Evolving imaging techniques for the assessment of cardiac structure and function and their potential clinical applications

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CHAPTER 2

Effect of Biventricular Pacing on Diastolic Dyssynchrony

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ABSTRACT

Background: Little is known about the effect of CRT on diastolic dyssynchrony.

Objectives: The study examined the changes in diastolic dyssynchrony with cardiac resynchronization therapy (CRT).

Methods: Consecutive heart failure patients (n = 266, age 65.7 ± 10.0 years) underwent color-coded tissue Doppler imaging at baseline, 48 hours, and six months after CRT. Systolic and diastolic dyssynchrony were defined as maximal time delay in peak systolic and early diastolic velocities respectively, in four basal LV segments. CRT responders were defined as ≥ 15% decrease in LV end-systolic volume at 6 months.

Results: Baseline LVEF was 25.2 ± 8.1%; 63.5% patients were CRT responders. Baseline incidence of systolic and diastolic dyssynchrony, and a combination of both was 46.2%, 51.9% and 28.6% respectively. Compared to non-responders, responders had longer baseline systolic (79.2 ± 43.4 ms vs. 45.4 ± 30.4 ms; $p < 0.001$) and diastolic (78.5 ± 52.0 ms vs. 50.1 ± 38.2 ms; $p < 0.001$) delays. In follow-up, systolic delays (45.4 ± 31.6 ms at 48 hours; 38.9 ± 26.2 ms at 6 months; $p < 0.001$) and diastolic delays (49.4 ± 36.3 ms at 48 hours; 37.7 ± 26.0 ms at 6 months; $p < 0.001$) improved only in responders.

Conclusion: At baseline: 1) diastolic dyssynchrony was more common than systolic dyssynchrony in HF patients; 2) non-responders had less baseline diastolic dyssynchrony compared to responders. After CRT: 1) diastolic dyssynchrony improved only in responders. Further insight into pathophysiology of diastolic dyssynchrony and its changes with CRT may provide incremental information on patient specific treatments.

INTRODUCTION

Systolic dyssynchrony is an independent predictor of clinical outcome and poor survival in heart failure (HF) patients.[1-3] Cardiac resynchronization therapy (CRT) is an accepted treatment of patients with drug refractory HF that improves synchronicity of left ventricular (LV) contraction[4-6], in particular in the responders to this treatment.[4, 5] Diastolic dyssynchrony is at least as common as systolic dyssynchrony in systolic HF patients, and is often present without a concurrent systolic dyssynchrony in this patient population.[5, 7-9] Little is known about the effect of biventricular pacing on the diastolic dyssynchrony, in particular about its changes in the responders and the non-responders to CRT. The present study examined the baseline incidence of the diastolic dyssynchrony and its changes with CRT in the responders and non-responders to this treatment.

METHODS

Patient population

Consecutive end-stage HF patients (n = 266) scheduled for implantation of CRT device were included in the present study. Patients were selected for CRT implantation according to the European Society of Cardiology guidelines[10], meeting the following criteria: 1) severe HF (New York Heart Association (NYHA) functional class III or IV) despite optimal medical treatment, 2) severely depressed LV ejection fraction (LVEF ≤ 35%), and 3) QRS duration > 120 ms. Patients with chronic atrial fibrillation were excluded.

All HF patients underwent a clinically indicated transthoracic echocardiogram at baseline, within 48 hours and at 6 months after CRT implantation, for assessment of LV volumes and systolic function, and LV systolic and diastolic dyssynchrony by color-coded tissue Doppler imaging (TDI).

Evaluation of the baseline 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. A standard 12-lead electrocardiogram was obtained in all subjects before and within 24 hours after the pacemaker implantation, and at 6 month follow-up. Responders were defined as showing ≥ 15% decrease in LV end-systolic volume at 6 months follow-up.[11]

To define the normal range of LV diastolic dyssynchrony, color-coded TDI analysis was performed in 38 age matched controls selected from an echocardiographic database. These individuals were referred to the echocardiography laboratory for evaluation of a cardiac murmur, atypical chest pain, palpitations, or syncope without a murmur and had a normal echocardiogram and no history of cardiovascular disease.

Echocardiography

Transthoracic echocardiography was performed with the subjects at rest in the left lateral decubitus position with commercially available ultrasound transducer and equipment (M3S probe, Vivid 7, GE-Vingmed, Horten, Norway). All images were digitally stored for offline analysis (EchoPac version BT07.0.0, GE-Vingmed, Horten, Norway).

