Chapter 24

Association of intraventricular mechanical dyssynchrony with response to cardiac resynchronization therapy in heart failure patients with a narrow QRS complex

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ABSTRACT

Background: Current criteria for cardiac resynchronization therapy (CRT) are restricted currently to patients with a wide QRS complex (>120 ms). Overall, only 30% of heart failure patients demonstrate a wide QRS complex, leaving the majority of heart failure patients without this treatment option. However, patients with a narrow QRS complex exhibit left ventricular (LV) mechanical dyssynchrony, as assessed with echocardiography. To further elucidate the possible beneficial effect of CRT in heart failure patients with a narrow QRS complex, this 2-center, non-randomized observational study focused on different echocardiographic parameters of LV mechanical dyssynchrony reflecting atrioventricular, interventricular and intraventricular dyssynchrony and the response to CRT in these patients.

Methods: A total of 123 consecutive heart failure patients with a narrow QRS complex (<120 ms) undergoing CRT were included at 2 centers. Several widely accepted measures of mechanical dyssynchrony were evaluated: LV filling ratio (LVFT/RR), LV pre ejection time (LPEI), inter ventricular mechanical dyssynchrony (IVMD), opposing wall delay (OWD) and anteroseptal posterior wall delay with speckle-tracking (ASPWD). Response to CRT was defined as a reduction ≥15% in LVESV at 6 months follow-up.

Results: Measures of dyssynchrony can frequently be observed in patients with a narrow QRS complex. Nonetheless, for LVFT/RR, LPEI and IVMD, presence of predefined significant dyssynchrony is less than 20%. Significant intraventricular dyssynchrony is more widely observed in these patients. With ROC curve analyses, both OWD and ASPWD demonstrated to be useful in predicting response to CRT in narrow QRS patients with a cut-off value of 75 ms and 107 ms, respectively.

Conclusions: Mechanical dyssynchrony can be widely observed in heart failure patients with a narrow QRS complex. In particular, intraventricular measures of mechanical dyssynchrony may be useful in predicting LV reverse remodeling at 6 months follow-up in heart failure patients with a narrow QRS complex, but with more stringent cut-off values than currently used in "wide" QRS patients.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is an established treatment for patients with severe symptomatic heart failure, depressed left ventricular (LV) ejection fraction (LVEF) and QRS complex ≥120 ms.[1] Several studies demonstrated that heart failure patients with depressed LVEF but a narrow QRS complex have mechanical dyssynchrony, as assessed with echocardiography.[2-4] Previous single center studies of CRT in patients with narrow QRS complex and mechanical dyssynchrony have suggested a therapeutic benefit.[4-7] However, the results of the first randomized trial of CRT in heart failure patients with QRS complexes (<130 ms) by Beshai et al were equivocal.[8] RethinQ could not demonstrate conclusive evidence to support CRT in narrow QRS patients by its primary end-point of peak myocardial oxygen consumption. Notwithstanding patients randomized to CRT demonstrated significant improvement in New York Heart Association (NYHA) functional class and showed a trend toward lower heart failure event rates compared with control patients, the potential benefits of CRT for patients with a narrow QRS complex remain still elusive. As such, the objectives of the current study were to test the hypotheses that CRT may be associated with favorable LV reverse remodeling in patients with a narrow QRS duration, and that specific echocardiographic markers of dyssynchrony may predict LV functional response in a 2-center, non-randomized observational study.

METHODS

Study population and protocol

A total of 123 consecutive patients with a QRS duration <120 ms, referred for echocardiographic dyssynchrony study prior to CRT were included at 2 centers (34 patients in Pittsburgh and 89 in Leiden). All patients were in NYHA class III and had a LVEF ≤35%. Patients were not part of a clinical trial, but were referred for CRT implantation, due to severe systolic heart failure with no other remaining treatment options. Before CRT implantation, all patients underwent extensive evaluation of clinical status as well as transthoracic echocardiography. Clinical evaluation included the assessment of NYHA functional class, quality-of-life score (according to Minnesota Living With Heart Failure Questionnaire)[9] and 6-minute walking test.[10]

