Advanced cardiac imaging in heart failure : from subclinical myocardial dysfunction to therapy optimization

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CHAPTER 3

EFFECT OF CARDIAC RESYNCHRONIZATION THERAPY ON THE SEQUENCE OF SYSTOLIC MECHANICAL ACTIVATION ASSESSED BY 2 DIMENSIONAL RADIAL STRAIN.

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Am J Cardiol. 2014 Mar 15; 113(6): 982-7.

ABSTRACT

Cardiac resynchronization therapy (CRT) induces left ventricular (LV) reverse remodelling by synchronizing LV segmental mechanical activation. Changes in segmental LV activation after CRT were assessed and related to CRT response.

A total of 292 heart failure patients (mean age 65 ± 10 years, 77% male) treated with CRT underwent baseline echocardiographic assessment of LV volumes. Timing of peak radial strain was measured for 6 midventricular LV segments with speckle tracking strain imaging. After 6 months, LV volumes and segmental LV mechanical activation timings were re-assessed. Response to CRT was defined as ≥15% decrease in LV end-systolic volume at 6 months follow-up.

Responders (n=177) showed LV resynchronization 6 months after CRT (LV dyssynchrony from 200 ± 127 ms to 85 ± 86 ms; P<0.001) by earlier activation of the posterior segment (from 438 ± 141 ms to 394 ± 132 ms; P=0.001) and delayed activation of the anteroseptal segment (from 295 ± 155 ms to 407 ± 138 ms; P<0.001). In contrast, non-responders (n=115) experienced an increase in LV dyssynchrony 6 months after CRT (from 106 ± 86 ms to 155 ± 112 ms; P=0.001) with an earlier activation of posterior wall (from 391 ± 139 ms to 355 ± 136 ms; P=0.039) that did not match the delayed anteroseptal activation (from 360 ± 148 ms to 415 ± 122 ms; P=0.001), creating a distinct sequence of mechanical activation.

Responders to CRT showed LV resynchronization through balanced lateral and anteroseptal activa tions. In non-responders, LV dyssynchrony remains by posterior wall preactivation and non-compensatory delayed septal wall activation.

INTRODUCTION

Cardiac resynchronization therapy (CRT) has been shown to induce sustained left ventricular (LV) reverse remodelling in severe heart failure patients, with significant improvements in LV systolic function and cardiac metabolism and decrease in mitral regurgitation.[1–3] These beneficial effects have been principally attributed to the restoration of synchrony within the left ventricle and further equilibration of the activation and contraction of the postero-lateral and septal walls.[4–7] However, up to 30-40% of patients do not experience significant mid-term LV reverse remodelling after CRT.[8] The absence of adequate resynchronization or LV dyssynchrony induction following CRT has been one of the pathophysiologic factors related to a lesser degree of response to the therapy.[4,9,10] Consequently, whereas responders to CRT seem to show resynchronization of the sequence of activation within the left ventricle, non-responders may exhibit a distinct sequence of activation after CRT that hampers LV reverse remodelling.[5,11] Accordingly, in the present evaluation changes in timing of segmental LV activation after CRT were assessed and related to CRT response.

METHODS

A total of 292 heart failure patients treated with CRT and who completed a 6 months follow-up period were selected from an ongoing registry.[12] Optimally treated heart failure patients (New York Heart Association [NYHA] functional class III or IV) with an LV ejection fraction (LVEF) ≤35% who showed a wide QRS complex (>120ms) were selected for CRT.[13] Patients with recent myocardial infarction (≤3 months) or decompensated heart failure requiring continuous intravenous therapy were excluded. Heart failure etiology was considered ischemic when the patient had previous myocardial infarction or revascularization, or significant angiographic coronary disease was documented (≥50% stenosis in one or more major epicardial artery).

According to the institutional protocol, clinical evaluation was performed before CRT implantation and included NYHA functional class, exercise capacity using the 6 minute walk test (6MWT) and quality of life (QoL) assessment using the Minnesota Living with Heart Failure Questionnaire.[14,15] In addition, all patients underwent 2D echocardiography at baseline to evaluate LV volumes and LVEF. In addition, LV dyssynchrony and the sequence of activation and site of latest activation were evaluated with 2D radial strain speckle tracking.