Complete 2-dimensional, color, pulsed and continuous-wave Doppler images were acquired according to standard techniques.[12, 13] Left ventricular end-systolic volume index and end-diastolic volume index were calculated using Simpson's biplane method of discs and indexed to body surface area.[14] Left ventricular ejection fraction was subsequently derived and expressed as percentage. As previously described, the intraobserver agreement for assessment of LV end-systolic and end-diastolic volumes and LVEF were: 7.4 ± 11.2 ml, 7.0 ± 10.1 ml, 1.9 ± 4.4%, respectively.[15] The interobserver agreement for LVEDV, LVESV, LVEF were 12.9 ± 14.7 ml, 11.3 ± 13.9 ml, 2.5 ± 4.9%, respectively.[15] Left atrial volumes were calculated using the ellipsoid model as recommended by the American Society of Echocardiography and indexed to body surface area.[16] Spectral Doppler velocities were measured from the apical 4-chamber view using a 2 mm sample volume. Diastolic function was evaluated by measuring the transmitral early (E wave) and late (A wave) diastolic velocities, and the E wave deceleration time at the mitral leaflet tips. In addition, TDI early diastolic velocities (E') were measured at the septal and lateral mitral valve annulus, as previously described. According to current recommendations, diastolic dysfunction was defined by septal E' ≥8 cm/s or lateral E' ≥ 10 cm/s and indexed left atrial volume ≥ 34 ml/m.[217] Diastolic dysfunction was graded (grade I, II and III) according to E/A ration, E wave deceleration time and average E/E'.[17] Mitral regurgitation severity was determined semi-quantitatively from color Doppler images obtained from the conventional parasternal long-axis and apical views using the regurgitant jet area to left atrial area ratio as previously published.[18]

Color-coded TDI of the LV obtained in the apical 2- and 4-chamber views were acquired during end-expiration, with the sector size and depth optimized for the highest frame rates possible (> 115 frames/s). Care was taken to keep the incidence angle between the direction of the Doppler beam and the analyzed vector of myocardial motion as small as possible.

Data analysis

Regional myocardial color-coded TDI velocity profiles were analyzed offline by positioning the sample volume (6 x 6 mm) in the middle of the basal portion of 4 different LV wall segments (septal, lateral, anterior, and inferior). Aortic valve opening and closure timing intervals were determined using pulse-wave spectral Doppler with the sample volume placed at the LV outflow tract to define the ejection period. Maximal peak systolic myocardial velocity within this ejection period was selected and the time interval between the onset of the QRS complex and the peak systolic velocity (maximal systolic electromechanical delay) per region was derived as previously described.[4, 19, 20] Similarly, maximal diastolic electromechanical delay for each

region was obtained using the peak early diastolic myocardial velocity.[21-23] Intra-ventricular dyssynchrony was determined using the time difference between the shortest and longest electromechanical delays between any 2 out of 4 basal LV segments during systole and early diastole. Significant systolic intra-ventricular dyssynchrony was defined as the maximal systolic electromechanical delay of ≥ 65 ms that was previously shown to predict reverse LV remodeling with CRT [4]. Significant diastolic intra-ventricular dyssynchrony was classified as a maximal diastolic electromechanical delay above that of mean + 2 SD of the control group.[6, 22, 23] All TDI recordings were analyzed by an observer who was blinded to the clinical data and outcome results.

Pacemaker implantation

All patients received a biventricular pacemaker (Contak Renewal 4RF, TR or CD, Boston Scientific St. Paul, Minnesota; or InSync Sentry or III, Medtronic Inc. Minneapolis, Minnesota; Lumax 340 HF-T, Biotronik, Berlin). When a conventional indication for an internal cardioverter defibrillator existed, a combined device was implanted. All pacemaker-implantation procedures were performed under local anesthesia. Pacemaker leads were inserted through the right- or left-sided cephalic or subclavian veins. The right atrial and ventricular leads were positioned conventionally. A coronary sinus venogram was obtained using a balloon catheter, followed by the insertion of the LV pacing lead. An 8-F guiding catheter was used to place the LV lead (Easytrak, Boston Scientific; or Attain-SD, Medtronic; or Corox OTW Biotronik) in the coronary sinus. The LV lead position was targeted to the lateral coronary vein; if unavailable, the posterolateral coronary vein or anterior vein was used. One day after implantation, the LV lead position (anterior, lateral, and posterior) was assessed from a chest X-ray, using the lateral views.[24] Optimization of the atrio-ventricular delays was performed in all the patients within 48 hours after the pacemaker implantation, using iterative method. The optimal atrio-ventricular delay was determined by pulsed-wave Doppler recordings of the transmitral inflow as the shortest atrio-ventricular delay that does not compromise left atrial contribution to the LV diastolic filling.[25] The ventricles were paced simultaneously with an inter-ventricular delay set at 0 ms.

