Chapter 11

Site of latest activation in patients eligible for cardiac resynchronization therapy; patterns of dyssynchrony among different QRS configurations and impact of heart failure etiology

van Bommel RJ, Ypenburg C, Mollema SA, Borleffs CJ, Delgado V, Bertini M, Marsan NA, van der Wall EE, Schalij MJ, Bax JJ

Am Heart J 2011;161(6):1060-6

ABSTRACT

Background: Cardiac resynchronization therapy (CRT) has emerged as a treatment option for patients with end-stage heart failure and a QRS duration ≥120 ms. Nonetheless, many patients with a prolonged QRS do not demonstrate left ventricular (LV) mechanical dyssynchrony and discrepancies between electrical and mechanical dyssynchrony have been observed. In addition, several studies demonstrated that superior benefits after CRT could be achieved when the LV pacing lead was positioned at the most delayed myocardial segment.

Methods: A total of 248 heart failure patients scheduled for CRT were included. In all patients, a 12 lead ECG and 2D echocardiogram were obtained. Patients were divided into five QRS configuration sub-groups: narrow, left bundle branch block (LBBB), right bundle branch block (RBBB), intraventricular conduction delay (IVCD) and right ventricular (RV)-pacing. With speckle-tracking radial strain analysis, we evaluated time to peak radial strain. Next, the segments with the least and with the most mechanical activation delay were identified and LV dyssynchrony was defined as the time delay between the two.

Results: Mean QRS duration was 164±31 ms. Mean LV dyssynchrony in all patients was 186±122 ms. Site of latest activation was predominantly located in the lateral (27%), posterior (26%) and inferior (20%) segments. Furthermore, extent of LV dyssynchrony was comparable between QRS configuration sub-groups. An unequal distribution of LV segments with the most mechanical delay was observed in the LBBB and RV-pacing sub-groups ($p<0.001$ for both), while in the narrow, RBBB and IVCD sub-groups, a more heterogeneous distribution was noted. No differences in distribution pattern or in extent of LV dyssynchrony were observed between ischemic and non-ischemic heart failure patients.

Conclusions: The lateral, posterior and inferior segments take up 73% of total latest activated segments in heart failure patients eligible for CRT. Presence of LV dyssynchrony can be observed in all QRS configurations. The site of latest activation may be outside the lateral or posterior segment, making echocardiographic assessment of LV dyssynchrony and site of latest activation a valuable technique to optimize patient outcome after CRT.

INTRODUCTION

In recent years, cardiac resynchronization therapy (CRT) has emerged as an effective treatment option for patients with drug-refractory heart failure.[1] Multiple single- and multi-center studies have demonstrated an improvement in clinical symptoms and left ventricular (LV) systolic function.[2,3] Moreover, significant reductions in mortality and morbidity have been noted in heart failure patients after CRT implantation.[1-5] Although results of large clinical trials support the role of CRT as an important therapeutic option in selected heart failure patients, around 30% of individual patients do not improve clinically after CRT. In an effort to optimize patient selection criteria and to improve response to CRT, numerous studies have used echocardiography for the detection of mechanical dyssynchrony.[3, 6-9]

More recently, further improvements in the success of CRT have been related to the position of the LV pacing lead. Several studies demonstrated that superior benefits of CRT could be achieved when the LV pacing lead was positioned at the latest activated myocardial segment, as assessed with echocardiography. In these patients, with so-called concordant LV lead position, greater reduction in LV volumes could be achieved[10, 11]; conversely, in patients with a discordant LV lead position (LV lead positioned outside the most delayed myocardial segment) less reduction in LV volumes was observed.

However, LV mechanical activation patterns may vary between patients, depending on QRS configuration, heart failure etiology and other pathophysiological factors, complicating LV lead positioning. Consequently, the aim of the current study was 1) to evaluate LV dyssynchrony, and 2) to identify the site of latest mechanical activation in ischemic and non-ischemic heart failure patients with different QRS configurations, being potential candidates for CRT.