Echocardiography

All patients underwent echocardiography in the left lateral decubitus position before and 6 months after CRT 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 views (long-axis, 2- and 4-chamber images). Standard 2-dimensional (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 off-line analysis (EchoPac 7.0.0, General Electric Vingmed Ultrasound, Milwaukee, USA). Sector width was optimized to allow for complete myocardial visualization while maximizing frame rate. Gain settings were adjusted for routine clinical grayscale 2D images to optimize endocardial definition. For speckle-tracking analysis, standard 2D grayscale images were acquired at a mean frame rate of 65±15 frames/s (range 30-100 frames/s). In addition, color coded tissue Doppler imaging (TDI) was performed at a frame rate >80 frames/s in all subjects and aliasing velocity of 16-32 cm/s. Left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV) and LVEF were measured from the apical 2- and 4-chamber images, using the modified biplane Simpson's rule.[11] Response to CRT was defined as a reduction ≥15% in LVESV at 6 months follow-up.[12, 13]

Dyssynchrony measurements

A comprehensive assessment of cardiac dyssynchrony was performed, comprising the analysis of atrioventricular, inter- and intraventricular dyssynchrony:

Atrioventricular dyssynchrony analysis

To assess atrioventricular dyssynchrony, recordings of transmitral flow with pulsed-wave Doppler were used.[14] Diastolic filling time was defined as the sum of E wave + A wave duration (LVFT). This diastolic filling time was then divided by the RR interval, see Figure 1A. A diastolic filling ratio (LVFT/RR) <40% was considered to represent significant atrioventricular dyssynchrony.[15]

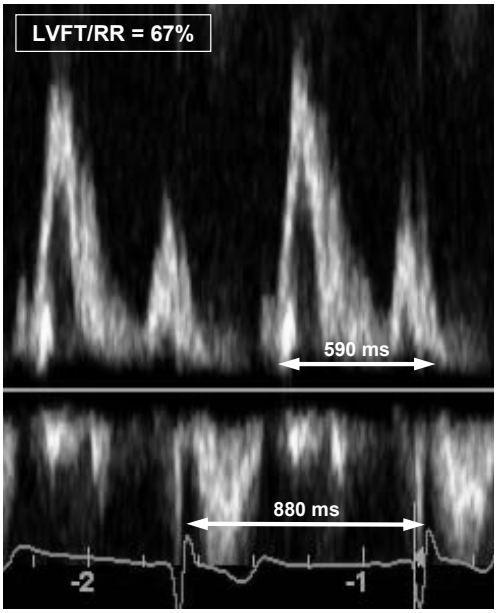

Figure 1A. Example of left ventricular filling ratio (LVFT/RR). LVFT/RR in this patient is 67%.

Interventricular dyssynchrony analysis

Two parameters were measured to evaluate interventricular dyssynchrony: the left pre-ejection interval (LPEI) and the interventricular mechanical delay (IVMD). The LPEI was obtained using standard pulsed-wave Doppler echocardiography on the apical long-axis view, measuring the time from onset of the QRS complex to onset of aortic flow, see Figure 1B. The previously proposed cut-off value of 140 ms was used to define a prolonged delay.[15] To calculate the interventricular mechanical delay (IVMD), time from onset of the QRS to onset of pulmonary flow was measured at the parasternal short-axis view, using pulsed wave Doppler. The difference between these 2 values resulted in the IVMD,[16] see Figure 1C. Based on previous work, an IVMD greater than 40 ms represented significant delay.[15, 17]

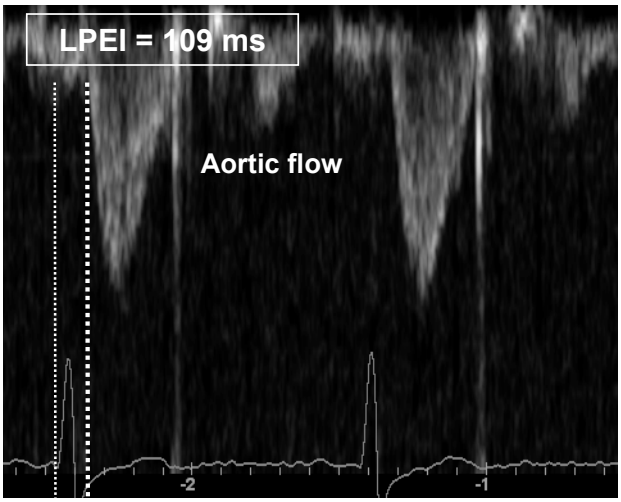

Figure 1B. Example of left pre ejection interval (LPEI). LPEI in this patient is 109 ms.