Statistical analysis

Normal distribution of the data was evaluated with the Kolmogorov-Smirnov test. Continuous variables normally distributed are presented as mean and standard deviation whereas continuous variables non-normally distributed are presented as median and interquartile range (25%, 75%). Categorical data are summarized as frequencies and percentages. The Chi-square test with Yates' correction was used to compare categorical variables. The Student's t test and Mann-Whitney U-test were used to compare 2 groups of unpaired continuous data, as appropriate. One-way analysis of variance (ANOVA) and Kruskal-Wallis test were used to compare more than 3 groups of continuous variables, as appropriate. Post-hoc analyses for

significant results were performed using Bonferroni correction. Linear regression analysis was used to calculate the correlation between electrical and echocardiographic parameters. Changes in the maximal systolic and diastolic delays during follow-up after the pacemaker implantation in the responders and non-responders were assessed using repeated measures ANOVA test. Changes in mitral regurgitation grade during follow-up were assessed with McNemar test. Univariable and multivariable logistic regression analyses were performed to evaluate the independent determinants of favorable response to CRT. Baseline clinical (age, HF etiology, baseline QRS duration and serum creatinine) and baseline echocardiographic (LVEF, systolic and diastolic LV dyssynchrony) characteristics of the patients were evaluated. Only variables with $p < 0.05$ at univariable analysis were entered as covariates in the multivariable model. The multivariate logistic regression analysis was performed using an enter method. Odds ratio (OR) and 95% confidence intervals (CI) were calculated. All statistical analyses were performed using SPSS for Windows (SPSS Inc, Chicago), version 16.

RESULTS

Clinical and echocardiographic characteristics of the patients and controls

The patient population consisted of 183 male (68.8%) and 83 female (31.2%) patients with a mean age of 65.7 ± 10.0 years. Biventricular pacemaker implantation was successful in all patients, with 256 (96.2%) patients receiving a combined device with an internal cardioverter defibrillator. The baseline clinical characteristics of the patients are described in Table 1. Approximately equal numbers of the patients had HF of ischemic and non-ischemic etiology. Posterior and lateral lead placements were achieved in 50% and 43.8% patients, respectively, while the leads were placed anteriorly in 6.2% patients. Most patients were in NYHA functional class III at the time of CRT implantation (94.4%). The baseline QRS duration was 165.3 ± 21.7 ms.

Clinically indicated echocardiograms were performed at baseline, 48 hours and 6 months after CRT implantation with the mean color-coded TDI frame rate of 118.5 ± 34.7, 123.9 ± 34.3 and 128 ± 35.5 frames/s and the mean heart rate of 70.9 ± 14.9, 72.1 ± 13.0 and 68.7 ± 11.9 beats/min respectively. The baseline echocardiographic characteristics of the patients are described in Table 1.

Finally, clinical and echocardiographic characteristics of the control population are described in Table 2. Maximal diastolic delay exceeding 55 ms, derived from the mean + 2 standard deviations (54.6 ms) of the maximal diastolic electromechanical delay in the controls, was used to define diastolic intra-ventricular dyssynchrony.

Incidence of systolic and diastolic dyssynchrony in HF patients

Overall, dyssynchrony was present in 69.5% patients at baseline (Table 1). The incidence of diastolic dyssynchrony was higher than that of systolic dyssynchrony (51.9% vs. 46.2%, p =

0.002). Both systolic and diastolic dyssynchrony were present in 28.6% patients, while isolated systolic dyssynchrony (without concurrent diastolic dyssynchrony) was present in 17.6% patients, and 23.7% patients had isolated diastolic dyssynchrony (Table 1). There were no significant differences in the majority of the baseline clinical and echocardiographic characteristics among patients without LV dyssynchrony, with isolated systolic or isolated diastolic dyssynchrony or with concomitant systolic and diastolic LV dyssynchrony (Table 3). There were only statistically significant differences in the quality of life score and in the antiplatelet treatment that was significantly less frequent in patients with isolated diastolic LV dyssynchrony.

Responder vs. non-responder patients

At 6 month follow-up, 63.5% patients were classified as responders based on reverse LV remodeling (≥ 15% decrease in LV end-systolic volume). No significant differences in the baseline clinical and echocardiographic characteristics were observed between the responders and non-responders to CRT (Table 4). By definition, the responder patients showed a significant reduction in LV indexed volumes (end-systolic volume index: from 92.4 ± 43.3 ml/m^2 to 70.5 ± 30.8 ml/m^2, $p < 0.001$; and end-diastolic volume index: from 120.5 ± 47.5 ml/m^2 to 101.1 ± 34.9 ml/m^2, $p < 0.001$) and a significant increase in LVEF (from 24.7 ± 8.1% to 31.8 ± 10.1%, $p < 0.001$). In addition, the percentage of patients showing mitral regurgitation severity ≥2+ significantly reduced (from 51.8% to 14.8%, $p < 0.001$). In contrast, the non-responder patients did not show significant changes in LV volumes (end-systolic volume index: from 85.0 ± 36.2 ml/m^2 to 86.3 ± 30.4 ml/m^2, $p = 0.180$; and end-diastolic volume index: from 112.8 ± 40.1 ml/m^2 to 116.4 ± 37.5 ml/m^2, $p = 0.064$) or LVEF (from 26.2 ± 8.0% to 26.0 ± 8.9%, $p = 0.850$). Finally, non-significant reduction in the percentage of patients showing mitral regurgitation severity ≥ 2+ was noted (from 46.9% to 36.1%, $p = 0.078$).

