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REVIEW ARTICLE

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Role of echocardiography before cardiac resynchronization therapy: new advances and current developments

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The role of echocardiography in improving the selection of patients who will benefit from cardiac resynchronization therapy (CRT) remains a source of debate. Although previous landmark reports have demonstrated a link between mechanical dyssynchrony, assessed by delays between left ventricle (LV) walls and response to CRT, the predictive value of these findings has not yet been confirmed in multicenter trials. Indeed, recent studies demonstrated that the classical assessment of LV mechanical dyssynchrony using delay between walls by echocardiography depends not only on LV electrical activation delay (electrical dyssynchrony), but also on abnormalities in regional contractility of the LV and/or loading conditions, which do not represent an appropriate target for CRT. Recent reports highlighted the value of new indices of electromechanical dyssynchrony obtained by echocardiography, to predict LV response and outcome after CRT including septal flash, left bundle branch block—typical pattern by longitudinal strain, apical rocking, septal strain patterns, and systolic stretch index. This was achieved using a mechanistic approach, based on the contractile consequences of electrical dyssynchrony. These indices are rarely found in patients with narrow QRS (<120 ms), whereas their frequency rises in patients with an increase in QRS duration (>120 ms). Theses indices should improve candidate selection for CRT in clinical practice, especially for patients in whom the benefit of CRT remains uncertain, for example, patients with intermediate QRS width (120–150 ms).

KEYWORDS
cardiac resynchronization therapy, echocardiography, EKG, heart failure, outcome, speckle tracking

Cardiac resynchronization therapy (CRT) represents one of the major advances in the past two decades, for patients with heart failure and reduced left ventricular (LV) ejection fraction (HFrEF).[1] Besides coordinating contraction of LV segmental walls, CRT improves LV performance, LV filling function, reverses LV remodeling, and also reduces the amount of mitral regurgitation.[2,3] CRT improves both quality of life and symptoms in HFrEF patients having electrical dyssynchrony (prolonged QRS duration).[4,5] Also, CRT is correlated with a reduction in mortality in both symptomatic (NYHA functional class III–IV) and minimally symptomatic (class I–II) patients.[6,7] However, CRT is an invasive and costly procedure; thus appropriate patient selection is particularly important. Indeed, 20% to 40% of patients fail to improve after CRT, despite having baseline electrical dyssynchrony.[5] Due to the low cost and wide availability of echocardiography, it can be considered as an adequate tool to detect CRT indications, by assessing LV myocardial mechanical dyssynchrony. However, despite initial encouraging results, a multicenter report failed to demonstrate benefit of echocardiographic assessment of mechanical dyssynchrony, in predicting

successful outcome after CRT, for improvement in heart failure symptoms or reverse remodeling.[8] The present review aims to describe recent developments in the assessment of myocardial dyssynchrony, using echocardiography in HFrEF patients, to improve the selection of those who may derive benefit from CRT.

1 | ECHOCARDIOGRAPHY TO PREDICT RESPONSE TO CRT: THE CLASSICAL APPROACH

Response to CRT is commonly evaluated in terms of LV reverse remodeling. In clinical practice, a relative reduction of 15% or more in LV end-systolic volume compared to baseline defines LV reverse remodeling and has been associated with better long-term outcome after CRT.[9–11] Other echocardiographic surrogates including improvement in LV ejection fraction and LV global longitudinal strain are also used in clinical practice.[11] Landmark reports from the early 2000s, describe the ability of echocardiographic indices to predict CRT response in HFrEF patients with electrical dyssynchrony (prolonged QRS duration >120 ms). Classically, mechanical dyssynchrony is evaluated in terms of atrioventricular dyssynchrony, interventricular dyssynchrony, and intraventricular dyssynchrony (Fig. 1). Intraventricular dyssynchrony was frequently evaluated by tissue Doppler imaging (TDI) (Fig. 1). Some TDI indices were developed including the basal septal to basal lateral delay in time-to-peak myocardial systolic velocity during the ejection phase, with reference to the onset of the QRS complex (Ts) (Fig. 1) or the standard deviation of Ts from 12 LV segments. These indices were highly predictive of CRT response in monocenter trials.[12–15] However, despite these initial promising results, echocardiographic assessment of mechanical dyssynchrony was not predictive of CRT response in the multicenter PROSPECT trial.[8] Moreover, reproducibility of echocardiographic indices, especially for TDI-derived indices was of concern, in this trial.[8] Consequently, the 2010 ESC guidelines did not recommend the use of echocardiography and TDI-based indices of mechanical synchrony in patient selection.[16]