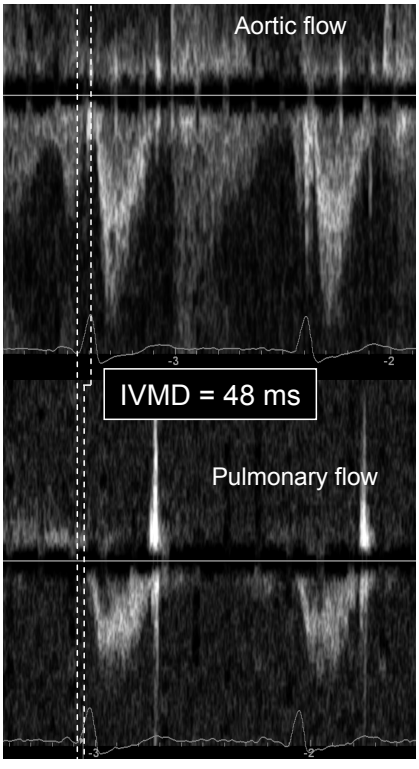

Figure 1C. Example of inter ventricular mechanical delay (IVMD). IVMD in this patient is 48 ms.

Intraventricular dyssynchrony analysis

The intraventricular dyssynchrony was evaluated by TDI derived longitudinal dyssynchrony and speckle-tracking 2D radial strain dyssynchrony. For assessment of longitudinal left ventricular (LV) dyssynchrony, TDI was performed using the apical 2- and 4-chamber views. Regions of interest were placed in the basal portions of the anterior, inferior, septal and lateral segments.[13] For all patient studies, regions of interest were manually adjusted within the segment in the longitudinal plane of the LV and within the wall to identify the most reproducible peak velocity during LV ejection. Systolic peaks after aortic valve closure were not included. Dyssynchrony by TDI was determined as a minimum time difference in peak systolic velocities ≥65 ms between any two opposing walls (OWD),[13] see Figure 1D.

For assessment of radial dyssynchrony, speckle-tracking analysis of routine grayscale mid LV short-axis images was performed as previously described.[18] In brief, an end-systolic circular region of interest was manually traced on the endocardial-border (minimum cavity area). The software then automatically created a second larger circle at the epicardial level, such that the region of interest spans the LV myocardium. The width of this automatically created region of interest could be adjusted manually by the operator, depending on the thickness of the LV wall. Speckle-tracking automatically analyzed frame-by-frame movement of the stable acoustic markers distributed within the myocardial wall, or speckles, over the cardiac cycle.[18, 19] From this frame-by-frame movement, it calculated regional strain vectors as change in length/initial length, with myocardial thickening toward the LV center represented as a positive value. Next, the traced endocardium was automatically divided into 6 standard segments: septal, anteroseptal, anterior, lateral, posterior and inferior. Finally, corresponding time-strain curves for all 6 segments were constructed. Significant radial dyssynchrony was defined as the time difference between the anteroseptal and posterior wall segmental peak strain (ASPWD) ≥130 ms,[18] see Figure 1E.

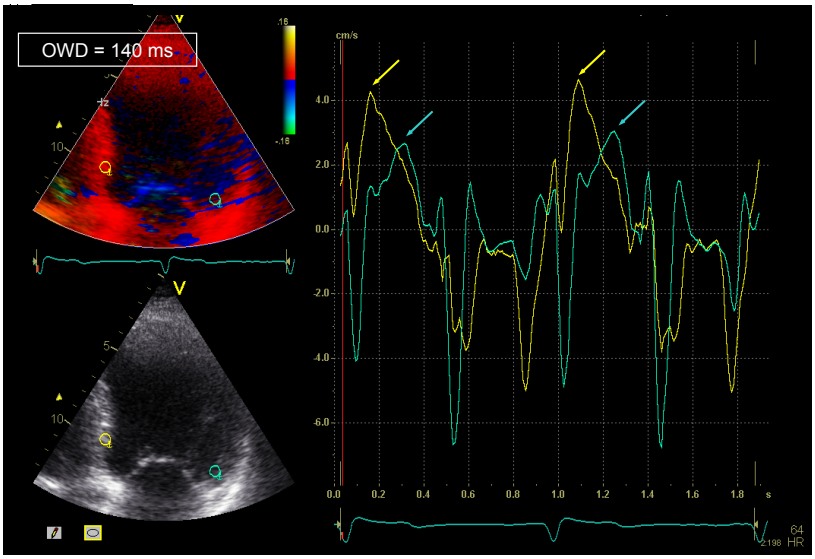

Figure 1D. Example of opposing wall delay (OWD). OWD in this patient exists between the septum and the lateral wall and is 140 ms.