The responders were more likely to have baseline systolic and/or diastolic dyssynchrony compare to the non-responders (Figure 1). In addition, over 80% of those patients who had dyssynchrony of any type at baseline responded to CRT, compared to 23.8% of those without baseline dyssynchrony. Moreover, response to CRT was also seen in over two-thirds of the patients who had isolated diastolic dyssynchrony (71.0%), in 82.6% with isolated dyssynchrony and in 86.7% in patients with concomitant systolic and diastolic dyssynchrony.

Table 1. Baseline clinical and echocardiographic characteristics of the patients

	All patients (n = 266)
Age (years)	65.7 ± 10.0
Male /Female (number)	183 / 83
Etiology of heart failure (%)	
Ischemic	52.1
Dilated	47.9
Diabetes mellitus (%)	18.8
Serum creatinine (µmol/L)	102.5 (82, 128.7)
QRS (ms)	165.3 ± 21.7
NYHA (%)	
III	94.4
IV	5.6
Quality of life score	37.1 ± 18.6
6 minute walking test (m)	308.9 ± 115.5
Medications (%)	
Beta blockers	70.3
ACE inhibitors / ARB	93.2
Diuretics	82.7
Spironolactone	50.4
Antiplatelets / anticoagulation	89.8
Amiodarone	20.7
Statins	53.8
2-dimensional Echocardiography and Doppler	
LV ejection fraction (%)	25.2 ± 8.1
End-systolic volume index (ml/m^2)	89.7 ± 41.0
End-diastolic volume index (ml/m^2)	117.7 ± 45.0
Left atrial volume index (ml/m^2)	42.5 ± 13.7
Transmitral E/A ratio	1.7 ± 1.3
E-wave Deceleration time (ms)	176.8 ± 72.2
E/E' ratio	24.1 ± 19.9
Diastolic dysfunction grade (%)	
I	42.9
II	31.6
III	25.6
Mitral regurgitation grade ≥ 2 (%)	50.0
Dyssynchrony by color-coded TDI (%)	
Systolic dyssynchrony	46.2
Diastolic dyssynchrony	51.9
Systolic and diastolic dyssynchrony	28.6
Isolated systolic dyssynchrony	17.6
Isolated diastolic dyssynchrony	23.7

Table 2. Clinical and echocardiographic characteristics of the control population

Variable	Controls (n = 38)
Age (years)	63.4 ± 4.3
Male /Female (number)	23 / 15
2-dimensional Echocardiography	
LV ejection fraction (%)	60.6 ± 7.8
End-systolic volume index (ml/m^2)	28.9 ± 8.0
End-diastolic volume index (ml/m^2)	76.6 ± 17.4
Color-coded TDI	
Maximal LV systolic delay (ms)	27.0 ± 17.2
Maximal LV diastolic delay (ms)	27.8 ± 13.4

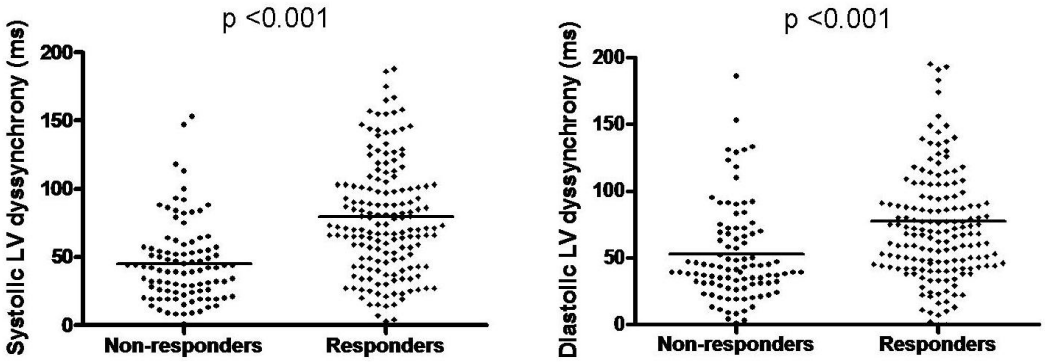

Figure 1. Baseline systolic and diastolic LV dyssynchrony in responders and non-responders. Responder patients showed significant larger systolic and diastolic delays at baseline as compared to non-responder patients (79.2 ± 43.4 ms vs. 45.4 ± 30.4 ms for systolic delays, and 78.5 ± 52.0 vs. 50.1 ± 38.2 ms for diastolic delays; p < 0.001 for both).