At 6 months follow-up the clinical status was re-evaluated and echocardiography was repeated to evaluate LV volumes, LVEF, LV dyssynchrony and sequence of LV mechanical activation. Response to CRT was defined as a ≥15% decrease in LV end-systolic volume (LVESV) 6 months after CRT implantation.[11] The changes in sequence of LV mechanical activation after CRT were related to the echocardiographic response. All clinical and echocardiographic data were prospectively entered into the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, the Netherlands) and retrospectively analyzed.

All echocardiographic data were obtained at rest in the left lateral decubitus position using a commercially available system (Vingmed System 7 and E9, GE-Vingmed Ultrasound AS, Horten, Norway) with a 3.5 –MHz transducer. Apical 2- and 4-chamber views were used to calculate LV end-diastolic volume (LVEDV) and LVESV and to derive LVEF according to the Simpson's method.[16] LV volumes and ejection fraction were assessed before and after 6 months of CRT.

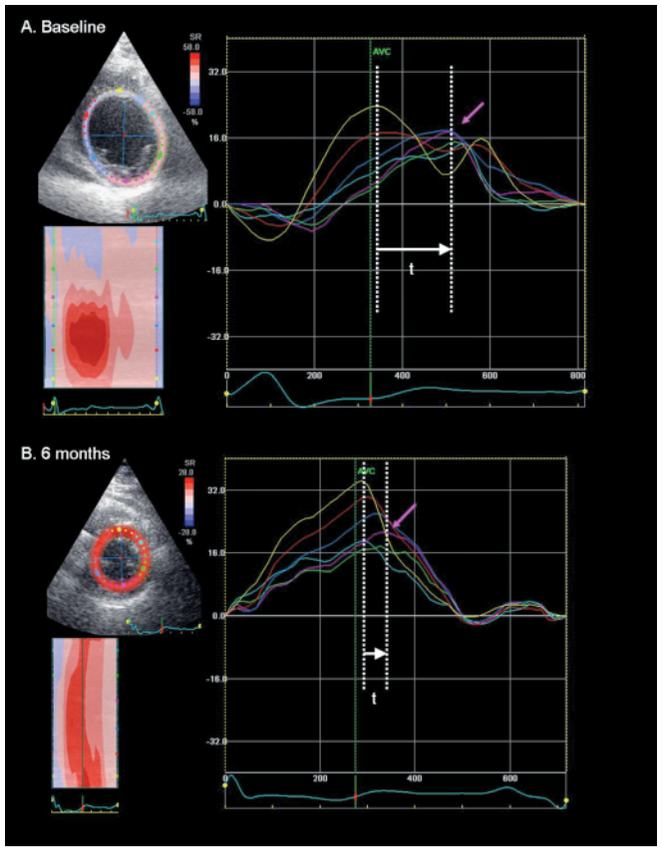
In addition, LV dyssynchrony, sequence of LV mechanical activation and identification of the site of latest mechanical activation were assessed with 2D radial strain speckle tracking.[17,18] These parameters were evaluated using commercially available software (EchoPac 111.0.00, General Electric – Vingmed). The mid LV short-axis view, at the level of the papillary muscles, is first acquired at the highest possible frame rate to permit adequate tracking of the speckles.[17] Secondly, the endocardial border is manually traced at an end-systolic frame. Subsequently, two concentric regions of interest are automatically provided by the software allowing further adjustment for optimal tracking of the myocardium along the cardiac cycle. The mid LV short-axis view is divided in 6 segments and the time-strain tracings are provided for each segment (***Figure 1***). The time difference between the peak radial strain of the anteroseptal and the posterior segments is calculated to define LV dyssynchrony. An established cut-off value of ≥130 ms indicates significant LV dyssynchrony, as previously described.[18] Furthermore, the time to peak radial strain of the 6 LV segments were recorded creating the sequence of mechanical activation of the LV. The latest activated segment was identified.[19] A distinct sequence of activation was defined as ≥94ms absolute timing of mechanical activation difference between a preactivated posterior wall and a delayed anteroseptal wall 6 months after CRT.[10]

Figure 1. **Two-dimensional radial strain speckle tracking for the assessment of left ventricular sequence of activation**

Panel A. The evaluation of LV dyssynchrony, sequence of mechanical activation and site of latest activation by 2-dimensional radial strain speckle tracking in a heart failure patient before CRT is shown. LV dyssynchrony was defined as the absolute time difference between peak systolic radial strain in the posterior wall (pink curve) and the anteroseptum (yellow curve) was assessed. This patient exhibited significant LV dyssynchrony (183ms).[18] Furthermore, there was a delayed mechanical activation of the posterior wall compared to the anteroseptum. The site of latest activation was the posterior wall (pink arrow).

