



How to treat cardiac dyssynchrony in heart failure with reduced ejection fraction

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Abstract

Cardiac resynchronization therapy (CRT) has become part of the standard of care for symptomatic patients with heart failure, reduced ejection fraction (HFrEF), and wide QRS, despite optimal medical therapy. Device technology, operator experience, and post-implant optimization on follow-up have significantly improved CRT response during the last decade. In parallel, conduction system pacing (CSP) has emerged as a new and potentially better tool for maintaining physiological ventricular activation in patients with atrial fibrillation, as well as an alternative for dyssynchrony correction in HFrEF patients. The current review focuses on cardiac dyssynchrony pathophysiology and correction methods, clinical evidence on CRT and CSP as therapies for cardiac dyssynchrony, and the role of each according to clinical evidence and current guidelines for HFrEF treatment.

Keywords

cardiac resynchronization therapy, left bundle branch area pacing, heart failure, LBBB, reduced left ventricular ejection fraction

Rezumat

Terapia de resincronizare cardiacă (CRT) face parte din arsenalul terapeutic standard pentru pacienții simptomatici cu insuficiență cardiacă, fracție de ejeție redusă (HFrEF) și QRS larg, în ciuda tratamentului medicamentos optimal. Tehnologia dispozitivelor implantate, experiența operatorilor și optimizarea post-implant au îmbunătățit semnificativ rata de răspuns la CRT în ultima decadă. În același timp, stimularea sistemului de conducere cardiac (CSP) a apărut ca o unealtă nouă și posibil mai bună pentru menținerea activării ventriculare fiziologice la pacienți cu necesar de stimulare antibradicardică, și ca o alternativă pentru corecția disincronismului la pacienții cu HFrEF. Actualul articol analizează fiziopatologia disincronismului cardiac și metodele de corecție, dovezile clinice privitoare la CRT și CSP ca terapii pentru disincronismul cardiac, și rolul fiecăruia conform datelor clinice actuale și a recomandărilor de ghid in vigoare pentru tratamentul HFrEF.

Cuvinte cheie

terapie de resincronizare cardiacă, stimularea ariei ramului stâng, insuficiență cardiacă, BRS, fracție de ejeție redusă a ventriculului stâng

Key messages

- Cardiac resynchronization therapy (CRT) targets **electromechanical dyssynchrony correction**;
- **Wide QRS / LBBB morphology** remains the main selection criterion for CRT in HFrEF patients;
- **Cardiac biventricular resynchronization therapy (BiV-CRT)** is the mainstay treatment for HF patients with LVEF $\leq 35\%$ and wide QRS;
- Conduction system pacing can be currently considered:
 - an alternative for cases with failed BiV-CRT,
 - complementarily, when BiV-CRT is suboptimal/ in the case of CRT non-response.

Introduction

In 1994, Prof. Cazeau was performing the first implant of a cardiac biventricular resynchronization therapy (BiV-CRT) device, showing

the beneficial effects of four-chamber pacing in a 54-year old patient with dilated cardiomyopathy and left bundle branch block (LBBB).^[1] Since then, BiV-CRT has come a long way, as it has become a well-established therapy for symptomatic heart failure patients with severe left ventricular systolic dysfunction and wide QRS (> 130 ms), who remain symptomatic despite optimal medical treatment. Evidence from multiple large randomized trials, currently encompassing over 20,000 patients, have shown the clinical (improvement in symptoms and survival) and structural (left ventricular ejection fraction [LVEF] increase, cardiac reverse remodeling, mitral regurgitation reduction) benefits of BiV-CRT and represent the basis for current guidelines.^[2] Response to BiV-CRT is uneven, however, as some patients will show lesser or no apparent benefit following CRT. Significant efforts were made during the last decade to improve response, by better patient selection (using clinical, electrocardiographic, and imaging criteria), as well as improved CRT delivery, with new evidence suggesting that conduction system pacing (CSP)—especially left bundle branch area pacing (LBBAP)—may play an important role.^[3]

The following review focuses on cardiac dyssynchrony, pathophysiology, and correction methods; clinical evidence on BiV-CRT and CSP as therapies for cardiac dyssynchrony; and the role of each according to clinical evidence and current guidelines for HFrEF treatment.