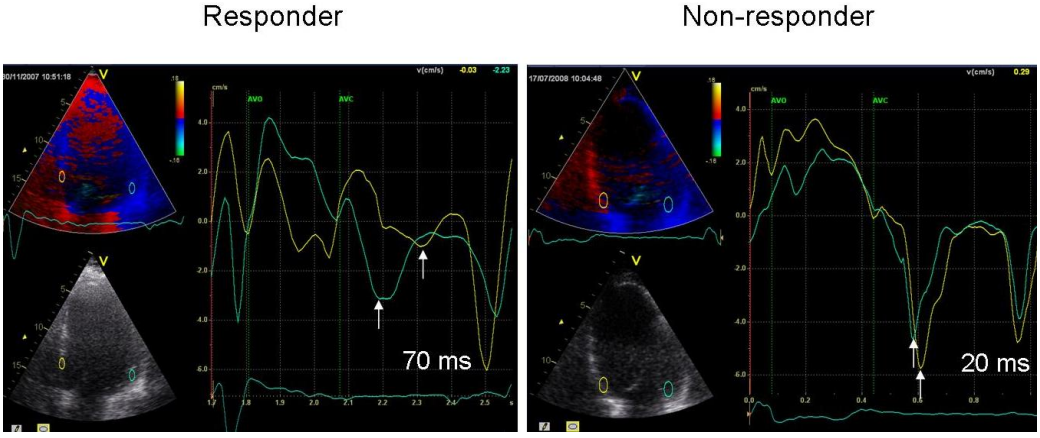

Figure 2. Diastolic LV dyssynchrony with color-coded TDI in responders and non-responders. The responder patient showed significant diastolic LV dyssynchrony as measured with color-coded TDI. The maximum time delay between two opposing walls was 70 ms. In contrast, the non-responder patient did not show significant diastolic LV dyssynchrony (20 ms).

Table 3. Baseline clinical and echocardiographic characteristics of the HF patients according to the presence and type of LV dyssynchrony

Variable	No LV dyssynchrony (n = 84)	Isolated systolic LV dyssynchrony (n = 46)	Isolated diastolic LV dyssynchrony (n = 61)	Systolic and diastolic LV dyssynchrony (n = 75)	p-value
Age (years)	65.3 ± 11.2	63.9 ± 11.3	66.3 ± 8.9	66.7 ± 8.4	0.467
Male /Female (number)	62 / 22	29 / 17	40 / 21	52 / 23	0.763
Etiology of heart failure (%)					0.122
Ischemic	54.8	50	41	58.7	
Dilated	45.2	50	59	41.3	
Diabetes mellitus (%)	20.2	23.9	14.8	17.3	0.464
Serum creatinine (µmol/L)	102.0 (82.0, 136.0)	101.5 (89.0, 120.5)	104.5 (81.0, 138.2)	102.0 (81.0, 126.0)	0.535
QRS (ms)	164.7 ± 19.7	166.1 ± 20.8	163.7 ± 23.8	165.9 ± 22.4	0.922
NYHA III-IV(%)					0.037
III	98.8	97.8	95.1	86.7	
IV	1.2	2.2	4.9	13.3	
Quality of life score	34.3 ± 18.3	32.9 ± 16.5*	38.1 ± 19.3	42.0 ± 18.6	0.040
6 minute walking test (m)	332.8 ± 113.2	305.1 ± 116.3	298.3 ± 105.6	293.6 ± 123.8	0.880
Medications (%)					
Beta blockers	69.0	80.4	62.3	72.0	0.231
ACE inhibitors / ARB	95.2	89.1	91.8	94.7	0.531
Diuretics	79.8	87.0	82.0	84.0	0.753
Spironolactone	41.7	54.3	59.0	50.7	0.198
Antiplatelets / anticoagulation	94.0	93.5	78.7	92.0	0.012
Amiodarone	22.6	13.0	27.9	17.3	0.234
Statins	51.2	63.0	45.9	57.3	0.294
2-D echocardiography and Doppler					
LV ejection fraction (%)	25.8 ± 7.6	25.3 ± 9.1	24.3 ± 7.1	25.3 ± 8.5	0.748
End-systolic volume index (ml/m^2)	83.9 ± 37.4	91.3 ± 47.7	90.4 ± 34.6	90.7 ± 43.8	0.995
End-diastolic volume index (ml/m^2)	111.3 ± 42.5	119.4 ± 51.5	117.8 ± 39.8	118.9 ± 46.9	0.983
Left atrial volume index (ml/m^2)	42.2 ± 12.1	43.5 ± 12.6	43.1 ± 13.8	41.4 ± 16.1	0.841
Transmitral E/A ratio	1.5 ± 1.2	1.7 ± 1.3	1.6 ± 1.5	1.8 ± 1.4	0.655
E-wave Deceleration time (ms)	185.0 ± 74.4	175.5 ± 60.6	173.7 ± 72.3	171.1 ± 76.7	0.947
E/E' ratio	24.9 ± 20.6	19.5 ± 13.7	23.7 ± 16.2	26.4 ± 24.7	0.370
Diastolic dysfunction grade (%)					0.556
I	46.4	47.8	44.2	34.7	
II	27.4	34.8	27.9	37.3	
III	26.2	17.4	27.9	28.0	
Mitral regurgitation grade ≥ 2 (%)	44.0	56.5	45.9	56.0	0.678

Values are mean ± SD, n, %, or interquartile range (25%, 75%). Continuous variables with normal distribution were compared with 1-way ANOVA test, whereas continuous variables not normally distributed (serum creatinine) were compared with Kruskal-Wallis test. *p - 0.034 isolated systolic LV dyssynchrony versus systolic and diastolic LV dyssynchrony. HF - heart failure; other abbreviations as in Tables 1 and 2.