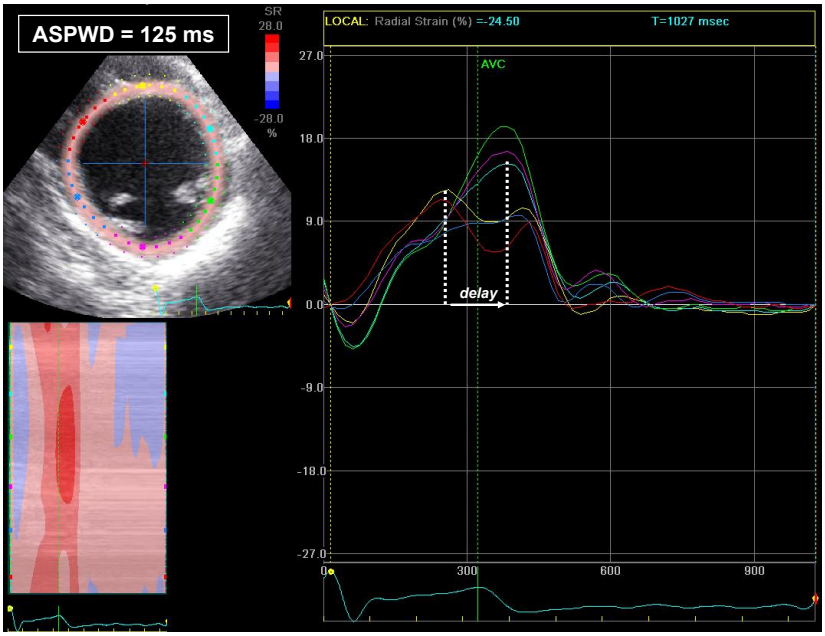

Figure 1E. Example of anteroseptal to posterior wall delay (ASPWD). ASPWD in this patient is 125 ms.

Device implantation

The LV 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 an 8Fr guiding catheter and positioned as far as possible in the venous system, preferably in a (postero-) lateral vein. The right atrial and ventricular leads were positioned conventionally, and all leads were connected to a dual-chamber biventricular implantable cardiac device. When an indication for internal defibrillator existed, a combined CRT-D device was used. Simultaneous biventricular pacing was applied without exception for the first 6 months. The programmed atrioventricular delays ranged from 100 ms to 130 ms.

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. Data for LVEDV, LVESV, QRS duration, IVMD and ASPWD were not normally distributed (as evaluated by Kolmogorov–Smirnov tests) and therefore presented as medians and corresponding 25th and 75th percentiles. Consequently, comparison of these data between patient groups was performed with the Mann-Whitney U-test. 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. Comparison of data for LVEDV, LVESV, QRS duration, IVMD and ASPWD within patient groups was performed with the Wilcoxon test. Receiver operator characteristic (ROC) curves were constructed for different dyssynchrony measurements to determine the optimal cut-off value. An optimal cut-off value was defined as the value that yielded the highest sum of sensitivity and specificity. All analyses were performed with SPSS for Windows, version 16.0 (SPSS, Chicago, IL). All statistical tests were two-sided. A p-value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

A total of 123 patients were included; baseline characteristics of these patients are summarized in Table 1. All patients were in NYHA functional class III and had enlarged LV volumes with severely depressed LV function (mean LVEF 27±7%). Medication included diuretics in 94%, angiotensin-converting enzyme-inhibitors in 90% and beta-blockers in 93%. All medication was continued after CRT implantation. According to study protocol, all subjects had QRS duration <120 ms with a mean of 105±10 ms.

Table 1. Patient characteristics (n = 123)

Age (years)	61 ± 11
Men / women	97 / 26
Etiology (n)	
Ischemic	75 (61%)
Non-ischemic	48 (39%)
NYHA class III	123 (100%)
6 MWT (m)	310 ± 100
QoL score	34 ± 19
QRS duration (ms), 25^{th}-75^{th} percentiles	106 (98-114)
PR interval (ms)	176 ± 28
Medication (n)	
Diuretics	116 (94%)
ACE-inhibitors/AII-blocker	111 (90%)
Beta-blockers	114 (93%)
Spironolactone	75 (61%)
LVEDV (ml), 25^{th}-75^{th} percentiles	189 (155-237)
LVESV (ml), 25^{th}-75^{th} percentiles	141 (110-176)
LVEF (%)	27 ± 7
LVFT/RR (%)	52 ± 7
LPEI (ms)	121 ± 20
IVMD (ms), 25^{th}-75^{th} percentiles	16 (7-28)
OWD (ms)	81 ± 38
ASPWD (ms), 25^{th}-75^{th} percentiles	107 (57-179)

6 MWT = 6-minute walk test; ACE = angiotensin-converting enzyme; ASPWD = anteroseptal to posterior wall delay; IVMD = inter ventricular mechanical delay; LPEI = left pre ejection interval; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVFT/RR = left ventricular filling ratio; NYHA = New York Heart Association; OWD = opposing wall delay; QoL = quality of life

Dyssynchrony measurements

Atrioventricular dyssynchrony analysis was feasible in 118 patients (96%) and resulted in a mean LVFT/RR of 52±7%. Only 4 patients (3%) met the predefined cut-off value for significantly reduced LVFT/RR <40%.