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Pathophysiology of cardiac dyssynchrony

Cardiac mechanical dyssynchrony refers to a difference in the contraction/relaxation timing (lack of synchrony) between different areas of the heart, which usually occurs in the setting of electrical conduction disease (electrical dyssynchrony). Significant differences in contraction/relaxation timings can result in reduced cardiac efficiency and are correlated with heart failure.^[4] Cardiac imaging (by advanced echocardiography, cardiac magnetic resonance, and radionuclide imaging) plays an important role in mechanical dyssynchrony as well as substrate assessment. There are three main types of dyssynchrony: atrioventricular, interventricular, and intraventricular (Table 1).^[5]

Atrioventricular dyssynchrony occurs when the timing between atrial and ventricular contractions is impaired, in the presence of prolonged PR interval/AV block, wide QRS, or both. The hemodynamic consequence is an alteration of the left ventricular (LV) filling, secondary to a diastole shortening. Using pulsed-wave Doppler echocardiography, atrioventricular dyssynchrony can be evaluated by measuring the LV filling time from transmitral flow recordings. In the presence of a prolonged atrioventricular interval, the early (E wave) and late (A wave) diastolic waves are fused with a shortening of the ventricular filling time. A ratio of the LV filling time (ms)/RR interval (ms) < 40% indicates atrioventricular dyssynchrony.^[5] An opposite type of AV dyssynchrony may occur following pacemaker implantation, after programming a too short AV delay so that the atrial systole is truncated (resulting in one wave). Furthermore, in patients with prolonged PR, echocardiographic studies have documented the presence of diastolic mitral regurgitation, which could be an aggravating HF factor.^[6]

Inter-ventricular dyssynchrony occurs in the setting of a delay between right ventricular and left ventricular contractions, due to a wide QRS. This delay affects cardiac output by creating paradoxical septal motion that reduces contraction efficacy. One of the first indexes used to assess inter-ventricular dyssynchrony was the inter-ventricular mechanical delay (IVMD), obtained by calculating the difference between aortic and pulmonary pre-ejection intervals (time from QRS onset to flow onset) with pulsed-wave Doppler echocardiography.^[7] Using a cut-off value > 40 ms for defining inter-ventricular dyssynchrony, the CARE-HF trial showed a correlation between IVMD and response to CRT.^[8]

Intra-left ventricular dyssynchrony (LV dyssynchrony) occurs because of delayed contraction of certain LV segments (usually a segment of the lateral wall that is last to contract while the inter-ventricular septum contracts first). This phenomenon is associated with, but not limited to the setting of prolonged QRS duration—typically left bundle branch block (LBBB). The difference in activation timing results in contraction delay, loss of contraction efficiency, impaired relaxation, reduced stroke volume, and malfunction of the mitral apparatus. In the setting of prolonged LV contraction, while the atria relax and atrial pressure falls, the LV pressure might exceed the atrial pressure, resulting in diastolic mitral regurgitation. Dys-coordinated papillary muscle function can also cause or further

Table 1 - Cardiac electrical dyssynchrony types and functional consequences. Wide QRS, QRS duration > 120 ms; LV, left ventricle; LBBB, left bundle branch block

Type of dyssynchrony	Underlying electrical disease	Functional consequence
Atrioventricular	Prolonged PR/AV block	Diastolic impairment
Inter-ventricular	Wide QRS	Systolic impairment
Intra-ventricular LV	Wide QRS (LBBB)	Systolic and diastolic impairment Mitral regurgitation

aggravate the mitral regurgitation.^[9] These dyssynchrony-related changes promote adverse LV remodeling.^[5]

Assessment of cardiac dyssynchrony—electrical versus mechanical

While all types of electro-mechanical cardiac dyssynchronies can be corrected by using dedicated cardiac-implantable electronic devices, only the intra-left ventricular dyssynchrony correction, in the setting of LBBB, was definitely proven in randomized controlled trials to improve prognosis in patients with HFrEF.^[10]

Therefore, the first and most important step for cardiac dyssynchrony assessment is electrical dyssynchrony diagnosis by standard 12-lead ECG, showing wide QRS (>130 ms). QRS duration and morphology are important: wider QRS (>150 ms) and typical LBBB morphology are correlated with significantly more severe intra-LV mechanical dyssynchrony.