METHODS

Patient cohort and study protocol

Two hundred and forty-eight consecutive heart failure patients scheduled to undergo CRT were included. Patients were in New York Heart Association (NYHA) class III or IV, despite optimal medical therapy. In all patients, a 12-lead ECG was obtained and two-dimensional (2D) and Doppler echocardiography was performed to measure left ventricular (LV) volumes, LV ejection fraction (LVEF), LV dyssynchrony and the site of latest mechanical activation in all patients prior to device-implantation. Based on the 12-lead ECG, patients were divided into 5 different QRS configuration sub-groups:

1)narrow QRS (defined as a QRS duration <120 ms)
2)left bundle branch block (LBBB)
3)right bundle branch block (RBBB)
4)other intraventricular conduction delays (IVCD)
5)right ventricular (RV) pacing

Subsequently, extent of dyssynchrony and the distribution of the site of latest mechanical activation were evaluated in the 5 different QRS configuration sub-groups. Finally, differences between patients with ischemic and non-ischemic etiology of heart failure were assessed.

Echocardiographic evaluation

All patients underwent echocardiography in the left lateral decubitus position. Studies were performed using a commercially available 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 off-line analysis (EchoPac 108.1.5, General Electric Vingmed Ultrasound, Milwaukee, USA). LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV) and LVEF were measured from the apical 2- and 4-chamber images, using the modified biplane Simpson's rule.[12]

2D Speckle-tracking radial strain analysis

To determine LV dyssynchrony and the site of latest mechanical activation within the left ventricle, 2D speckle-tracking radial strain analysis was performed on the LV short-axis image at the level of the papillary muscles.[13, 14] From 2D gray-scale images, the software detects the myocardial speckles, stable natural acoustic markers that result from scattering of the ultrasound beam. These speckles are tracked frame to frame along the cardiac cycle, allowing tagging of the myocardial motion and direct calculation of myocardial strain.[13] The change in length compared to the initial length of the speckle pattern of a myocardial segment provides the dimensionless amount of myocardial deformation. From the short-axis view of the LV, the change in thickening of the myocardial segments along the cardiac cycle estimates the amount of radial strain or deformation. Conventionally, myocardial thickening is represented as positive strain whereas myocardial thinning is presented as negative strain.

From an end-systolic frame, a region of interest is manually drawn at the endocardial-cavity boundary of the LV and, subsequently, the software automatically creates a second larger region of interest at the epicardial level, such that the region of interest spans the LV myocardial wall. The width of the region of interest can be adjusted manually by the operator, depending on the thickness of the LV wall. Next, the region of interest is automatically divided into 6 standard segments: septal, anteroseptal, anterior, lateral, posterior, and inferior, respectively, using the insertion points of the right ventricle into the LV as anatomical landmarks. The tracking quality of each LV segment is scored by the software which permits manual overriding in order to assure good quality tracking. Finally, the time-strain curves for all 6 segments are displayed and time from QRS complex onset to peak radial strain can be measured (Figure