2 | ELECTRICAL VS MECHANICAL DYSSYNCHRONY

In patients without electrical dyssynchrony (narrow QRS duration <120–130 ms), CRT failed to consistently improve heart failure symptoms, functional capacity and outcome in clinical studies.[17–21] The recent randomized controlled EchoCRT trial aimed to evaluate whether the identification of mechanical dyssynchrony using

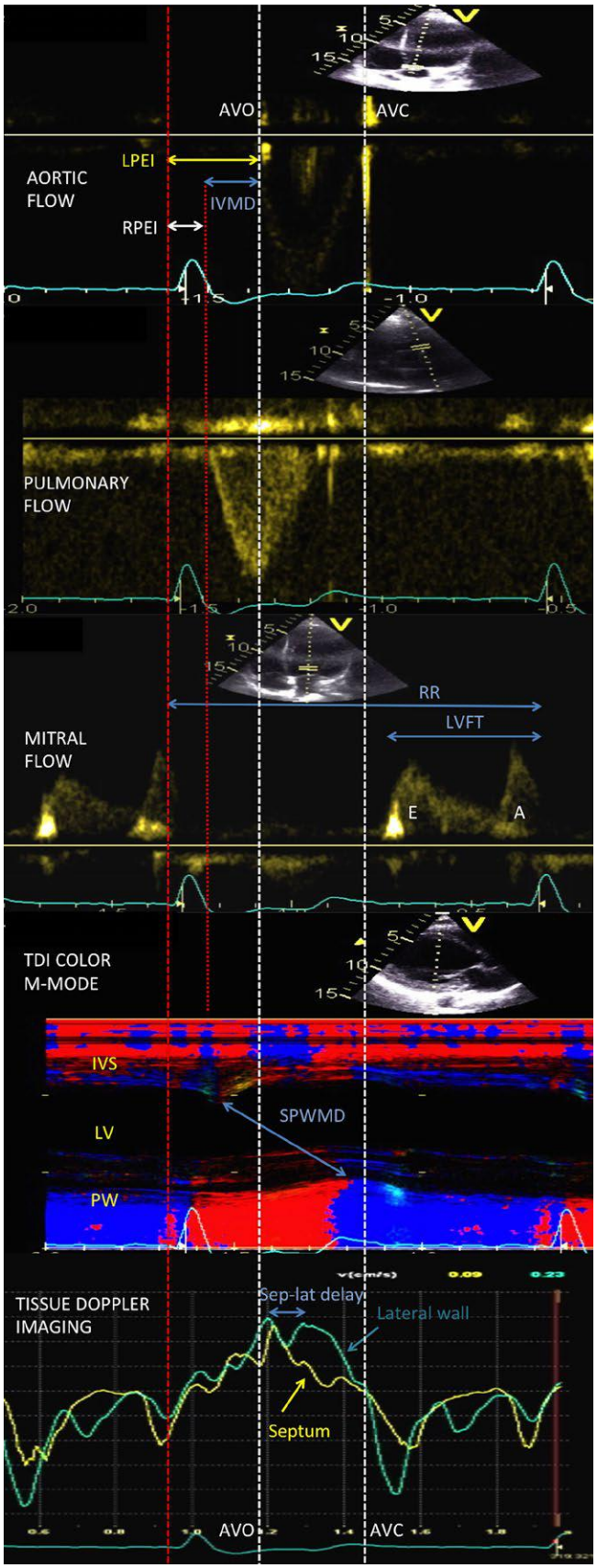

FIGURE 1 Classical echocardiographic indices of dyssynchrony obtained by blood flow Doppler, M-mode imaging, and pulsed-wave tissue Doppler imaging. LPEI = left ventricular preejection interval; RPEI = right ventricular preejection interval; IVMD = interventricular mechanical delay; LVFT = left ventricular filling time; IVS = interventricular septum; PP = posterior wall; LV = left ventricle; SPWMD = septal-to-posterior wall-motion delay; Sep-Lat delay: septal-to-lateral delay by tissue Doppler imaging; AVO = aortic valve opening; AVC = aortic valve closure

TDI (septal-to-lateral wall delay >80 ms) and radial strain by speckle tracking (septal-to-posterior delay >130 ms) improved the outcome of HFrEF patients with narrow QRS (QRS duration <130 ms).[22] In this trial, patients randomized to the CRT-On group displayed a significantly increased risk of overall mortality compared with those in the CRT-Off group.[15] In addition, 76% of patients enrolled in this trial had persistent or worsened mechanical dyssynchrony 6 months after CRT, which translated into an unfavorable outcome in a post hoc analysis. Furthermore, a similar persistence or worsening of mechanical dyssynchrony in both CRT-Off and CRT-On groups was observed.[23] These findings clearly demonstrate that echocardiographic mechanical dyssynchrony without electrical dyssynchrony is frequently observed in HFrEF patients and is not affected by CRT, and thus do not represent an appropriate target for this therapy.

Lumens et al. used the computer-based Circ-Adapt model to demonstrate that besides electrical dyssynchrony, changes in regional LV function influence delays between LV walls in the event of LV systolic dysfunction.[24] Using speckle tracking radial strain, a simulated decrease in LV free wall contraction was associated with increased delays between walls (Fig. 2B). Similarly, LV free wall scarring generated increased intraventricular delays (Fig. 2C). Accordingly, patients with ischemic cardiomyopathy and posterolateral myocardial scarring have been previously identified as poor responders to CRT.[25] Impact of LV loading conditions on LV mechanical dyssynchrony has also been documented using speckle tracking radial strain, in patients with nonischemic dilated cardiomyopathy and mainly narrow QRS.[26] Increasing afterload results in greater mechanical dyssynchrony, whereas decreasing afterload reduces mechanical dyssynchrony. Mechanical dyssynchrony in patients with HFrEF without electrical dyssynchrony is primarily related to changes in LV regional function and loading conditions and does not represent an appropriate target for CRT.