Cardiac imaging is important for substrate assessment and mechanical dyssynchrony documentation. Imaging techniques for dyssynchrony assessment rely mainly on direct or indirect assessment of opposite LV walls' contraction delay. The most widely available and used tool is echocardiography (standard and advanced tissue Doppler imaging techniques, including 3D techniques). Numerous parameters have been assessed regarding their predictive values in terms of BiV-CRT response and patient selection (Table 2).

However, despite all efforts, prospective randomized, multicenter trials—such as the PROSPECT trial—failed to provide any reliable single echocardiographic parameter for dyssynchrony measurement that might improve patient selection for CRT beyond current guidelines.^[17,18] Furthermore, the ECHO-CRT trial has shown that resynchronization therapy based solely on the presence of mechanical dyssynchrony (echocardiographic evidence of LV dyssynchrony) in NYHA III/IV HFrEF patients without electrical conduction disease (narrow QRS < 130 ms), did not improve outcome and was even associated with harm.^[19] Cardiac magnetic resonance (CMR) has emerged during the last decade as the gold standard imaging technique for myocardial substrate assessment. Efforts are being made to develop CMR-based tools for dyssynchrony measurement.^[20]

To conclude, mechanical dyssynchrony documentation by cardiac imaging is not mandatory for CRT patient selection. The

Table 2 - Mechanical intra-left ventricular dyssynchrony evaluation by cardiac echography.^[10–16] Ts, time-to-peak systolic velocity; SD, standard deviation; LV, left ventricular; 2D, two dimensional; 3D, three dimensional

Echography parameter	Method	Cut-off values
Septal to posterior wall motion delay ^[11]	M-mode	≥ 130 ms
Septal flash ^[12]	M-mode	Nonquantifiable ¹
Apical rocking ^[12]	2D apical 4 chambers	Nonquantifiable ²
Basal septal to lateral Ts delay ^[13]	Tissue Doppler imaging	≥ 60 ms
Maximum delay in Ts in 4 basal LV segments ^[14]	Tissue Doppler imaging	> 65 ms
SD of Ts of 6 basal LV segments ^[15]	Tissue Doppler imaging	≥ 34.4 ms
Antero-septal to posterior time to peak strain difference (radial strain) ^[16]	2D speckle tracking	≥ 130 ms
SD of time to minimum systolic volume of 16 LV segments (systolic dyssynchrony index) ^[16]	3D echocardiography	$> 5.6\%$

¹Septal flash: early septal systolic thickening and thinning leading to a short inward motion of the septum

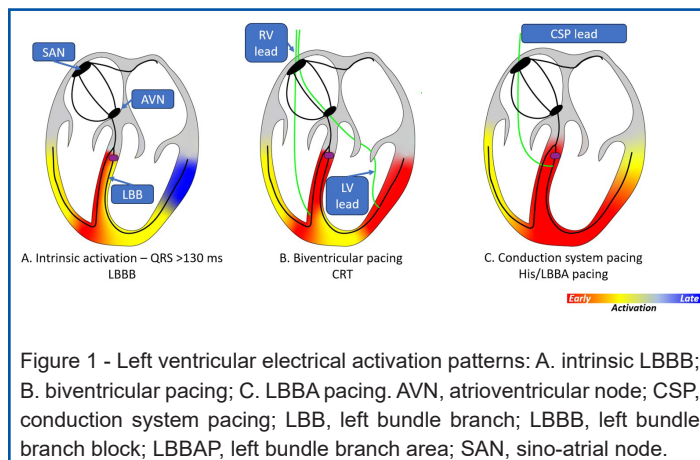
²Apical rocking: initial septal contraction pulling the apex towards the septum, followed by delayed lateral wall contraction, pulling the apex laterally while stretching the septum

presence of echocardiographic dyssynchrony parameters (as simple as septal flash or apical rocking) is associated with better BiV-CRT response,^[12] but their absence does not preclude CRT for that particular patient.