Panel B. The evaluation of LV dyssynchrony, site of latest activation and sequence of activation with 2-dimensional radial strain speckle tracking were repeated 6 months after CRT. Of interest, a decrease in the value of LV dyssynchrony was noted (52ms), by earlier mechanical activation of the lateral wall (pink curve and arrow) that is synchronized to the timing of mechanical activation of the anteroseptum (yellow curve).

Abbreviations: CRT=cardiac resynchronization therapy; LV=left ventricle; t=time.



All CRT devices were implanted in the pectoral region and during implantation pacing, sensing and defibrillation thresholds were tested. CRT leads were implanted via the subclavian vein. First, a coronary

sinus venogram was obtained using a balloon catheter. Thereafter, with the help of an 8F guiding catheter, the LV lead was positioned (Easytrak, Guidant Corporation, St. Paul, Minnesota; Attain, Medtronic Inc., Minneapolis, Minnesota; or Corox, Biotronik, Berlin) via the coronary sinus preferably in the posterolateral vein, at the mid-ventricular level. The right atrial and ventricular leads were positioned conventionally. A defibrillator was combined to CRT in all patients.[13] Finally, all leads were connected to a dual chamber biventricular CRT-device (Contak Renewal, Guidant Corporation; Consulta, Insync III or Insync Sentry, Medtronic Inc; or Lumax, Biotronik). The cardiologist performing the procedure was unaware of the site of latest mechanical activation identified on 2D speckle tracking echocardiography. Within 24 hours after CRT device implantation, the atrioventricular delay was adjusted to optimize LV diastolic filling. The interventricular delay was set at 0 ms and was not adjusted during the first 6 months of follow-up.

According to protocol, all patients underwent a conventional chest X-ray before discharge to confirm the position of the LV lead. Using the lateral views, LV lead position was recorded as anterior, lateral, posterior, or inferior.[20] Using the frontal views, the LV lead position was scored as basal, mid, or apical.[20] Concordance between segment of latest activation and LV lead position was established when the LV lead was positioned at the site of latest activation.[21]

Continuous variables are presented as mean ± standard deviation (SD), unless otherwise specified, and were compared between responders and non-responders to CRT using the independent sample t-test. In addition, the comparison between the timings of mechanical activation at baseline and at 6 months follow-up was performed using the paired t-test. Categorical variables are presented as number and percentage and were compared with chi-squared test. A multivariate logistic regression model was created introducing the significant univariate variables as covariates with the stepwise enter method to identify independent predictors of a distinct sequence of activation (≥94ms absolute timing of mechanical activation difference between a preactivated posterior wall and a delayed anteroseptal wall 6 months after CRT). For each variable, the odds ratio (OR) and the 95% of confidence intervals (CI) were calculated. A P-value <0.05 was considered statistically significant. Data were analyzed with SPSS 21.0 (IBM, Chicago, Illinois).

RESULTS

The baseline characteristics of the population are listed in ***Table 1***. In most patients the LV lead was implanted at the mid-ventricular level (91%). Concordance between site of latest activation and final LV lead position was found in 60.2% of patients (n=164).

According to the pre-specified definition of response (≥15% decrease in LVESV at 6 months follow-up), 60.6% of patients were responders to CRT (n=177) and 39.4% were non-responders (n=115). Comparisons between baseline characteristics in responders and non-responders to CRT are outlined in ***Table 2***.

Table 1. Baseline characteristics

Variable	N=292
Age (years)	65±10
Male/Female	227/65
Coronary artery disease	183 (62.7%)
Sinus rhythm	242 (82.9%)
QRS duration ≥130ms	237 (81%)
LBBB	213 (72.9%)
NYHA class	
III	273 (93.5%)
IV	19 (6.5%)
6MWT (meters)	311±111
QoL score	36±18
Left ventricular end-diastolic volume (mL)	218±78
Left ventricular end-systolic volume (mL)	163±68
Left ventricular ejection fraction (%)	26±8
Left ventricular dyssynchrony (ms)	163±121
Site of latest activation lateral of posterior	185 (63.4%)
Medications	
Beta-blockers	220 (75.3%)
ACE Inhibitors/ARB	264 (90.4%)
Diuretics/spironolactone	242 (82.9%)

Abbreviations: ACE=Angiotensin II converting enzyme; ARB=Angiotensin receptor blocker; LBBB=left bundle branch block; NYHA=New York Heart functional class; QoL=Quality of life questionnaire (Minnesota living with Heart Failure); 6MWT=6-minute walk distance test.