Table 4. Baseline clinical and echocardiographic characteristics of the responder and non-responder patients

Variable	Responders (n = 169)	Non-responders (n = 97)	p-value
Age (years)	65.5 ± 9.2	66.0 ± 11.3	0.708
Male /Female (number)	116 / 53	67 / 30	0.942
Etiology of heart failure (%)			0.704
Ischemic	51.2	53.6	
Dilated	48.8	46.4	
Diabetes mellitus (%)	20.7	15.5	0.292
Serum creatinine (µmol/L)	104.0 (80.0, 138.0)	102.0 (84.0, 126.0)	0.908
QRS (ms)	166.9 ± 22.7	162.5 ± 19.8	0.112
NYHA (%)			0.055
III	92.3	97.9	
IV	7.7	2.1	
Quality of life score	37.4 ± 18.7	36.6 ± 18.3	0.737
6 minute walking test (m)	303.7 ± 116.0	318.3 ± 114.6	0.357
Medications (%)			
Beta blockers	71.0	69.1	0.740
ACE inhibitors / ARB	92.9	93.8	0.775
Diuretics	82.8	82.5	0.939
Spironolactone	49.7	51.5	0.772
Antiplatelets / anticoagulation	89.9	89.7	0.948
Amiodarone	20.1	21.6	0.767
Statins	55.6	50.5	0.421
2-dimensional Echocardiography			
LV ejection fraction (%)	24.7 ± 8.1	26.2 ± 8.0	0.130
End-systolic volume index (ml/m^2)	92.4 ± 43.3	85.0 ± 36.2	0.270
End-diastolic volume index (ml/m^2)	120.5 ± 47.5	112.8 ± 40.1	0.327
Left atrial volume index (ml/m^2)	42.0 ± 13.5	43.3 ± 13.9	0.440
Transmitral E/A ratio	1.8 ± 1.5	1.5 ± 1.1	0.125
E-wave Deceleration time (ms)	170.8 ± 70.0	187.4 ± 75.0	0.076
E/E' ratio	25.3 ± 21.6	21.3 ± 17.1	0.252
Diastolic dysfunction grade (%)			0.159
I	38.5	50.5	
II	33.7	27.8	
III	27.8	21.6	
Mitral regurgitation grade ≥ 2 (%)	51.8	46.9	0.330

Values are mean ± SD, n, %, or interquartile range (25%, 75%). Continuous variables with normal distribution were compared with Student *t* test, whereas continuous variables not normally distributed (serum creatinine) were compared with Mann-Whitney *U* test.

Intra-ventricular electromechanical systolic and diastolic delays after CRT

Baseline intra-ventricular systolic and diastolic delays were significantly longer in the responders compared to the non-responders (79.2 ± 43.4 ms vs. 45.4 ± 30.4 ms for systolic delays, and 78.5 ± 52.0 vs. 50.1 ± 38.2 ms for diastolic delays; $p < 0.001$ for both). Figure 2 illustrates the examples of responder and non-responder patients. The responder patient showed significant LV isolated diastolic dyssynchrony whereas the non-responder patient did not show LV dyssynchrony (Figure 2). After CRT implantation, a significant improvement in both systolic and diastolic delays was observed in the responders. In contrast, the non-responders had further worsening of the systolic delays and no change in the diastolic delays after the device implantation. At follow-up, the responder patients showed a significant decrease in systolic LV dyssynchrony (from 79.2 ± 43.4 ms to 45.4 ± 31.6 ms at 48 hours and to 38.9 ± 26.2 ms at 6 months follow-up; ANOVA p-value < 0.001) and in diastolic dyssynchrony (from 78.5 ± 52.0 ms to 49.4 ± 36.3 ms at 48 hours and to 37.7 ± 26.0 ms at 6 months follow-up; ANOVA p-value < 0.001). In contrast, the non-responders showed a significant increase in systolic LV dyssynchrony (from 45.4 ± 30.4 ms to 65.3 ± 45.9 ms at 48 hours and to 62.1 ± 38.3 ms at 6 months follow-up; ANOVA p-value < 0.001) but diastolic LV dyssynchrony remained unchanged (from 50.7 ± 38.0 ms to 58.6 ± 37.5 ms at 48 hours and to 55.7 ± 42.0 ms at 6 months follow-up; ANOVA p-value = 0.206). Interestingly, in the group of patients with isolated diastolic LV dyssynchrony at baseline, there was a slight but significant increase in systolic dyssynchrony measures at 48 hours and 6 months follow-up (from 35.6 ± 15.9 ms to 51.5 ± 47.3 ms and to 46.2 ± 35.1, ANOVA p-value = 0.003). Importantly, a significant reduction in diastolic dyssynchrony measures was observed at 48 hours and at 6 months after CRT (from 108.9 ± 61.7 ms to 60.0 ± 43.7 ms to 44.8 ± 29.5 ms, ANOVA p-value < 0.001). Improvement in the systolic and diastolic delays was seen regardless of the etiology of HF (65.3 ± 38.2 ms at baseline, 54.0 ± 40.5 ms at 48 hours, 45.6 ± 37.4 ms at 6 months after CRT for ischemic cardiomyopathy; $p < 0.001$, and 74.8 ± 60.8 ms at baseline, 50.8 ± 32.1 ms at 48 hours, 42.9 ± 30.5 ms at 6 months for dilated cardiomyopathy; ANOVA p-value < 0.001).