A

B

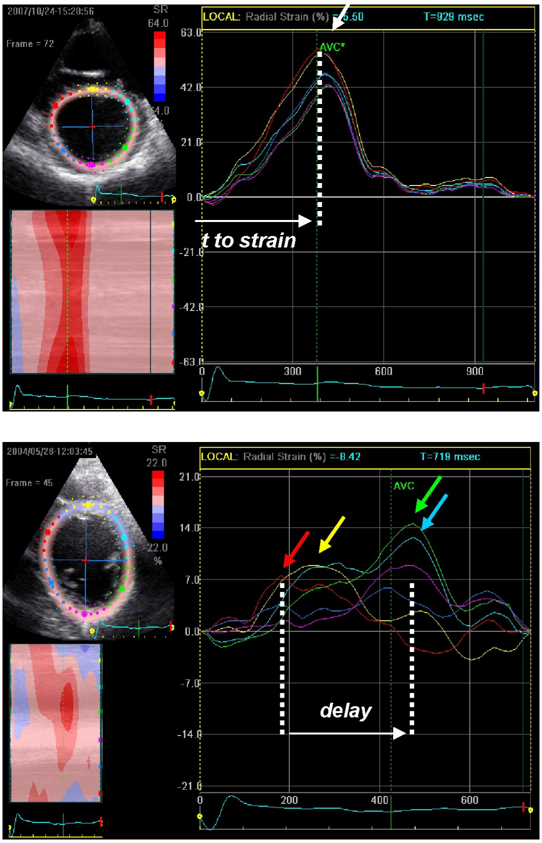

Figure 1. Two examples of 2D speckle-tracking radial strain curves.
Panel A: A synchronous contraction pattern; no difference in time to peak radial strain exists between the 6 segments.
Panel B: A dyssynchronous contraction pattern; a marked delay in time to peak radial strain of 280ms between the 6 segments is present.

1A). Consequently, the location of the earliest and latest activated segment as well as the time difference between them can be determined (Figure 1B). Time of segment activation was defined as the time between onset of the QRS complex to peak radial strain. From these regional timings, the extent of dyssynchrony was derived, defined as the absolute difference in time to peak radial strain between the earliest and the latest activated segment.

Previously reported intra- and inter-observer reproducibility for 2D speckle-tracking radial train dyssynchrony measurements were −3±23ms (r = 0.98) and 0.3±24ms (r = 0.97), respectively.[15]

Statistical analysis

Continuous data are presented as mean±SD, and categorical data are presented as frequencies and percentages. Comparison of continuous data between patient groups was performed using the Student t test or one-way analysis of variance (ANOVA), as appropriate. Fisher's exact tests or χ^2 tests were used as appropriate to compare categorical data. All analyses were performed with SPSS for Windows, version 16.0 (SPSS, Chicago, IL). A p-value <0.05 was considered statistically significant.

RESULTS

Clinical and echocardiographic characteristics

The study comprised 248 patients (mean age 66±11 years, 191 male) who were scheduled for CRT implantation. The cause of heart failure was ischemic in 55% of patients and non-ischemic in 45%. Patients had severely depressed LV function, with a mean LVEF of 23±7%. In all patients, a 12-lead ECG was obtained and 2D and Doppler echocardiography was performed successfully. Mean QRS complex duration was 164±31ms and the majority of patients (58%) had LBBB configuration (Table 1). Using 2D speckle-tracking radial strain analysis, time to peak radial strain was assessed for the 6 segments: septal, anteroseptal, anterior, lateral, posterior and inferior. Of all 1488 attempted segments, 1369 (95%) provided reliable time-strain curves. In the total study population, a heterogeneous distribution in mean time to peak radial strain between segments was observed (p<0.001, Figure 2). Next, the earliest and latest activated segments could be identified, and subsequently, the extent of LV dyssynchrony was calculated. Mean LV dyssynchrony in the study population was 186±122 ms. Finally, when identifying the latest activated segment per individual, an unequal distribution of latest activated segments was observed. The lateral segment was latest activated in 27%

of patients, posterior in 26%, inferior in 20%, anteroseptal in 13%, anterior in 8% and finally, septal in 6% of patients (p<0.001, Figure 3).

Table 1. Patient characteristics (n = 248)

Age (years)	66 ± 11
Men / Women	191 / 57
NYHA class (n)	
III	215
IV	33
Etiology of HF (n)	
Ischemic	137 (55%)
Non-ischemic	111 (45%)
Rhythm (n)	
Sinus rhythm	207 (83%)
Atrial fibrillation	27 (11%)
Paced	14 (6%)
QRS duration (ms)	164 ± 31
QRS configuration (n)	
Narrow	34 (14%)
LBBB	145 (58%)
RBBB	14 (6%)
IVCD	22 (9%)
Paced	33 (13%)
LVEDV (ml)	246 ± 86
LVESV (ml)	193 ± 77
LVEF (%)	23 ± 7
Medication (n)	
Diuretics	213 (86%)
ACE-inhibitors	192 (77%)
B-blockers	182 (73%)
Spironolactone	124 (50%)
Digoxine	59 (24%)
Ca-antagonists	14 (6%)
Nitrates	77 (31%)