For interventricular mechanical delay, 2 measurements were performed; LPEI and IVMD. Measurement of LPEI could be achieved in 119 patients (97%). Mean LPEI in the study population was 121±20 ms, with 20 patients (17%) meeting a significant value >140 ms. Second, IVMD analysis was successfully performed in 110 subjects (89%) and the mean value for IVMD was 18±14 ms. Seven patients (6%) demonstrated a prolonged IVMD >40 ms.

Finally, intraventricular dyssynchrony was assessed in the longitudinal and radial direction. Opposing wall delay, as measured with TDI, was feasible in 120 patients (98%) and resulted in a mean OWD of 81±38 ms. In 77 patients (66%), significant OWD ≥65 ms was observed. For radial dyssynchrony, speckle-tracking analysis was performed on standard short-axis images of the left ventricle. The analysis was feasible in 111 patients (90%) and mean radial dyssynchrony was 128±99 ms. Forty-three patients (39%) had an ASPWD ≥130 ms, see Figure 2. Of note, patients with a QRS duration >100 ms had an overall larger extent of dyssynchrony than patients with a QRS duration ≤100 ms (Table 3).

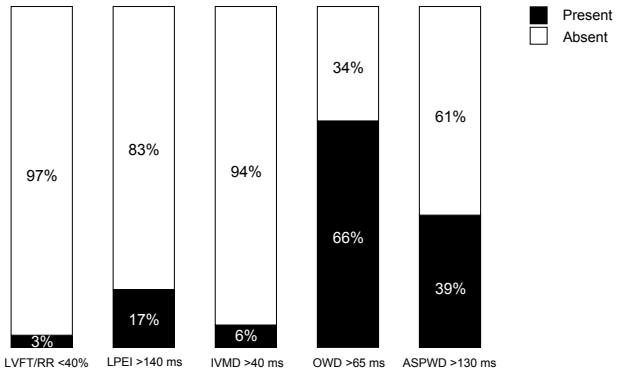

Figure 2. Presence of pre-defined dyssynchrony measures in patients with a narrow QRS complex.
ASPWD = anteroseptal to posterior wall delay; IVMD = inter ventricular mechanical delay; LPEI = left pre ejection interval; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVFT/RR = left ventricular filling ratio; OWD = opposing wall delay.

CRT responders vs. non-responders

At follow-up, 89 (72%) patients had a reduction in NHYA functional class. Moreover, LVEDV decreased from 201±64 ml to 189±64 ml (p = 0.001) and a similar decrease from 147±52 ml to 130±55 ml (p<0.001) was observed for LVESV. LVEF increased from 27±7% to 33±10% (p<0.001). Fifty-nine patients (48%) showed response to CRT, defined as a reduction of ≥15% in LVESV. There were no differences in baseline clinical characteristics between responders and non-responders, see Table 2. In addition, baseline LV volumes and LVEF were comparable between the 2 groups of patients; however, responders demonstrated a larger extent of IVMD, OWD and ASPWD at baseline than non-responders. Of note, only 7 (12%) responders had no dyssynchrony by any predefined cut-off, vs. 24 (38%) non-responders (p = 0.003). Finally, more dyssynchrony was observed in patients with a QRS duration >100 ms as compared to