Cardiac imaging remains very important for better understanding the underlying disease, in terms of etiology, global cardiac size and function, myocardial contractility and functional reserve, and scar extent and localization, all of which correlate with prognosis and outcome beyond cardiac dyssynchrony in patients undergoing CRT.^[21] Despite recent changes in the guideline's definition of HFrEF for LVEF $< 40\%$, the cut-off for BiV-CRT implantation remains 35%, as all major CRT trials have used this specific value (or even a lower cut-off of $\leq 30\%$) as an inclusion criterion.^[22] Scar localization and cardiac venous anatomy assessment play an important role for CRT delivery, as they can guide the LV lead implantation.^[2]

Cardiac dyssynchrony correction

Cardiac resynchronization therapy refers to intra-LV electro-mechanical dyssynchrony treatment in HFrEF patients via a dedicated cardiac implantable electronic device, classically by a biventricular device—the BiV-CRT (with dedicated leads for right atrium/ventricle and left ventricle, with epicardially inserted lead, via the coronary sinus or surgically).^[2] More recently, the same objective has been achieved with a special ventricular lead used for conduction system pacing (CSP), either by HIS fascicle pacing or left bundle branch area pacing.^[3] For this review, the term BiV-CRT will be used for the standard biventricular pacing, whereas CSP will be used for HIS/left bundle branch area pacing.



Although both methods target the same goal, the way for achieving it differs: While classical bi-ventricular CRT pacing improves intra LV dyssynchrony by introducing a second activation wavefront coming from the lateral LV wall, CSP has the potential to correct it by direct LV conduction system pacing, which may lead to complete restoration of physiological LV depolarization (Figure 1).

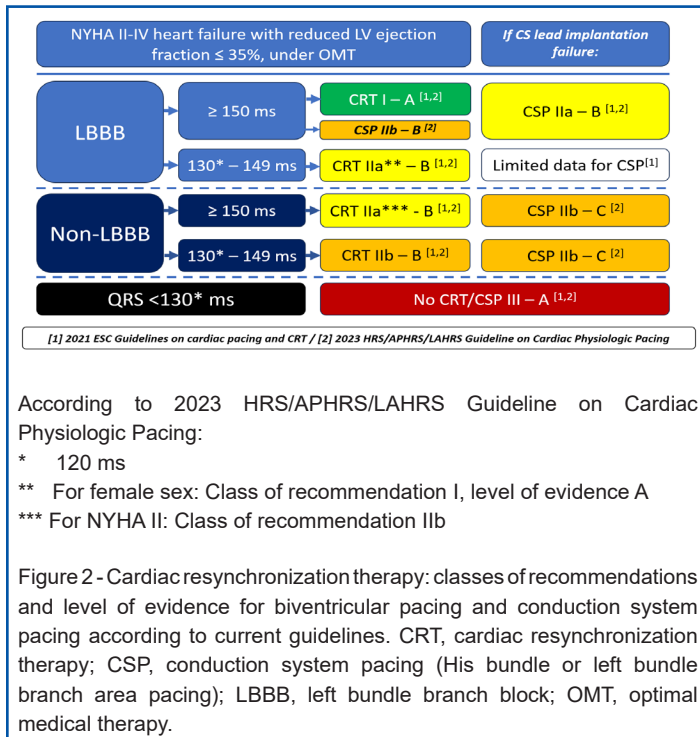
Conceptually, in the setting of LBBB, successful His/LBBAP can “cure” LV electro-mechanical dyssynchrony, whereas biventricular CRT corrects it but cannot fully restore physiological LV activation.^[23]

1. Benefits and limitations of cardiac resynchronization therapy for HFrEF treatment

Over the last 25 years, multiple randomized control trials (RCTs) have provided solid evidence concerning the benefits of BiV-CRT in heart failure treatment (Table 3). For symptomatic patients with HF, mainly in sinus rhythm, with an LVEF $< 35\%$ and a QRS duration > 130 ms of LBBB morphology, under optimal medical therapy, cardiac resynchronization therapy improves symptoms, functional capacity, quality of life, and leads to LV reverse remodeling, while reducing heart failure hospitalizations and long-term mortality.^[2,22]

MADIT-CRT remains one of the cornerstone trials. It included 1820 patients with NYHA class I–II HF, wide QRS ≥ 130 ms, and reduced LVEF $\leq 30\%$, who were randomized into CRT-D versus ICD alone. Initial results showed, after an average follow-up of 2.4 years, a significant (41%) reduction in the risk of HF events ($p = 0.001$), a finding primarily evident in a pre-specified subgroup of patients with a QRS ≥ 150 ms. CRT was also associated with a significant reduction in LV volumes and LVEF improvement, with no influence on survival. Upon long-term follow-up, however, among the 1818 patients enrolled in the post-trial registries, CRT-D was associated with significant mortality reduction in LBBB patients (hazard ratio (HR): 0.59; 95% confidence interval (CI) 0.43 – 0.80; $p < 0.001$). In contrast, in patients without LBBB, CRT-D had no clinical benefit and proved to be potentially harmful (HR: 1.57; 95% CI 1.03 – 2.39; $p = 0.04$).^[10]