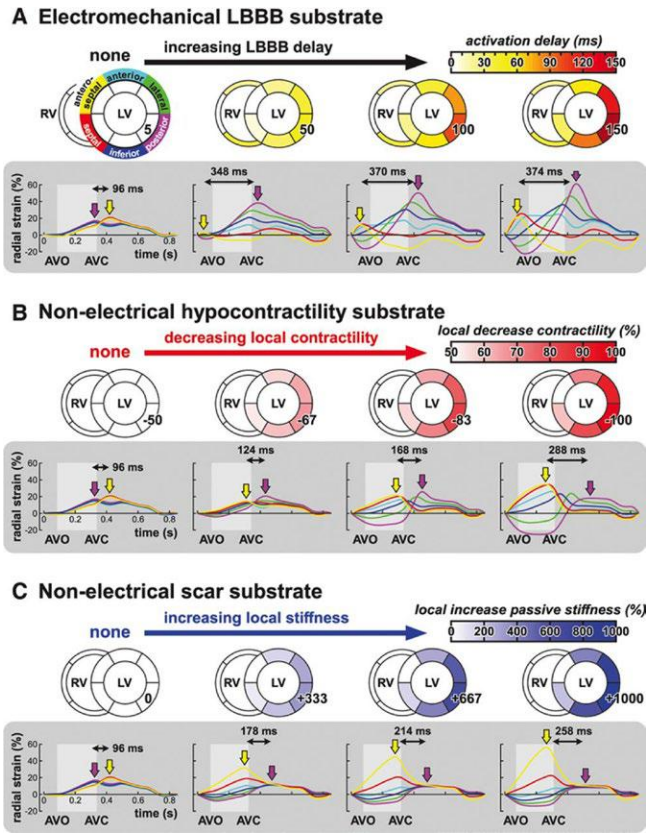

FIGURE 2 Simulated substrates of mechanical dyssynchrony. **A.** electromechanical dyssynchrony induced by a LBBB; **B.** mechanical dyssynchrony induced by a more pronounced deterioration in LV free wall contractility compared with the LV septal wall; **C.** mechanical dyssynchrony induced by increased stiffness of LV walls with a LV septal-to-lateral gradient. Reproduced from Lumens et al.,[24] with permission

In randomized control studies testing the effect of CRT on outcome, patients had electrical dyssynchrony with a majority also having a left bundle branch block (LBBB). It has been suggested that only patients with LBBB benefit from CRT, compared to those with right bundle branch block or nonspecific intraventricular conduction delay. In addition, patients with a "true" LBBB (QRS duration ≥140 ms for men and ≥130 ms for women, along with mid-QRS notching or slurring in ≥2 contiguous leads) experienced more frequently reverse remodeling following CRT, compared to patients with a "false" LBBB (left ventricular hypertrophy and left anterior fascicular block).[27] Consistently, in a meta-analysis of five randomized control trials which included around 80% of patients with a LBBB, CRT was associated with an improved outcome when QRS duration was of 150 ms or more, while the benefit of CRT in patients with QRS duration of less than 150 ms remained unclear.[28]

In normal conduction, activation begins within the LV and right ventricular endocardium. In a true LBBB, activation begins in the right ventricle and proceeds across the septum for 40 to 50 ms before reaching the LV endocardium and requires another 50 ms for reentry into the LV Purkinje network, to propagate to the endocardium of the posterolateral wall. Finally, another 50 ms is required to activate the posterolateral wall, producing a total QRS duration of 140 to 150 ms.[29] The first activation site of the LV endocardium is called the breakthrough site, which is a single site located in the mid-to-apical septum. Hence, the first notching/slurring on the EKG surface reflects the activation of the endocardial left ventricular septum, whereas the second represents the activation of the epicardial posterolateral wall. As the LV free wall is still not activated in LBBB during early systole, LV pressure does not rapidly increase. Thus, the septum can easily contract due to the reduced afterload, producing the distinctive, early rapid movement of the interventricular septum at the breakthrough site. This early movement is followed by a subsequent counter wall motion toward the right ventricle, mainly caused by the increasing LV pressure.[30] This movement has been called the "septal flash" or "septal beaking" and can be identified visually or using M-mode and/or TDI (Fig. 3, movie clips S1 and S2). As the septal wall cannot generate wall stress against the increased LV pressure, the septal wall is pushed back toward the right ventricle, resembling dyskinesis, even if the septal wall continues to contract. Late activation of