Table 2. Baseline characteristics of responders and non-responders to cardiac resynchronization therapy

Variables	Responders (n=177)	Non-responders (n=115)	P-value
Age (years)	64±10	66±10	0.047
Male/Female	135/42	92/23	0.274
Coronary artery disease	103 (56.0%)	74 (68.0%)	0.032
QRS (ms)	160±29	150±31	0.010
LBBB	138 (78.0%)	75 (65.2%)	0.017
QRS≥130ms	152 (86%)	85 (73%)	0.014
NYHA	3.1±0.1	3.3±0.2	0.840
6MWT (meters)	315±104	305±123	0.521
QoL score	34±116	37±19	0.784
Left ventricular end-diastolic volume (mL)	223±82	208±72	0.111
Left ventricular end-systolic volume (mL)	169±73	152±61	0.051
Left ventricular ejection fraction (%)	26±7	27±8	0.075
Left ventricular dyssynchrony (ms)	200±127	106±86	<0.001
Patients with concordant left ventricular lead position	83.0%	25.0%	<0.001

Abbreviations: CRT=Cardiac Resynchronization Therapy; LBBB=left bundle branch block; LVESV=left ventricular end-systolic volume; NYHA=New York Heart functional class; QoL=Quality of life questionnaire (Minnesota living with Heart Failure); 6MWT=distance walked in 6 minutes.

The sequence of activation in responders and non-responders to CRT at baseline and after 6 months of CRT is illustrated in ***Figure 2***. Of interest, responders and non-responders showed a comparable sequence of mechanical activation at baseline. The mechanical activation of the posterior wall was delayed compared to the anteroseptum in both responders and in non-responders. However, different sequences of mechanical activation were observed after 6 months of CRT in responders and in non-responders. In particular, responders experienced LV resynchronization at 6 months follow-up (LV dyssynchrony from 200 ± 127ms to 85 ± 86 ms; P<0.001) by earlier activation of the posterior segment (438 ± 141ms to 394 ± 132 ms; P=0.001) and delayed activation of the anteroseptal segment (295 ± 155 ms to 407 ± 138 ms; P<0.001). In contrast, non-responders showed worsening of LV dyssynchrony (from 106 ± 86 ms before CRT to 155 ± 112 ms 6 months after CRT; P=0.001) with an earlier mechanical activation of posterior wall (391 ± 139 ms to 355 ± 136 ms; P=0.039) that did not match the delayed anteroseptal mechanical activation (360 ± 148ms to 415 ± 122ms; P=0.001).

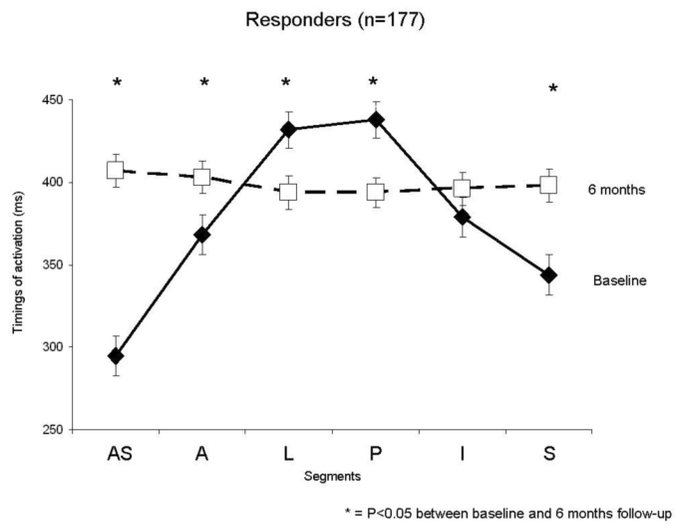
Figure 2. **Left ventricular sequence of activation at baseline and at 6 months follow-up in responders and in non-responders to cardiac resynchronization therapy.**

Upper panel. The left ventricular sequence of mechanical activation in responders to CRT is shown. Of interest, at baseline, marked LV dyssynchrony was present.[18] Moreover, responders show a delayed mechanical activation of the posterior segment compared to the anteroseptum's timing of mechanical activation. At 6 months follow up, responders to CRT show resynchronization of the sequence of mechanical activation within the LV. In particular, the mechanical activations of anteroseptum and the (infero)septum occur significantly later compared to baseline, whereas the activation of the posterior and lateral segments occurs significantly earlier than at baseline.