One of the biggest challenges of BiV-CRT remains the apparent lack of benefit or even worsening in a significant number of patients—a clinical condition characterized as “non-response to CRT” and the patient as “non-responder.” Depending on the CRT



response definition (clinical, structural, biological), non-response rates varied among studies from 20% to 40%.^[24]

During the last decade, significant efforts have been made to improve the response rate to CRT by means of careful procedure planning (correct patient selection; scar and apical segments avoidance for LV lead implantation), the use of last generation tools (quadripolar LV lead, special coronary sinus sheaths and catheters), and CRT optimization by the long-term use of validated automated algorithms and multipoint pacing.

The latest BiV-CRT randomized controlled trial published in August 2023, the AdaptResponse trial, enrolled 3797 patients with HFrEF successfully implanted with a BiV-CRT systems and followed-up for a median of 60 months. Although negative in terms of primary endpoint (by failing to demonstrate a significant added clinical benefit of using an optimized LV, only pacing algorithm versus standard biventricular pacing), the AdaptResponse trial has shown that mortality in HFrEF in the era of modern pathogenic treatment combined with CRT has dropped spectacularly (16.5% in 5 years). In addition, 93% of all patients either improved or stabilized clinically with CRT—which is the highest response rate yet reported in any randomized CRT trial.^[25] Response to CRT was evaluated by using a clinical composite score at 6 months (NYHA class, quality of life, adverse events, healthcare service utilization, device data).^[26] The exceptionally high response rate was explainable mainly by patient selection: NYHA II-III, LVEF $\leq 35\%$, adjudicated LBBB with a QRS duration $n \geq 140$ ms (men) or ≥ 130 ms (women). These are the patients for which CRT is actually intended.

The question remains, for its application in HFrEF patients with wide non-LBBB QRS, may these patients still benefit from CRT?

The only non-LBBB subgroup of patients from the MADIT-CRT trial who showed benefit following CRT-D was the subgroup with

prolonged PR ≥ 230 ms (significant 73% reduction in the risk of HF/death [HE:0.27; 95% CI 0.13–0.57; $p < 0.001$]) and 81% reduction in the risk of all-cause mortality [HR: 0.19; 95% CI 0.13–0.57; $p < 0.001$]). At the same time, CRT-D use in non-LBBB patients with normal PR < 230 ms was associated with increased risk of HF/death.^[27]

A recent meta-analysis has confirmed that RBBB morphology is not associated with lower risk for heart failure hospitalization or death, regardless of QRS duration. Interestingly though, intra-ventricular conduction delay (IVCD) morphology with a QRS duration ≥ 150 ms was still associated with a benefit in terms of reduced heart failure hospitalization and death. This suggests that among IVCD patients, some may still benefit from CRT.^[28] Ongoing registry trials (such as FACT-CRT) are currently trying to identify those IVCD candidates for CRT.

2. Cardiac resynchronization therapy and conduction system pacing

Conduction system pacing has emerged as the new method for ventricular physiological pacing in patients for whom antibradycardia therapy is indicated.^[2] Through the ability to intercept and directly pace the His bundle or its branches, conduction system pacing has the potential to correct the intra-LV dyssynchrony in a more physiological way and without the need for a coronary sinus catheter.

The idea has gone beyond proof of concept as there is already clinical data published showing that CSP can successfully replace BiV-CRT. Some of the most compelling data come from Vijayaraman et al., showing that in a large cohort of 325 patients with wide QRS (152 ± 32 ms; LBBB 39%) and a LVEF $< 50\%$ ($33 \pm 10\%$), CSP was successfully achieved in 85% of the cases, leading to significant QRS narrowing (137 ± 22 ms) and LVEF increase ($44 \pm 11\%$).⁽²⁹⁾ Numerous case reports and series of patients with CSP replacing BiV-CRT have been reported since with variable but generally high rates of success. Recently, data from the multicenter European MELOS registry study have shown that across 14 European centers, CSP lead^[2] implantation was successfully achieved in 82.2% of cases for heart failure indications. There is a learning curve, which was steepest for the initial 110 cases, with heart failure, broad baseline QRS and left ventricular end-diastolic diameter as independent predictors for CSP lead implantation failure. Complication rates were quite high: 11.7%, a reminder of the need for safety improvements.