Table 2. Patient characteristics in CRT responders and non-responders

Variable	Responders (n = 59)	Non-responders (n = 64)	p-value
Age (years)	61 ± 11	60 ± 12	0.618
Men / Women	44 / 15	53 / 11	0.279
Etiology (n)			0.095
Ischemic	31 (53%)	44 (69%)	
Non-ischemic	28 (47%)	20 (31%)	
QRS duration (ms), 25th-75th percentiles	106 (100-112)	106 (98-114)	0.847
follow-up	128 (112-148)	140 (120-154)	0.217
Medication (n)			
Diuretics	55 (93%)	61 (95%)	0.709
ACE-inhibitors/AII-blocker	54 (92%)	57 (89%)	0.765
Beta-blockers	57 (97%)	57 (89%)	0.167
Spironolactone	33 (56%)	42 (66%)	0.355
LVEDV (ml), 25th-75th percentiles	195 (160-246)	188 (152-231)	0.199
follow-up	157 (127-199)	208 (160-247)	**<0.001**
LVESV (ml), 25th-75th percentiles	154 (113-182)	139 (103-167)	0.125
follow-up	98 (74-136)	151 (113-186)	**<0.001**
LVEF (%)	26 ± 7	28 ± 8	0.250
follow-up	38 ± 9	28 ± 8	**<0.001**
LVFT/RR (%)	53 ± 8	51 ± 7	0.142
LPEI (ms)	123 ± 22	119 ± 19	0.344
IVMD (ms), 25th-75th percentiles	23 (9-33)	13 (6-21)	**0.013**
OWD (ms)	92 ± 39	70 ± 35	**0.002**
ASPWD (ms), 25th-75th percentiles	146 (100-200)	68 (36-110)	**<0.001**

ACE = angiotensin-converting enzyme; ASPWD = anteroseptal to posterior wall delay; IVMD = inter ventricular mechanical delay; LPEI = left pre ejection interval; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVFT/RR = left ventricular filling ratio; OWD = opposing wall delay

patients with a QRS duration ≤100 ms (Table 3). However, this did not result in a significantly higher response rate. In patients with a QRS duration >100 ms, 42 (51%) showed response, compared to 17 (41%) patients with a QRS duration ≤100 ms (p = 0.307).

Table 3. Baseline dyssynchrony parameters in patients with a QRS duration >100 ms and patients with a QRS duration ≤100 ms

Variable	QRS duration ≤100 ms (n = 41)	QRS duration >100 ms (n = 82)	p-value
LVFT/RR (%)	51 ± 7	53 ± 7	0.156
LPEI (ms)	115 ± 21	124 ± 20	**0.022**
IVMD (ms), 25th-75th percentiles	15 (4-25)	17 (9-30)	0.081
OWD (ms)	67 ± 37	87 ± 37	**0.007**
ASPWD (ms), 25th-75th percentiles	75 (43-121)	122 (66-187)	**0.024**

Dyssynchrony and response to CRT

ROC curve analyses were performed to investigate whether other cut-off values for this population (as compared to patients with a wide QRS complex) are more suitable to predict response to CRT. Since the predefined cut-off values for LVFT/RR, LPEI and IVMD were only sporadically met, no ROC curve analyses for these measures of dyssynchrony were performed. The ROC curves for the intraventricular measures of dyssynchrony (OWD and ASPWD) are provided in Figure 3, panels A and B. ROC curve analysis for TDI derived OWD demonstrated an optimal cut-off value of 75 ms, with a sensitivity of 70.7% and specificity of 56.5% (Panel A). The positive predictive value (PPV) for a cut-off of 75 ms was 70%. Conversely, a cut-off value of 83 ms yielded a sensitivity of 55.4% and a specificity of 65%. The sensitivity and specificity for the predefined cut-off value of 65 ms were 76.8% and 48.3% respectively. For ASPWD, assessed with speckle-tracking imaging, a cut-off value of 107 ms resulted in a sensitivity of 70.9% and a specificity of 75.0% (Panel B), and predicted response to CRT with a PPV of 71%. The sensitivity and specificity for the predefined cut-off value of 130 ms were 56.4% and 78.6% respectively.

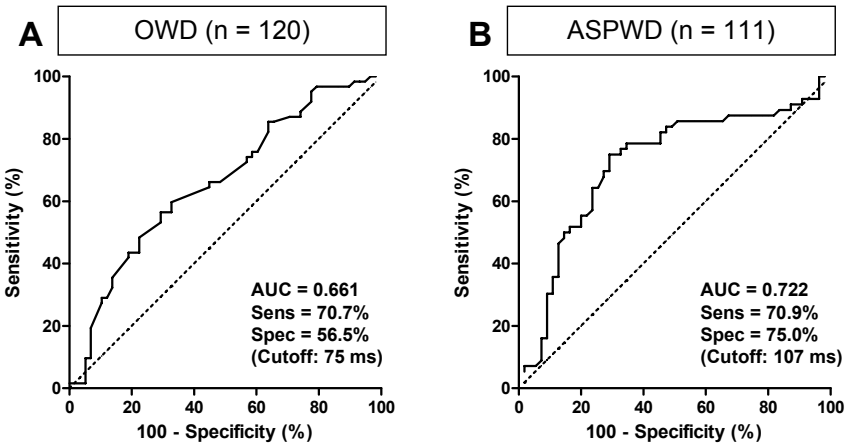

Figure 3. ROC curve analyses for predicting reduction in LVESV ≥15% after CRT for: opposing wall delay using TDI (OWD, panel A) and anteroseptal to posterior wall delay using speckle-tracking (ASPWD, panel B).