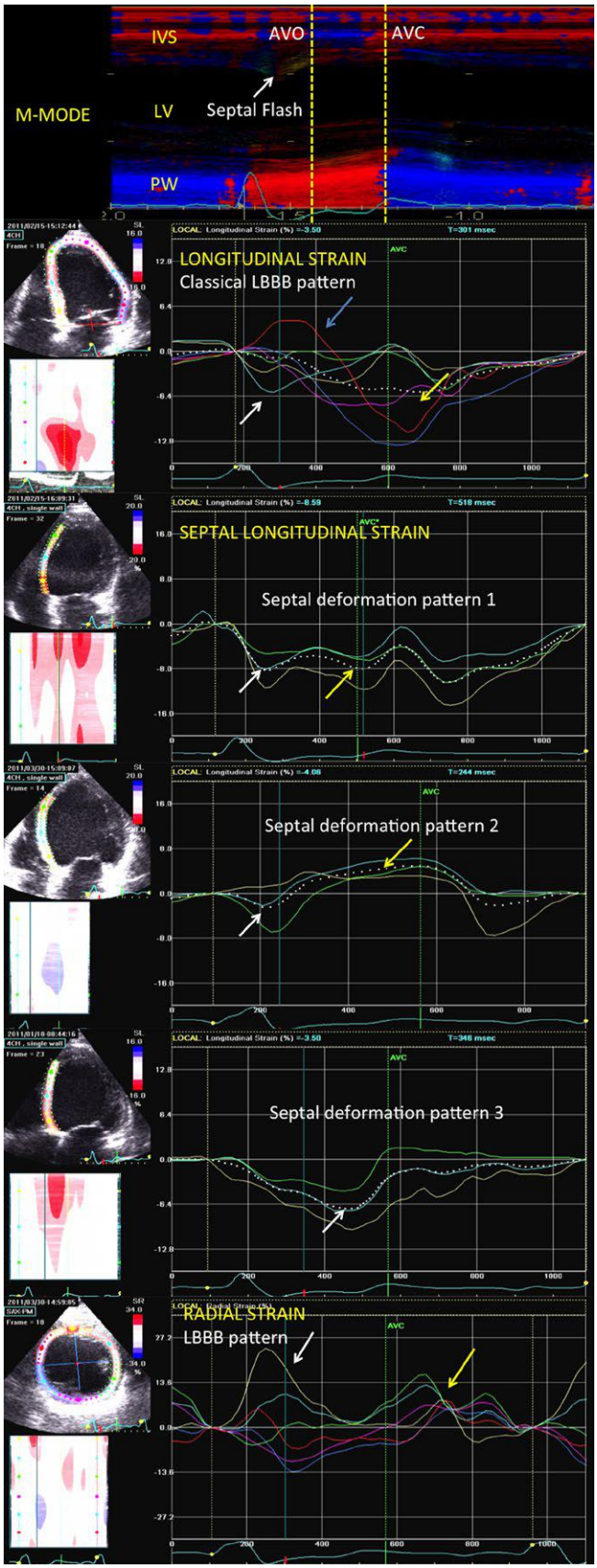

FIGURE 3 Indices of electromechanical dyssynchrony responsive to CRT by M-mode imaging, speckle tracking longitudinal and radial strain. AVO= aortic valve opening; AVC= aortic valve closure; IVS= interventricular septum; PP= posterior wall; LV= left ventricle. The septal flash (SF) corresponds to an early terminated posterior movement of the interventricular septum toward the left ventricle. The classical longitudinal LBBB pattern is defined as (1) early shortening of at least one basal or mid-ventricular segment in the septal wall (white arrow) and early stretching in at least one basal or mid-ventricular segment in the lateral wall (blue arrow); (2) early septal peak shortening (within the first 70% of the ejection phase); and (3) lateral wall peak shortening after aortic valve closure (yellow arrow). Septal deformation patterns were classified on the basis of the septal shortening and stretching sequence (dotted curves). Pattern 1 was considered in case of a double-peaked systolic shortening (white and yellow arrows). Pattern 2 was considered in case of an early shortening peak followed by prominent systolic stretching (white arrow). Pattern 3 was considered if pseudo-normal shortening with a late systolic shortening peak (white arrow). The radial LBBB pattern is characterized by an early deformation of the anteroseptal wall (white arrow) and a late postsystolic deformation of the posterolateral wall (yellow arrow)

the epicardial posterolateral wall is consequently identified by a late postsystolic contraction occurring after aortic valve closure (Fig. 3).