Currently, conduction system pacing can be considered as an alternative to BiV-CRT when BiV-CRT has failed. There are no long-term randomized trials supporting CSP as first-line therapy for HFrEF with LBBB, instead of BiV-CRT. Several small randomized control trials including a total of 125 patients with HFrEF and wide QRS, have shown that CSP versus BiV-CRT can achieve similar degrees of cardiac resynchronization, ventricular reverse remodeling, and clinical outcomes at 6-months follow-up.^[30,31,32]

Concerns remain regarding the long-term performance and effect of CSP leads as well as their behavior when the need for extraction arises. Furthermore, there are no dedicated cardiac implantable electronic devices to be used with CSP leads and the tools for CSP lead implantation require improvements. Given the wide acceptance

of BiV-CRT based on randomized control trials with long-term follow-up, it is recommended for use more frequently than CRT.

Another possibility for BiV-CRT and CSP in HFrEF is to combine both methods, leading to a new hybrid technique: the His-optimized CRT (HOT-CRT)^[33] and the left bundle branch area pacing-optimized CRT (LOT-CRT).^[34] By introducing one lead for CSP (either His or LBBB area) and one LV lead via the coronary sinus, both HOT-CRT and LOT-CRT were proven to be feasible and safe. It is also worth noting that in the latter study, LOT-CRT reduced QRS duration to a greater extent than biventricular pacing or left bundle branch area pacing alone.^[35]

Similarly to using CSP as an alternative to BiV-CRT, these hybrid methods require randomized controlled trials in order to assess the actual benefits in comparison to standard CRT, as the majority of data on CSP is observational and long-term data on lead survival is lacking.

Current guidelines and conclusions

Current European and American guidelines remain unchanged for symptomatic HFrEF patients with wide LBBB > 150 ms and LVEF < 35%, as well as with BiV-CRT having a class of recommendation (COR) I Level of Evidence A indication (Figure 2).^[2,36] There are differences regarding the inferior QRS duration cut-off concerning CRT patient selection (European guidelines setting the inferior cutoff at 130 ms, while the North American guidelines allow CRT up until 120 ms, with a COR IA in case of female patients).

The 2021 ESC guidelines mention His bundle pacing as an alternative to BiV-CRT in the case of coronary sinus lead implantation failure, whereas a more recent EHRA consensus on conduction system pacing implantation addresses CSP technique and mentions clinical scenarios where CSP or LOT-CRT can be taken into consideration, without making any recommendations.^[3] The most recent 2023 HRS/APHRS/LAHRs guidelines suggest left bundle branch area pacing as an alternative to His bundle pacing in

case of failed BiV-CRT (COR IIa C). Interestingly, for symptomatic HFrEF patients with LVEF ≤ 35% and LBBB ≥ 150 ms, His bundle pacing or left bundle branch area pacing can be offered as first-line therapy with a COR IIb C.

To conclude, biventricular cardiac resynchronization therapy remains the mainstay treatment for HFrEF patients with LVEF ≤ 35% and LBBB. Conduction system pacing is an emerging new technique that can offer an alternative for cases with failed BiV-CRT or can be used as a complementary therapy when BiV-CRT is suboptimal or in the case of CRT nonresponse. Further studies are required to better understand the role of conduction system pacing for CRT, as well as the role of CRT for HFrEF patients with IVCD.

List of abbreviations

AF = atrial fibrillation

BiV-CRT = biventricular cardiac resynchronization therapy

COR = class of recommendation

CRT = cardiac resynchronization therapy

HOT-CRT = His optimized cardiac resynchronization therapy

HFrEF = heart failure with reduced ejection fraction

IVCD = intra-ventricular conduction delay

LBBAP = left bundle branch area pacing

LBBB = left bundle branch block

LOT-CRT = left bundle branch area pacing optimized cardiac resynchronization therapy

LV = left ventricle

LVEF = left ventricular ejection fraction

SR = sinus rhythm

Conflict of authors

none declared.

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