Lower panel. The left ventricular sequence of mechanical activation in non-responders to CRT is shown. Of interest, at baseline, non-responders exhibit a lesser degree of LV dyssynchrony than responders. The posterior wall's mechanical activation is delayed to a compared to the mechanical activation of the septum, generating a sequence of mechanical activation similar to responders. However, at 6 months follow up, non-responders to CRT show increased LV dyssynchrony and absence of resynchronization by reversion of the sequence of activation within the left ventricle. Precisely, although the activations of anteroseptum and the (infero)septum occur significantly later compared to baseline, the earlier activation of the posterior segment does not equate the later activation of the anteroseptum, creating an unbalanced sequence of mechanical activation within the left ventricle.

Mean values of timing of systolic mechanical activation ± standard error of the mean are displayed.

Abbreviations: A=anterior; AS=anteroseptum; I=inferior; L=lateral; P=posterior; S=(infero) septum



In the subgroup of patients exhibiting a left bundle branch block (LBBB) pattern of activation on surface EKG, responders (n=138 [65%]) experienced LV resynchronization at 6 months follow-up (LV dyssynchrony from 210 ± 124ms to 83 ± 87 ms; P<0.001) by earlier activation of the posterior segment (443 ± 144ms to 387 ± 132 ms; P=0.001) and delayed activation of the anteroseptal segment (288 ± 155 ms to 402 ± 133 ms; P<0.001). Non-responders (n= 75 [35%]) showed non-significant worsening

of LV dyssynchrony (from 120 ± 94 ms before CRT to 140 ± 115 ms 6 months after CRT; P=0.273) by posterior wall preactivation (386 ± 140 ms to 360 ± 136 ms; P=0.253) that did not match the delayed anteroseptal mechanical activation (344 ± 159ms to 417 ± 119ms; P=0.001).

In the subgroup of patients exhibiting a non-LBBB pattern of activation on surface EKG, responders (n=39 [51%]) experienced LV resynchronization at 6 months follow-up (LV dyssynchrony from 166 ± 129ms to 91 ± 90 ms; P=0.011). No significant posterior segment preactivation (421 ± 132ms to 416 ± 133 ms; P=0.881) was seen. However, posterior wall mechanical activation matched the significantly delayed activation of the antero-septal segment (321 ± 155 ms to 423 ± 158 ms; P=0.003). In contrast, non-responders (n=40 [49%]) showed worsening of LV dyssynchrony (from 80±61 ms before CRT to 174±104 ms 6 months after CRT; P<0.001) with an earlier mechanical activation of posterior wall (403±136 ms to 347±136 ms; P=0.047) that did not match the anteroseptal mechanical activation (390±122ms to 409±130ms; P=0.475).

In the subgroup of patients exhibiting a non-left bundle branch block EKG morphology, a distinct sequence of mechanical LV activation was found in 9 (23%) of the responders vs. 22 (54%) non-responders (P=0.005).

Univariate and multivariate predictors of a distinct sequence of mechanical activation within the LV 6 months after CRT are displayed in ***Table 3***.

Table 3. Univariate and multivariate predictors of a distinct sequence of mechanical activation after 6 months of cardiac retsynchronization therapy

	Univariate		Multivariate	
Variables	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (years)	0.992 (0.969-1.016)	0.519	…	…
Coronary artery disease	1.346 (0.796-2.275)	0.292	…	…
LBBB	0.579(0.337-0.997)	0.049	0.923 (0.493-1.731)	0.804
QRS ≥130ms	0.591 (0.322-1.087)	0.091	…	…
Lead concordance	0.212 (0.123-0.367)	<0.001	0.289 (0.162-0.517)	<0.001