ACE = angiotensin-converting enzyme; HF = heart failure; IVCD = Intraventricular Conduction Delay; LBBB = Left Bundle Branch Block; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association; RBBB = Right Bundle Branch Block

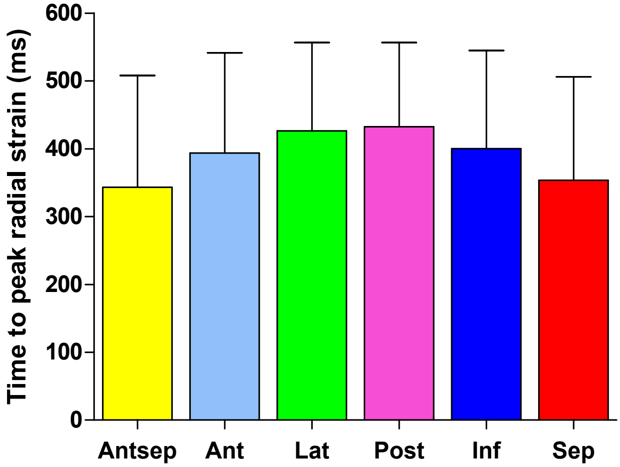

Figure 2. Time to peak radial strain for the 6 basal segments in all patients (p<0.001, mean time to peak radial strain between segments). Antsep = Anteroseptal; Ant = Anterior; Lat = Lateral; Post = Posterior; Inf = Inferior; Sep = Septal.

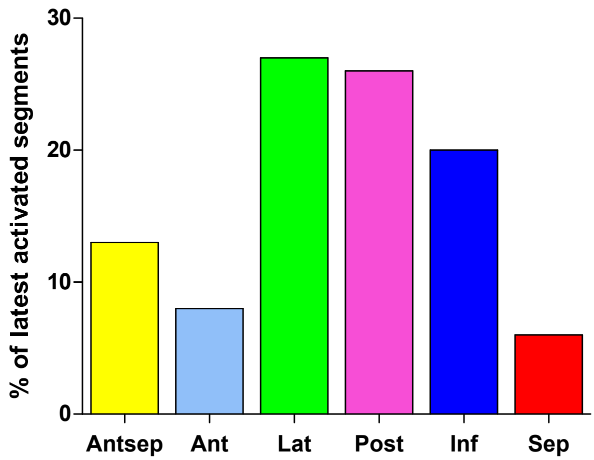

Figure 3. Distribution of site of latest mechanical activation in all patients (p<0.001, frequencies of segments).Antsep = Anteroseptal; Ant = Anterior; Lat = Lateral; Post = Posterior; Inf = Inferior; Sep = Septal.

Distribution of latest activated site vs. QRS configuration

After patients were divided in the 5 QRS sub-groups, the extent of LV dyssynchrony and distribution of the site of latest mechanical activation was again determined. No significant differences in the extent of LV dyssynchrony between the different QRS sub-groups were observed (Figure 4).

Conversely, distribution of the latest activated segments per QRS configuration showed a significant heterogeneity in the LBBB and RV-pacing sub-groups (p<0.001 and p = 0.001 respectively), with maximum delay in mechanical activation being predominantly located in the posterolateral region in both groups (Table 2). In the narrow QRS, RBBB and IVCD sub-groups, the latest activated segments were more homogeneously distributed (Table 2).