There was no significant correlation between the QRS duration and the systolic delays ($r = 0.072$; $p = 0.245$) and the diastolic delays ($r = 0.042$; $p = 0.500$) at baseline. A weak correlation was noted between the shortening of QRS duration and the improvement of the systolic dyssynchrony within 48 hours after CRT (0.154; $p = 0.022$), and at 6 months ($r = 0.131$; $p = 0.038$), while no correlation was observed in the diastolic dyssynchrony ($r = 0.011$; $p = 0.868$ within 48 hours after CRT, and $r = 0.029$; $p = 0.649$ at 6 months).

Table 5. Univariable and multivariable determinants of favorable response to CRT.

	Univariable analysis		Multivariable Analysis	
	p-value	OR (95% CI)	p-value	OR (95% CI)
Age	0.707	0.995 (0.970 – 1.021)		
HF etiology	0.704	0.908 (0.550 – 1.498)		
Serum creatinine	0.379	1.002 (0.998 – 1.006)		
QRS duration	0.113	1.010 (0.998 – 1.022)		
Left atrial indexed volume	0.439	0.993 (0.975 – 1.011)		
LVEF	0.086	0.969 (0.935 – 1.004)		
Systolic dyssynchrony	< 0.001	7.085 (3.885 – 12.919)	< 0.001	7.631 (3.972 – 14.663)
Diastolic dyssynchrony	< 0.001	5.776 (3.327 – 9.995)	< 0.001	4.607 (2.459 – 8.633)

CI - confidence interval; CRT _ cardiac resynchronization therapy; HF - heart failure; LVEF - left ventricular ejection fraction; OR odds ratio.

Univariable and multivariable determinants of favorable response to CRT.

Univariable and multivariable logistic regression analyses demonstrated that the strongest determinants of favorable response to CRT were baseline systolic and diastolic LV dyssynchrony (Table 5). In contrast, any other clinical or echocardiographic parameters were selected in the multivariable model.

DISCUSSION

The major findings of this study were: 1) baseline incidence of diastolic dyssynchrony in HF patients was higher than that of systolic dyssynchrony; 2) baseline intra-ventricular systolic and diastolic delays were significantly longer in the CRT responders compared to the non-responders; 3) significant improvement in the systolic delays and the diastolic delays post-CRT was observed only in the responders, but not in the non-responders to CRT.

Incidence of diastolic dyssynchrony in HF patients

The benefits of cardiac resynchronization therapy include improvement in the symptoms and LV systolic function, and promotion of LV reverse remodeling in heart failure patients who are refractory to medical treatment. Improved synchronicity of systolic contraction explains in part the benefit derived from CRT. Consequently, most studies have focused on the assessment of systolic dyssynchrony in CRT population. However, it has been shown that left bundle branch block is associated with not only systolic, but also diastolic dyssynchrony.[26] In addition, cardiac output is dependent not only on systolic emptying but also on diastolic filling. Therefore, not only systolic, but also diastolic dyssynchrony may contribute to hemodynamic compromise in

the failing heart.[8] The effect of biventricular pacing on diastolic dyssynchrony is less clear and whether its improvement plays an important role in the mechanism of response CRT is not known.

In a few recent studies, diastolic dyssynchrony in HF patients with wide QRS complex was found to be at least as common as systolic dyssynchrony, with the prevalence ranging between 40% - 81% for diastolic dyssynchrony and 40% - 73% for systolic dyssynchrony depending on the echocardiographic definition of dyssynchrony used.[7-9] Similar to the previous reports[7-9], the present study showed that diastolic dyssynchrony was more prevalent than systolic dyssynchrony in HF patients scheduled for CRT. Furthermore, the results of the present study supported the previous evidence that systolic and diastolic dyssynchrony do not always co-exist despite wide QRS complex. Relatively low prevalence of concomitant systolic and diastolic dyssynchrony of 28.6% in our study population was similar to the previous reports (25% – 49%).[7, 9, 27] Although coexistence of systolic and diastolic dyssynchrony has been shown to be more common in the patients with wide QRS complex compare to those with narrow QRS complex[7], no correlation between the QRS duration and systolic or diastolic dyssynchrony was demonstrated in the present study. In addition, those patients who responded to CRT were much more likely to have not only baseline systolic, but also diastolic dyssynchrony compared to the non-responders. These findings suggest that the underlying pathophysiology of the two conditions may differ and they may not be regarded as a condition in common.[7, 27]