3 | IDENTIFICATION OF ELECTROMECHANICAL DYSSYNCHRONY BY ECHOCARDIOGRAPHY

3.1 | Septal flash and apical rocking

Previous reports demonstrated that the presence of a septal flash is associated with reverse remodeling following CRT in HFrEF patients.[31,32] Inclusion of the septal flash recorded by echocardiography in a multiparametric predictive score of LV reverse remodeling resulted in significant improvement of the predictive value of the score, over clinical and electrocardiographic data.[33] However, it has been suggested that performing a dobutamine stress echocardiography, compared with a resting examination, may enhance the identification of the septal flash to help predict CRT response.[31] Apical rocking, identified in apical four-chamber view, is characterized by a short septal motion of the apex due to early contraction of the septum in systole and a subsequent long motion to the lateral side during ejection, due to the late lateral contraction caused by the LBBB. This rocking movement results in a clockwise motion of the LV apical myocardium perpendicular to the LV long axis (movie clip S3). Clockwise apical rocking is strongly linked to the etiology of LV dysfunction (dilated cardiomyopathy) as patients with ischemic heart disease may have a counter clockwise rotation or no rotation of the LV apex.[34] The magnitude of the apical rocking is proportional to LV end-diastolic volume in dilated cardiomyopathy and is not influenced by QRS duration.[34] Apical rocking in multivariable analyses has been associated with fewer major adverse cardiac events in patients receiving CRT.[35] In the recent PREDICT-CRT trial, absence of apical rocking and unsuccessful correction of the septal flash were associated with a high risk for CRT failure and unfavorable long-term survival.[36] Unfortunately, inter-observer agreement for both apical rocking and septal flash was only moderate, with a Kappa value of 0.71,[36] indicating that

the assessment of these parameters may not be sufficient in routine practice.

Delay between the early activated septum and the late activated posterolateral wall can also be identified using speckle tracking strain echocardiography. Lumens and colleagues used the Circ-Adapt model to show that simulating a progressive increase in LBBB-mediated LV activation delays resulted in increasing delays between septal and posterolateral walls, assessed by radial strain speckle tracking imaging (Figs 2A and 3). Identification of a large delay between an early septal flash and a postsystolic delayed posterior wall contraction, obtained from standard M-mode recordings or from radial strain time-dependent curves, may help to differentiate patients with electromechanical dyssynchrony responsive to CRT from those with mechanical dyssynchrony.[37,38] However, reproducibility issues may occur with radial strain by speckle tracking and may be highly sensitive to the out-of-plane motion of the speckles owing to the longitudinal movement of the heart.[39]

3.2 | Classical LBBB longitudinal strain pattern

Longitudinal strain obtained by speckle tracking is highly reproducible and has been widely accepted when compared with radial strain, in most clinical situations.[40] Among patients with a LBBB, some have a typical LBBB longitudinal deformation pattern, including all three following criteria: (1) early shortening of at least one basal or mid-ventricular segment in the septal wall and early stretching in at least one basal or mid-ventricular segment in the lateral wall; (2) early septal peak shortening (within the first 70% of the ejection phase); and (3) lateral wall peak shortening after aortic valve closure (Fig. 3).[41] This typical pattern was more frequently found in patients with strict LBBB criteria.[42] This was additionally observed in patients with QRS width duration of 150 ms or more [43] and was strongly associated with effective CRT response.[41] In a recent bicenter report, absence of a typical LBBB pattern was strongly associated with poor outcome in patients receiving CRT, even in the subgroup of patients with intermediate QRS width (duration from 120 to 150 ms) (Fig. 4).[43] This approach was highly reproducible. Poor prognosis of the absence of this typical pattern was also found in RV-paced patients upgraded to CRT, the apex being more often the first activated segment in this latter case.[44]

3.3 | Septal deformation patterns

The septal motion associated with LBBB can also be evaluated using speckle tracking longitudinal strain. The amount of stretching following prematurely terminated preejection septal shortening has been associated with LV reverse remodeling and determines outcome following CRT.[45] Leenders et al., using computer-based simulation in humans, reported that the septal deformation pattern integrates the effects of dyssynchronous activation of the heart and differences in septal and LV free wall contractility, providing integrated information on two key determinants of CRT response.[46] Pattern 1 was obtained by simulating typical LBBB dyssynchrony of ventricular activation

