval	p-value
LV dyssynchrony (per ms)	1.02	1.01 – 1.03	**<0.001**
Age (per year)	0.98	0.95 – 1.01	0.141
LV end-diastolic volume (per ml)	1.02	0.98 – 1.05	0.441
LV end-systolic volume (per ml)	0.98	0.94 – 1.03	0.449
LV ejection fraction (per %)	0.96	0.86 – 1.07	0.541
QRS duration (per ms)	1.00	0.99 – 1.01	0.802
Ischemic cardiomyopathy	1.05	0.61 – 1.79	0.870

LV = left ventricular

Table 4B. Multivariate predicting echocardiographic response to cardiac resynchronization therapy

Variable	Odds ratio	95% Confidence interval	p-value
LV dyssynchrony (per ms)	1.02	1.02 – 1.03	**<0.001**
Ischemic cardiomyopathy	0.56	0.34 – 0.93	**0.025**
QRS duration (per ms)	1.00	0.99 – 1.01	0.832
Age (per year)	1.00	0.98 – 1.02	0.923

LV = left ventricular

DISCUSSION

During recent years, CRT has become a well-established therapy for patients with advanced heart failure. Large clinical trials have shown improvement in heart failure symptoms, exercise capacity, LV systolic function, LV reverse remodeling and survival after CRT.[8-11] Accordingly, the ACC/AHA/ESC guidelines have recommended a class I indication for CRT implantation in patients with severe heart failure (NYHA class III or IV), depressed LVEF (≤35%), and a wide QRS complex (≥120 ms).[12, 13] Although many patients selected according to these criteria benefit from CRT, around 30% of patients do not demonstrate improvement in clinical criteria and more than 40% of patients do not show a reduction in LVESV (the main echocardiographic measure for response to CRT).[11, 14]

In the current study with 361 patients referred for CRT, 28% of patients did not improve according to clinical criteria and 48% did not improve according to echocardiographic criteria (a reduction in LVESV ≥15%). This discrepancy in response to CRT as determined by echocardiographic vs. clinical criteria has been noted previously.[15] The issue of "non-responders" has attracted a lot of attention over the years and many parameters to improve response rates to CRT have since been proposed, including clinical parameters and echocardiographic parameters.[15-19]

A large amount of echocardiographic studies have demonstrated that cardiac dyssynchrony is a major predictor of response to CRT.[20] The main shortcoming of these studies is that nearly all studies included small numbers of patients and that each study relied on different technologies, with different definitions for LV dyssynchrony (including both the number of myocardial segments evaluated and the extent of LV dyssynchrony).

Color-coded TDI is currently one of the most frequently applied techniques to assess LV dyssynchrony. This technique permits assessment of longitudinal myocardial velocities, and also timing of these velocities. When measuring time-to-peak systolic velocities of different segments, the delay between the peak systolic velocities of these segments can be calculated and used to define LV dyssynchrony. In 2004, this group has introduced a cut-off value of 65 ms as a marker of substantial LV dyssynchrony.[3] This cut-off value was derived from so-called receiver operating characteristic curve analysis. Using this approach, optimal sensitivity and specificity are calculated. In this previous work, including 85 patients undergoing CRT, an optimized sensitivity and specificity of 80% were derived for prediction of clinical response, whereas the sensitivity and specificity were 92% when echocardiographic response (defined as a reduction in LVESV by 15% or more) was used. The presently observed values for diagnostic accuracy are to some extent lower as compared to the previous study. Some issues regarding this lower sensitivity should be addressed.

First, in this study also patients with atrial fibrillation were included. Less response to CRT has previously been observed in patients with atrial fibrillation.[21, 22] Furthermore, obtaining reliable echo measurements is more difficult during atrial fibrillation, and therefore inclusion of these patients may have led to more moderate predictive values.

Perhaps of greater importance is the fact that in the present study, more patients were included with ischemic heart failure (61% vs. 55% in the previous study). Patients with ischemic heart failure show less reverse remodeling after CRT and it has been proposed that this can be attributed to the presence of myocardial scar tissue.[17, 23-25]

Finally, some studies have addressed the interplay between LV lead position and response to CRT, focusing on the LV lead position in relation to the most delayed myocardial segment.[26, 27] It has been demonstrated that a concordant LV lead position (LV lead positioned at the most delayed segment) was an independent predictor of hospitalization-free survival after CRT (hazard ratio: 0.22, $p = 0.004$).[26] One study identified the latest activated myocardial segment in 244 CRT recipients using 2D strain and found that a concordant LV lead position (LV lead

positioned at the most delayed segment) was an independent predictor of hospitalization-free survival after CRT (hazard ratio: 0.22, p = 0.004).[26] Other studies on LV lead position in CRT patients have confirmed these findings.[27, 28]

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