Pathophysiology of diastolic dyssynchrony in HF Patients

There are several pathophysiological mechanisms that can account for diastolic dyssynchrony in patients with systolic HF. The most obvious explanation for the presence of diastolic dyssynchrony is systolic dyssynchrony: the segments with delayed contraction also show delayed relaxation.[23] However, as described earlier, less than half of the HF patients have a co-existent systolic and diastolic dyssynchrony.

Another potential reason is the presence of coronary artery disease. In the previous studies using radionuclide angiography, coronary artery disease was associated with asynchronous left ventricular regional diastolic function that improved after coronary revascularization.[28-30] Most patients had preserved LV systolic function and similar data in HF patients are lacking. The present study showed no significant differences in either systolic or diastolic dyssynchrony between the ischemic and non-ischemic etiologies of HF suggesting mechanisms other than myocardial ischemia.

Diastolic function and ventricular filling pattern appear to be important components of the underlying pathophysiology of diastolic dyssynchrony. The degree of diastolic but not systolic dysfunction, as expressed by the mean myocardial systolic and early diastolic velocity from the six basal LV segments using TDI, has been shown to predict diastolic dyssynchrony.[9] It also appears that filling abnormalities related to ventricular interaction in diastole are of crucial importance in CRT patients.[31] Left ventricular filling may be impeded in up to half of HF patients

due to ventricular interaction from raised right ventricular (RV) diastolic pressure and by external constraint from the pericardium, especially in the patients with increased LV filling pressures.[31] This diastolic interaction could explain the delayed onset of mechanical diastolic motion in the LV even in patients without concurrent systolic dyssynchrony.[7] In the present study, the effect of ventricular interaction on response to CRT was not addressed, and remains to be determined in further studies.

Effect of CRT on diastolic dyssynchrony

Limited information on the effect of CRT on diastolic dyssynchrony is available. In small cohort studies, either no improvement in diastolic dyssynchrony[20], or less improvement than in systolic dyssynchrony[7] has been demonstrated shortly after the initiation of biventricular pacing, compared to baseline. A mid-term follow-up study showed improvement in diastolic dyssynchrony only in the patients with non-ischemic cardiomyopathy, while systolic dyssynchrony improved regardless of the HF origin.[8]

The present study with a larger cohort of HF patients demonstrated a significant improvement in both systolic and diastolic dyssynchrony acutely and at 6 months after CRT, with no difference between the patients with ischemic and non-ischemic HF. In addition, both systolic and diastolic dyssynchrony improved only in the CRT responders, but not in the non-responders.

Despite of a significant shortening of QRS duration with CRT, there was only a weak correlation between the reduction of QRS duration and improvement in the systolic dyssynchrony. No such correlation was observed for the diastolic dyssynchrony, suggesting that the improved coordination of LV myocardial relaxation with CRT is independent of electrical activation.

Considering that only about one third of HF patients have concurrent systolic and diastolic dyssynchrony, the effect of CRT on diastolic dyssynchrony cannot be entirely explained by systolic resynchronization. CRT may influence favorably on diastolic ventricular interaction.[31] Up to half of the chronic HF patients have impaired LV diastolic filling due abnormal interventricular septum mechanics. The increased right ventricular diastolic pressure induces changes in the right ventricular geometry with a leftward shift and abnormal motion of the interventricular septum. In addition, dilatation of the right and left ventricular chambers increases the external constraint from the pericardium. This diastolic ventricular interdependence may explain the delayed onset of mechanical diastolic motion of the left ventricle, even in patients without systolic dyssynchrony. Acute benefit of CRT on LV filling pressures has been demonstrated particularly in patients with elevated filling pressures prior to CRT, irrespective of left bundle branch block.[32] Left ventricular pacing may result in LV filling before RV filling, thus reducing the ventricular interaction from the elevated right ventricular diastolic pressure, therefore permitting greater LV filling prior to the development of external constraint.[32] This could also be translated into a more synchronous relaxation pattern of the LV.

Therefore, CRT seems to exert beneficial effects also on LV diastolic performance that may be of importance for the clinical and echocardiographic response at long-term follow-up.

CONCLUSIONS

High incidence of the baseline intra-ventricular diastolic dyssynchrony in the responders to CRT, and its immediate and sustained improvement with biventricular pacing irrespective of the changes in QRS duration are suggestive of a pathophysiology independent of the electromechanical coupling. More comprehensive evaluation of the electrical and mechanical interactions of LV myocardium throughout the cardiac cycle may provide further information on the more patient-specific therapeutic strategies in HF patients.

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