DISCUSSION

The findings in the current study can be summarized as follows; mechanical dyssynchrony is often present in heart failure patients with a narrow QRS complex; atrioventricular and interventricular mechanical dyssynchrony are less frequently noted, while intraventricular dyssynchrony is frequently observed; and finally, intraventricular measures of mechanical dyssynchrony may be useful in predicting LV reverse remodeling at 6 months follow-up in heart failure patients with a narrow QRS complex.

Cardiac resynchronization therapy and mechanical dyssynchrony

Although cardiac resynchronization therapy is nowadays considered a class I indication in heart failure patients in NYHA functional class III or IV, a LVEF ≤35% and a QRS duration ≥120 ms,[1] nearly 30% of patients do not improve in clinical symptoms and approximately 40-50% do not show significant LV reverse remodeling after CRT. To optimize patient selection for CRT and to improve outcome after CRT, the use of echocardiographic measures of mechanical dyssynchrony has been proposed to better identify potential responders to CRT.[13, 15, 20-23] Underlying this search for better predictors of response were 2 vital assumptions: first, evidence of electrocardiographic dyssynchrony (QRS widening) is not always correlated to mechanical dyssynchrony, and second, restoring (mechanical) synchrony within the LV is the key mechanism that allows benefit from CRT. Heart failure patients with a narrow QRS complex can also exhibit LV mechanical dyssynchrony, as demonstrated by many studies us-

ing echocardiography.[2, 3, 24] Others have also confirmed that restoring synchrony within the LV ("resynchronization") is mandatory for response to CRT.[25] From that time, echocardiographic markers of baseline mechanical dyssynchrony have been used in identifying potential favorable responders before CRT implantation.[13, 15, 20-23]

Efficacy of CRT in patients with a "narrow" QRS complex

Since the use of echocardiographic markers of dyssynchrony in patients with a wide QRS complex has become more widespread, the abovementioned assumptions were extended to patients with a "narrow" QRS complex (<120 ms), as these patients can also exhibit mechanical dyssynchrony as a substrate for CRT.[4-7, 26]

Achilli and co-workers were among the first to investigate the effects of CRT in heart failure patients with a narrow QRS complex.[6] The authors studied 14 "narrow" QRS (≤120 ms) patients with evidence of mechanical dyssynchrony before CRT implantation and compared the clinical and echocardiographic changes at 6 months follow-up with 38 "wide" QRS patients. The patients in the narrow QRS group showed improvement in all clinical end-points: NYHA functional class improved from 3.3±0.5 to 1.7±0.6 ($p<0.001$) and distance covered in the 6-minute walking test increased from 276±89 m to 370±70 m ($p<0.001$). More importantly, a significant reduction in LV diameters (LV end-diastolic diameter decreased from 72±9 mm to 66±9 mm and LV end-systolic diameter decreased from 61±8 mm to 56±8 mm, $p<0.05$ for both) was observed at 6 months follow-up. Finally, LVEF increased from 24.6±5.0% at baseline to 33.6±5.9% ($p<0.001$), indicating improvement in LV systolic function.

Another study by Bleeker et al evaluated the effects of CRT in 33 patients with a narrow QRS complex whit significant LV dyssynchrony (septal to lateral delay ≥65 ms with TDI).[5] At 6 months follow-up, patients improved in heart failure symptoms (NYHA functional class decreased from 3.1±0.3 to 2.0±0.6, $p<0.001$) and also demonstrated marked LV reverse remodeling (LVESV decreased from 189±60 ml to 144±58 ml and LVEDV decreased from 238±72 ml to 203±66 ml, $p<0.001$ for both).