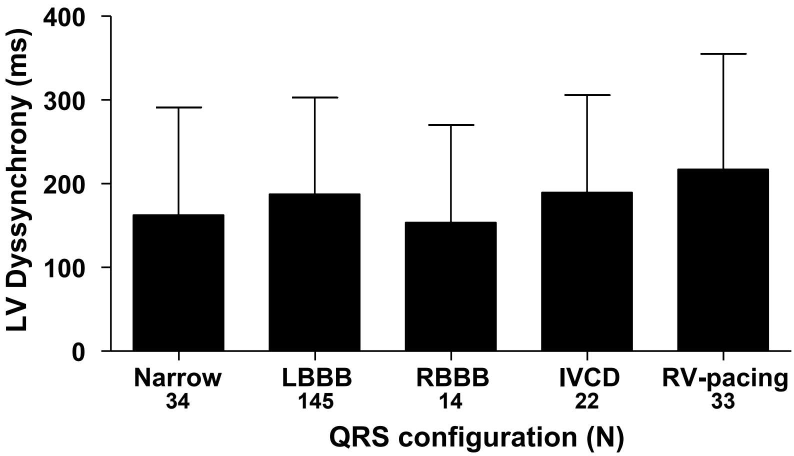

Figure 4. Mean extent of LV dyssynchrony between different QRS sub-groups (p = NS). LBBB = Left Bundle Branch Block; RBBB = Right Bundle Branch Block; IVCD = Intraventricular Conduction Delay; RV = Right Ventricular.

Table 2. Site of latest activation versus QRS configuration (n = 248)

QRS configuration (n)	Antsep (%)	Ant (%)	Lat (%)	Post (%)	Inf (%)	Sep (%)	p-value
Narrow (33)	15	6	15	29	20	15	0.284
LBBB (145)	11	10	29	27	17	6	**<0.001**
RBBB (14)	29	14	21	15	21	-	0.910
IVCD (22)	23	-	14	18	41	4	0.092
Paced (33)	6	-	46	27	18	3	**0.001**

Antsep = Anteroseptal; Ant = Anterior; Lat = Lateral; Post = Posterior; Inf = Inferior; Sep = Septal; LBBB = Left Bundle Branch Block; RBBB = Right Bundle Branch Block; IVCD = Intraventricular Conduction Delay

Ischemic vs. non-ischemic etiology of heart failure

In addition to LV dyssynchrony between different QRS configurations, it was also investigated whether extent of LV dyssynchrony, and distribution pattern of the site of latest activation were different between patients with ischemic etiology of heart failure and patients with non-ischemic heart failure. When mean time to peak radial strain for each segment was compared between ischemic and non-ischemic patients, a heterogeneous distribution of time to activation between the 6 segments was observed in both sub-groups (Table 3). More importantly, similar time to peak radial strain per segment was noted in ischemic vs. non-ischemic patients (Table 3). Of note, the extent of LV dyssynchrony was comparable between patients with non-ischemic heart failure and ischemic heart failure (201±135 ms vs. 174±109 ms, p = 0.09). Finally, no significant differences were noted between the distributions of latest activated segments. In both groups, the lateral segment was most frequently the latest activated segment, followed by the posterior segment (Figure 5).

Table 3. Time to peak radial strain for each segment, ischemic versus non-ischemic etiology (n = 248)

Heart failure etiology (n)	**Antsep (ms)**	**Ant (ms)**	**Lat (ms)**	**Post (ms)**	**Inf (ms)**	**Sep (ms)**	p-value
Ischemic (137)	352 ± 159	395 ± 144	425 ± 131	432 ± 127	411 ± 141	365 ± 144	**<0.001**
Non-ischemic (111)	331 ± 171	393 ± 152	427 ± 130	433 ± 121	387 ± 148	340 ± 162	**<0.001**
	NS	NS	NS	NS	NS	NS	

Antsep = Anteroseptal; Ant = Anterior; Lat = Lateral; Post = Posterior; Inf = Inferior; Sep = Septal