Abbreviations: LBBB=left bundle branch block; LV=left ventricle

DISCUSSION

Intraventricular conduction delay, reflected by a wide QRS complex, is a prevalent condition in heart failure patients.[22] In a study including 5517 heart failure patients, the prevalence of prolonged ventricular conduction was 37%, being LBBB the most frequent disruption (25.2%).[22] QRS complex width remains an important determinant of response and outcome after CRT.[13,23] Indeed, patients with QRS complex width ≥150ms seem to benefit the most form CRT.[23] Additionnaly, patients exhibiting a LBBB configuration conduction delay seem to show better outcome than patients with a non-LBBB pattern of activation.[23] Concordance between site of latest activation identified by 2D radial strain imaging and LV lead position as also been identified as a major determinant of outcome after CRT.[19,24,25] In the present study, heart failure patients with QRS width ≥120ms showing LBBB or a non-LBBB pattern of activation on their surface EKG were selected. 2D radial strain imaging was used to assess the LV mechanical sequence of activation. Responders to CRT showed a balanced sequence of mechanical activation after 6 months of CRT. Conversely, non-responders showed an unbalanced sequence of mechanical activation after 6 months of CRT. This unbalanced sequence of mechanical activation, with unmatched posterior wall and antero-septal wall activation, was seen in both LBBB and non-LBBB patients. Interestingly, the only factor independantly linked to a distinct sequence of mechanical activation (≥94ms absolute timing of mechanical activation difference between a preactivated posterior wall and a delayed anteroseptal wall) after 6 months of CRT was LV lead implantation site concordance to the site of latest activation at baseline (OR 0.289 (CI 0.162-0.517); P<0.001), regardless of surface EKG activation pattern. Therefore, although selection of patients with narrow QRS complex (<130ms) for CRT based on 2D radial strain imaging has not been proven to provide additional benefits, 2D radial strain imaging may help identify patients with intermediate (120-150ms) QRS complex width and/or non-LBBB surface EKG pattern who could possibly benefit from CRT. Similarly, Marek et al., recently used 2D radial strain imaging to identify the LV site of latest activation and consequently guide lead implantation in these prespecified subgroups of patients.[26] The STARTER trial randomized 187 heart failure patients with a QRS complex width ≥120 ms and LVEF ≤35% to LV lead guided to the site of latest mechanical activation compared to routine implantation.[26] Patients were followed-up for 2 years for death or heart failure hopitalization. Importanlty, patients with a QRS width of 120 to 149 ms or non-LBBB and LV lead concordant or adjacent to the site of latest mechanical activation showed equivalent primary outcome rates after CRT to those with LBBB or

a QRS width of ≥150 ms.[26] Conversely, patients with a QRS of 120 to 149 ms or non-LBBB and remote LV leads had higher death or heart failure hopsitalization rates.[26] Whether 2D radial strain imaging can be used to select patients with intermediate QRS width complex or non-LBBB surface EKG configuration for CRT warrants further investigations.

Currently, significant mid-term LV reverse remodelling is achieved in 60-70% of patients treated with CRT. Resynchronization of the sequence of mechanical activation within the LV is one of the pathophysiologic mechanisms underlying CRT response.[4,11] Yu et al. reported that patients who experienced significant LV reverse remodelling after 3 months of CRT (responders, n=17) showed a significant decrease in LV dyssynchrony, defined as the standard deviation of time to peak myocardial systolic contraction of the 12 LV segments (from 45.0±8.3 ms to 32.5±14.5 ms, P=0.003). In contrast, patients who did not show significant LV reverse remodelling had worsened LV dyssynchrony after CRT (from 24.8±4.5 ms to 34.1±13.5 ms, P=0.02).[11] Similarly, Bleeker et al. showed that the extent of resynchronization achieved with CRT independently predicted significant LV reverse remodelling at 6 months follow-up.[4] Furthermore, patients who exhibited ≤10% of LV resynchronization or worsening of LV dyssynchrony did not show significant response to CRT.[4] The present evaluation has demonstrated significant LV resynchronization in patients who showed significant LV reverse remodelling after CRT. The present study also confirms that CRT induces a sustained resynchronization of the sequence of mechanical activation within the LV by delaying the septal activation which consequently equates the timing of mechanical activation of the posterior and lateral walls. Additionally, this work has showed that resynchronization of the sequence of mechanical activation is also attribuable to lateral and posterior walls' preactivations. However, the earlier mechanical activation of the posterior and lateral walls may potentially worsen LV dyssynchrony in a subset of patients receiving CRT, creating an unbalanced and distinct sequence of mechanical activation within the LV.

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