A more recent study from Cazeau and co-workers (DESIRE) focused on the effect of pre-implantation LV dyssynchrony in a large cohort of patients with narrow and intermediate (120 - 150 ms) QRS complexes treated with CRT, rather than pre-selecting narrow QRS patients that demonstrated significant dyssynchrony and comparing them with wide QRS patients.[7] The authors included a total of 60 patients in NYHA class III, with a mean LVEF of 25.7% and a QRS duration of 121±191 ms. Patients were divided into 2 groups: 1 group of 27 patients that had ≥1 predefined echo criterion of mechanical dyssynchrony (DES+) and 1 group of 33 patients without dyssynchrony (DES-). Improvement in the primary end-point (a combination of all cause mortality, heart failure hospitalizations and NYHA functional class at 6 months follow-up) was observed in 19 of 27 DES+ patients (70%) vs. 14 of 33 DES- patients

(42%), p<0.04. This particular study used only conventional parameters of dyssynchrony (e.g. diastolic filling ratio, LPEI and IVMD), which may explain that only 27 (45%) patients met ≥1 predefined criterion. Although exact frequencies per positive criterion are not reported, it seems that (like in the present study) IVMD was rarely observed. Finally, mean QRS duration in the DESIRE study was higher, hampering exact comparison between reported results. Nonetheless, the results from DESIRE clearly demonstrate that narrow QRS patients with documented evidence of mechanical dyssynchrony derive greater benefit from CRT than narrow QRS patients without mechanical dyssynchrony.

Results from RethinQ and future perspectives

Thriving on the promising results of many of these smaller studies, a small pilot clinical trial on the effect of CRT in heart failure patients with a narrow QRS complex was performed.[8] The Resynchronization therapy in narrow QRS (RethinQ) study included 172 patients with a narrow QRS complex and documented echocardiographic evidence of mechanical dyssynchrony, defined as either septal to posterior wall motion delay ≥130 ms using M-Mode, or septal to LV free wall (lateral or posterior) delay ≥65 ms using TDI. Patients were randomized to a CRT *ON* and a CRT *OFF* group. The study could not demonstrate a significant difference in the primary end-point (increase in peak oxygen consumption ≥1.0 ml per kilogram of body weight per minute during exercise testing at 6 months) between the CRT *ON* and the CRT *OFF* group.

On the other hand, there was a significant difference in change in NHYA class (54% improved in the CRT *ON* group vs. 29% in the CRT *OFF* group, p = 0.006) and a trend towards reduction of heart failure events in the CRT group (22.3% vs. 16.1%, respectively).

While these inconsistencies between the respective end-points is remarkable and indicative for the currently ongoing quest for clinically relevant end-points in CRT research, it further underscores the need to base clinical decision making on hard clinical morbidity and mortality end-points rather than volumetric remodeling alone, for which a uniform definition is still lacking. Next to improvement in clinical symptoms and/or improvement in LV systolic function, also "no worsening/non-progressing" has been proposed as measure of success of CRT.[27, 28] Rationale for such an end-point is that heart failure is a progressive disease, and attenuation of the natural course (worsening) should also be considered as positive response. Clearly, the best end-point to assess success of a certain heart failure treatment (CRT in this case) is a benefit on all-cause mortality and/or cause-specific hospitalizations.[29] Currently there is a large randomized clinical trial ongoing to address that very issue in narrow QRS patients undergoing CRT. EchoCRT is designed to investigate the reduction in all-cause mortality or first hospitalization for worsening heart failure during a follow-up of at least 24 months in >1200 heart failure patients with a narrow QRS complex, but evidence

of mechanical dyssynchrony.[30] Moreover, this will be the first clinical trial to use the newly proposed speckle-tracking technique for evaluation of mechanical dyssynchrony. In many single center studies, this method proved to be superior for dyssynchrony assessment and had a higher predictive value for CRT response than more conventional echocardiographic measures.[18, 31, 32] The technique is not affected by insonation angle and has the advantage that it permits discrimination between active deformation and passive motion of the myocardium. Therefore, it may be the preferred method to assess dyssynchrony in patients with ischemic heart disease and areas of scar tissue. Also in the current study, speckle-tracking had the highest diagnostic accuracy for predicting LV reverse remodeling at 6 months follow-up. Possibly, EchoCRT will bring the answer about effectiveness of CRT in patients with a narrow QRS complex and echocardiographic evidence of mechanical dyssynchrony.

Conclusion and clinical implications

The present study suggests a beneficial effect of CRT on LV volumes and systolic function in heart failure patients with a narrow QRS complex, but with evidence of mechanical dyssynchrony as assessed by echocardiography. Accordingly, patients with drug-refractory heart failure and a narrow QRS complex, but mechanical dyssynchrony could be considered candidates for CRT. Main focus on identifying potential responders to CRT using echocardiography should be on measures of intraventricular dyssynchrony, rather than atrioventricular or interventricular dyssynchrony. Nevertheless, until the final results of EchoCRT, a clinical value and potential benefit from CRT in heart failure patients with a narrow QRS complex and mechanical dyssynchrony remains currently unclear.

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