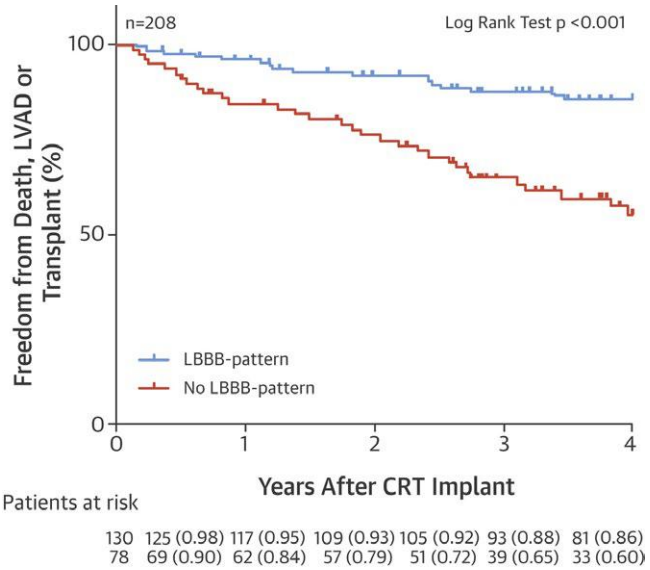

FIGURE 4 Kaplan–Meier curves showing freedom from death, left ventricular assist device, or heart transplant after CRT according to the presence of a typical LBBB longitudinal pattern. Reproduced from Risum et al.,[43] with permission

with preserved septal and LV free wall contractility. Hence, after the initial shortening, a second motion toward the left ventricle was observed after equalization of the wall stress between the septum and free wall, during the ejection phase (Fig. 3). Pattern 2 was obtained by additionally imposing septal hypocontractility to the activation delay, resulting in a dyskinetic motion of the septum within the whole systole, as it cannot counterbalance the increase in LV pressure owing to the preserved LV free wall contraction (Fig. 3). Lastly, deterioration in LV free wall contractility resulted in pattern 3. In this case, septal contraction is prolonged, as the free wall cannot generate wall stress against the septum to stop septal inward motion and push back toward the right ventricle (Fig. 3). Importantly, the mechanisms responsible for the septal flash and the amount of septal stretching (septal rebound stretch) seem to differ. Indeed, the mechanism driving the septal flash is early contraction of the right ventricular free wall, which exerts force on the septum and pulls it leftwards when unopposed by contraction of the left ventricular free wall. In contrast, septal rebound stretch depends on early shortening of the septum being terminated by late contraction of the left ventricular free wall.[47]

We previously demonstrated in a prospective study that patterns 1 and 2, present in 62% of patients with LBBB receiving CRT, were highly predictive of LV reverse remodeling after CRT (91% positive predictive value).[48] Patients with pattern 3 experienced LV reverse remodeling in only 59% of cases and had an increased risk of death or hospitalization for heart failure after CRT, compared to those with patterns 1 or 2. The kappa value for inter-reader variability for characterization of septal deformation pattern was excellent at 0.84. Larger studies are needed to identify predictors of "nonresponse" in patients with pattern 3 and to further explore the prognostic value of these patterns.

3.4 | Systolic stretch index (SSI)

Lumens et al., using computer-based simulations, designed a radial strain-based index, sensitive to the electromechanical substrates responsive to CRT and relatively insensitive to nonelectrical substrates.[24] This novel index, called SSI, was defined as the sum of posterolateral systolic prestretch and septal systolic rebound stretch, which characterized the electromechanical substrate responsive to CRT. Importantly, in a validation cohort of 191 patients receiving CRT, the authors observed that patients with SSI≥9.7% had significantly less heart failure hospitalizations or deaths 2 years after CRT (hazard ratio, 0.32; 95% confidence interval, 0.19–0.53) and less deaths, transplants, or LV assist devices (hazard ratio, 0.28; 95% confidence interval, 0.15–0.55). Consistently, SSI≥9.7% remained independently associated with significantly less heart failure hospitalizations or deaths (hazard ratio, 0.41; 95% confidence interval, 0.23–0.79; *P*=.004) and less deaths, transplants, or LV assist devices (hazard ratio, 0.27; 95% confidence interval, 0.12–0.60; *P*=.001) in patients with intermediate QRS duration or a non-LBBB morphology on the EKG.