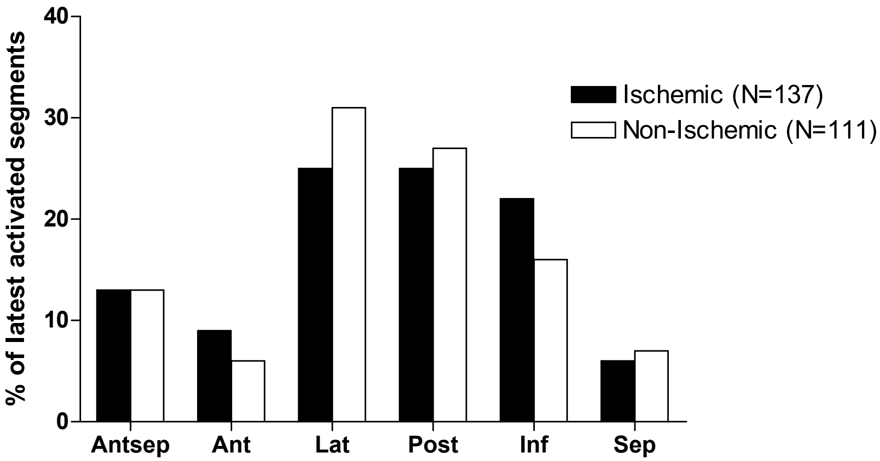

Figure 5. Distribution of site of latest mechanical activation in patients with ischemic versus non-ischemic heart failure (p = NS).Antsep = Anteroseptal; Ant = Anterior; Lat = Lateral; Post = Posterior; Inf = Inferior; Sep = Septal.

DISCUSSION

In this comprehensive study of patients scheduled for CRT implantation, 2D speckle-tracking strain was used to analyze LV dyssynchrony and to indentify the site of latest mechanical activation. Time to peak radial strain was heterogeneously distributed, with the longest time to peak radial strain observed for the lateral and posterior segments.

Furthermore, while total extent of LV dyssynchrony was comparable between different QRS configurations, distribution of latest activated segments varied significantly. Finally, no differences in distribution pattern of LV dyssynchrony or in extent of LV dyssynchrony were observed between ischemic and non-ischemic heart failure patients.

LV dyssynchrony among different QRS configurations

To date, there are only a few studies that investigated the prevalence and extent of LV dyssynchrony in heart failure patients with different QRS configurations and these studies mainly used tissue Doppler imaging (TDI) for dyssynchrony assessment, whereas the current study used the more robust speckle-tracking method.[16-18] Badano et al investigated 103 heart failure patients with a normal QRS duration (≤100 ms), RBBB and LBBB, using pulsed-wave TDI.[16] Time to peak systolic velocities were measured in the basal part of 6 LV segments (inferoposterior, lateral, anteroseptal, posterior, anterior and inferior) and LV dyssynchrony was defined as the time difference between the segment with shortest time to peak systolic velocity and the longest time to peak systolic velocity. The authors found significant LV dyssynchrony (>41 ms) in all QRS sub-groups, including the normal QRS group. More importantly, although the mean value of LV dyssynchrony (the extent) was slightly higher in the LBBB group, significant LV dyssynchrony (>41 ms) was equally observed in the LBBB group, the RBBB group and the normal QRS group. It was therefore concluded that echocardiographic LV dyssynchrony can be observed in all groups, regardless of QRS configuration or QRS duration.

Another study on LV mechanical dyssynchrony in comparison to QRS configuration was performed by Haghjoo et al.[18] The authors investigated extent and prevalence of several dyssynchrony parameters in 200 heart failure patients with LBBB, RBBB with left fascicular hemiblock (RBBB-LFG) and pure RBBB. Significant LV mechanical dyssynchrony was defined as a >100 ms time difference in peak systolic velocity between 6 mid and 6 basal segments using color-coded TDI. Patients with LBBB had a slightly (but significantly) higher mean value of LV dyssynchrony as compared to patients with RBBB-LFG and patients with pure RBBB (101 ms vs. 79 ms vs. 76 ms respectively, $p<0.001$). In the current study, no significant difference in extent of LV dyssynchrony was observed between patients with RBBB and LBBB. Possible explanations to this opposing finding can be the different methods used for dyssynchrony assessment (color-coded TDI vs. speckle-tracking radial strain in the current study) or the direction of dyssynchrony assessment (longitudinal vs. radial in the current study). This discrepancy between extent and prevalence of radial and longitudinal dyssynchrony in CRT candidates has been described previously.[15, 19] Gorcsan et al investigated both radial and longitudinal dyssynchrony in 190 patients undergoing CRT, and found a discrepancy between radial and longitudinal dyssynchrony in 54 patients (31%). Nineteen patients had significant longitudinal dyssynchrony but no significant radial dyssynchrony, and 35 patients had significant radial dyssynchrony but no significant longitudinal dyssynchrony.