3.5 | Relationship between electromechanical dyssynchrony and electrical dyssynchrony

In a recent report, we investigated classical mechanical dyssynchrony indices and electromechanical indices amenable to CRT in four groups of patients: patients with HFrEF, a prolonged QRS duration and an indication for CRT (group 1); patients with HFrEF and a narrow QRS (group 2); patients with heart failure and preserved ejection fraction (group 3); and patients with hypertension, without any history of heart failure (group 4).[49] Importantly, tissue Doppler–based indices of mechanical dyssynchrony were grossly similar among these four groups. In contrast, indices of electromechanical dyssynchrony (septal flash, typical LBBB longitudinal pattern, and septal deformation pattern 1 or 2) were highly prevalent in patients with HFrEF and prolonged QRS duration and very rare in other patients, including patients with HFrEF and narrow QRS.[49] Using a principal component analysis approach, we demonstrated that these indices of electromechanical dyssynchrony were mostly found in patients having HFrEF and prolonged QRS duration awaiting CRT. In contrast, patients with HFrEF and narrow QRS, and hypertensive or HFpEF patients were similar in terms of mechanical dyssynchrony. Hence, these findings demonstrate that electrical dyssynchrony on EKG is strongly related to echocardiographic indices of electromechanical dyssynchrony responsive to CRT.

4 | FUTURE DEVELOPMENTS AND POTENTIAL ROLE OF ECHOCARDIOGRAPHY IN THE SELECTION OF PATIENTS BEFORE CRT

None of the previously reported studies were randomized; therefore, the relationship between echocardiographic indices of electromechanical dyssynchrony responsible to CRT and outcome of patients who did not undergo CRT remains unknown. As patients with a very prolonged QRS duration (≥150 ms) derive maximal benefit from CRT in randomized controlled studies, excluding these patients from CRT would be unethical. In contrast, identification of reliable electromechanical indices of dyssynchrony by echocardiography in patients with QRS of 120–149 ms is of particular interest, as this subgroup of patients does not seem to derive benefit from CRT in a recent meta-analysis.[28] Accordingly, randomized controlled trials using electromechanical dyssynchrony may be considered in this subgroup of patients with intermediate QRS duration. Factors other than dyssynchrony may primarily negatively impact on outcome after CRT, including extent of LV myocardial scarring, identified by cardiac MRI and importance of LV diastolic and right systolic ventricular dysfunction. In addition, LV lead position optimization or technological advances in CRT devices as multipoint pacing, may improve cardiac resynchronization and consequently patient outcome. In the near future, a multimodal approach including echocardiography, cardiac CT and electro-anatomical mappings should improve patient selection for CRT.[50]

5 | CONCLUSION

Classical assessment of LV mechanical dyssynchrony using delay between walls by echocardiography depends not only on electrical dyssynchrony, but also on abnormalities in regional contractility of the LV and on loading conditions; therefore, it may not represent an appropriate tool to select appropriate patients for CRT. In contrast, the echocardiographic identification of electromechanical dyssynchrony based on a mechanistic approach using septal flash, apical rocking, typical LBBB longitudinal pattern, septal deformation patterns, and systolic stretch index may be a more effective approach, especially for patients with intermediate QRS width, for whom the benefit of CRT remains uncertain.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Movie clip S1. Parasternal long axis view illustrating the septal flash (arrow); LV: left ventricle; LA: left atrium.

Movie clip S2. Apical 4-chamber view illustrating the septal flash (arrow); LV: left ventricle; LA: left atrium.

Movie clip S3. Apical 4-chamber view illustrating apical rocking (arrows); LV: left ventricle; LA: left atrium.

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