Site of latest activation and LV lead position in CRT

Assessment of LV dyssynchrony and identification of the site of latest (mechanical) activation should result in clinical benefit for patients undergoing CRT. Where early studies already demonstrated that pacing the LV free wall resulted in better results (systolic function) after CRT as compared to pacing the anterior wall,[20] more recent studies have related the success of CRT to the LV lead position in relation to the site of latest mechanical activation.[10, 21, 22] The largest study investigating the interaction between LV lead concordance and outcome after CRT was performed by Ypenburg et al.[11] In 257 heart failure patients undergoing CRT, LV dyssynchrony and the site of latest mechanical activation were assessed using 2D speckle-tracking radial strain. At 6 months follow-up, a larger decrease in LVESV (from 189±83 ml to 134±71 ml, $p<0.001$) was observed in patients with the LV lead positioned at the site of latest mechanical activation ("concordant LV lead"), while in patients with the LV lead placed outside the area of latest mechanical activation (discordant LV lead"), no significant changes in LVESV were observed (172±61 ml to 162±63 ml, p = NS). More importantly, long-term follow-up of these patients revealed that the 2-year mortality rate in patients with a concordance between the LV lead position and the site of latest mechanical activation was lower as compared to patients with a discordance between the LV lead position and the site of latest mechanical activation (15% vs. 21%, $p<0.05$). These results suggest an important interplay between the site of latest mechanical activation and the LV lead position and the. A "concordant" LV pacing lead may result in more extensive LV reverse remodeling and greater long-term survival after CRT.

In the present study, the site of latest activation was predominantly located in the lateral and posterior segments. It is this region that is traditionally targeted by the LV pacing lead. Since this practice will result in a concordance between the site of latest activation and the location of the LV pacing lead in most cases, it makes targeting a postero-(lateral) vein for the LV pacing lead an acceptable approach. However, our results demonstrate that even in patients with LBBB, the latest activated segment may be located outside the lateral or posterior region. Consequently, evaluation of LV dyssynchrony and assessment of the site of latest activation before CRT implantation may yield better outcome after CRT.

Study limitations

Some limitations of this study should be addressed. 2D speckle-tracking has overcome many obstacles of "conventional" TDI such as angle dependency and the inability to discriminate between active motion [myocardial contraction] and passive motion [tethering of scar segments by adjacent segments]. However, this novel technique may be limited by low frame rate or poor acoustic windows. Finally, as this is a single-center observational study, no definitive conclusion can be drawn on whether pre-implantation assessment of LV dyssynchrony and site of latest activation, followed by targeted LV pacing lead placement, will improve outcome after CRT.

Conclusions

The present study provides novel insight in the extent and distribution of LV dyssynchrony in a variety of heart failure patients being potential candidates for CRT. Total extent of LV dyssynchrony was comparable between the different evaluated QRS configurations. Furthermore, the current observations demonstrate that the area with maximum delay in mechanical activation is predominantly located in the lateral and posterior segments. This makes the current practice of targeting a postero-(lateral) vein for LV pacing lead deployment during CRT implantation an acceptable approach. However, the latest activated segment may be located outside this region and this can be not easily depicted from the surface ECG before device implantation. Since superior results after CRT may be achieved by targeting the latest activated segment, evaluation of LV dyssynchrony and identification of the site of latest mechanical activation by echocardiography may be of great value to increase response rate in patients undergoing CRT.

REFERENCES

1. Abraham WT, Fisher WG, Smith AL et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845-1853.
2. Auricchio A, Stellbrink C, Sack S et al. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *J Am Coll Cardiol* 2002;39:2026-2033.
3. Bax JJ, Bleeker GB, Marwick TH et al. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. *J Am Coll Cardiol* 2004;44:1834-1840.
4. Bristow MR, Saxon LA, Boehmer J et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350:2140-2150.
5. Higgins SL, Hummel JD, Niazi IK et al. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. *J Am Coll Cardiol* 2003;42:1454-1459.
6. Pitzalis MV, Iacoviello M, Romito R et al. Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony. *J Am Coll Cardiol* 2002;40:1615-1622.
7. Yu CM, Fung JW, Zhang Q et al. Tissue Doppler imaging is superior to strain rate imaging and postsystolic shortening on the prediction of reverse remodeling in both ischemic and nonischemic heart failure after cardiac resynchronization therapy. *Circulation* 2004;110:66-73.
8. Sogaard P, Egeblad H, Kim WY et al. Tissue Doppler imaging predicts improved systolic performance and reversed left ventricular remodeling during long-term cardiac resynchronization therapy. *J Am Coll Cardiol* 2002;40:723-730.
9. Cazeau S, Bordachar P, Jauvert G et al. Echocardiographic modeling of cardiac dyssynchrony before and during multisite stimulation: a prospective study. *Pacing Clin Electrophysiol* 2003;26: 137-143.
10. Ansalone G, Giannantoni P, Ricci R, Trambaiolo P, Fedele F, Santini M. Doppler myocardial imaging to evaluate the effectiveness of pacing sites in patients receiving biventricular pacing. *J Am Coll Cardiol* 2002;39:489-499.
11. Ypenburg C, van Bommel RJ, Delgado V et al. Optimal left ventricular lead position predicts reverse remodeling and survival after cardiac resynchronization therapy. *J Am Coll Cardiol* 2008; 52:1402-1409.
12. Schiller NB, Shah PM, Crawford M et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989;2:358-367.
13. Leitman M, Lysyansky P, Sidenko S et al. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. *J Am Soc Echocardiogr* 2004; 17:1021-1029.
14. Reisner SA, Lysyansky P, Agmon Y, Mutlak D, Lessick J, Friedman Z. Global longitudinal strain: a novel index of left ventricular systolic function. *J Am Soc Echocardiogr* 2004;17:630-633.
15. Delgado V, Ypenburg C, van Bommel RJ et al. Assessment of left ventricular dyssynchrony by speckle-tracking strain imaging comparison between longitudinal, circumferential, and radial strain in cardiac resynchronization therapy. *J Am Coll Cardiol* 2008;51:1944-1952.
16. Badano LP, Gaddi O, Peraldo C et al. Left ventricular electromechanical delay in patients with heart failure and normal QRS duration and in patients with right and left bundle branch block. *Europace* 2007;9:41-47.

17. Haghjoo M, Bagherzadeh A, Fazelifar AF et al. Prevalence of Mechanical Dyssynchrony in Heart Failure Patients with Different QRS Durations. *Pacing Clin Electrophysiol* 2007;30:616-622.
18. Haghjoo M, Bagherzadeh A, Farahani MM, Haghighi ZO, Sadr-Ameli MA. Significance of QRS morphology in determining the prevalence of mechanical dyssynchrony in heart failure patients eligible for cardiac resynchronization: particular focus on patients with right bundle branch block with and without coexistent left-sided conduction defects. *Europace* 2008;10:566-571.
19. Gorcsan J, III, Tanabe M, Bleeker GB et al. Combined longitudinal and radial dyssynchrony predicts ventricular response after resynchronization therapy. *J Am Coll Cardiol* 2007;50:1476-1483.
20. Butter C, Auricchio A, Stellbrink C et al. Effect of resynchronization therapy stimulation site on the systolic function of heart failure patients. *Circulation* 2001;104:3026-3029.
21. Murphy RT, Sigurdsson G, Mulamalla S et al. Tissue synchronization imaging and optimal left ventricular pacing site in cardiac resynchronization therapy. *Am J Cardiol* 2006;97:1615-1621.
22. Becker M, Kramann R, Franke A et al. Impact of left ventricular lead position in cardiac resynchronization therapy on left ventricular remodelling. A circumferential strain analysis based on 2D echocardiography. *Eur Heart J* 2007;28:1211-1220.