Chapter 4
Cardiac Resynchronization Therapy for Heart Failure in Patients Without Left Bundle Branch Block

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Abbreviations

6MWT	6-min walk test
CARE-HF	Cardiac Resynchronization-Heart Failure
COMPANION	Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure
HF	Heart failure
LV	Left ventricular
LVEDD	Left ventricular end-diastolic dimension
LVEF	Left ventricular ejection fraction
LVESV	Left ventricular end-systolic volume
MADIT-CRT	Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy
MIRACLE ICD	Multicenter InSync Randomized Clinical Evaluation Implantable Cardioverter Defibrillator trial
MIRACLE	Multicenter InSync Randomized Clinical Evaluation
MR	Mitral regurgitation
MUSTIC	Multisite Simulation in Cardiomyopathies
NYHA	New York Heart Association
PATH-CHF	Pacing Therapies in Congestive Heart Failure trial
QOL	Quality-of-life score
RAFT	Resynchronization-Defibrillation for Ambulatory Heart Failure Trial
REVERSE	Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction
VO2	Volume of oxygen

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Cardiac Resynchronization Therapy

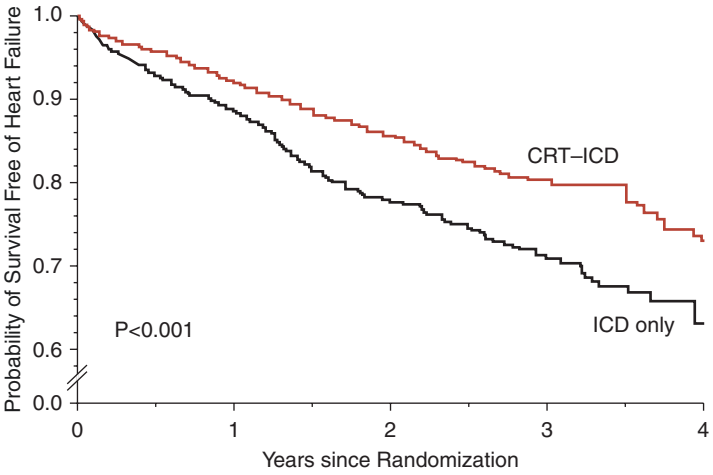
Heart failure is a global epidemic associated with high morbidity and mortality. According to recent estimates, the prevalence of HF is over 5.8 million in the USA and more than 23 million worldwide with an expected increase over time [1]. The 5-year mortality of HF is about 50%, competing with those of many cancers. Healthcare utilization associated with the care of HF is significant and costly; inpatient and outpatient visits for HF account for more than 39 billion in the USA alone [1].

Implantation of a CRT system in HF patients provided a remarkable therapeutic alternative to reduce HF symptoms and improve outcomes in advanced HF patients [2–5]. CRT is a three-lead system that delivers electrical stimuli to the right atrium, right ventricle, and left ventricle to synchronize the dyssynchronous left ventricular (LV) activation in patients with conduction abnormalities and severely reduced LV function. It should not be forgotten that CRT has been developed initially to ail the failing heart commonly impaired by three primary components of dyssynchrony: (1) atrioventricular dyssynchrony, (2) interventricular dyssynchrony, and (3) intraventricular dyssynchrony. Implantation of CRT results in an immediate decrease of intra- and interventricular dyssynchrony, a decrease in mitral regurgitation, and an increase in LV contractility [6]. During follow-up, patients exhibit a significant reduction in LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV), and improvement in LV ejection fraction (LVEF), a process described as LV reverse remodeling [7, 8]. LV reverse remodeling is the hallmark of CRT effectiveness, and it has been shown to be directly linked to improved clinical outcomes [9].

CRT alone or the combination of a CRT with an implantable cardioverter defibrillator (CRT-D) has been proven to reduce HF symptoms, improve functional capacity, and improve quality of life in HF patients with advanced HF symptoms (NYHA class III–IV), reduced LVEF≤35%, and a prolonged QRS duration (QRS≥120 ms) [4, 5, 10]. CRT has also been shown to significantly reduce the frequency of HF hospitalizations and improve survival [4, 5]. A meta-analysis of CRT trials in advanced HF showed an overall 29% risk reduction in all-cause mortality and a 38% risk reduction in mortality due to progressive HF [11].

The Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT), the Resynchronization-Defibrillation in Ambulatory Heart Failure Trial (RAFT), and Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trials have further broadened CRT indication to patients with mild HF, presenting with NYHA class I and II HF symptoms [12, 13]. Figure 4.1 shows the primary results of MADIT-CRT, demonstrating a 34% risk reduction in HF events or mortality. The subsequently published long-term follow-up of MADIT-CRT and REVERSE studies confirmed sustained benefit of CRT in mild HF patients with reduction in HF events and improved survival [14, 15].

Large, randomized controlled clinical trials on the effects of CRT or CRT-D to improve HF symptoms, functional capacity, and outcomes are listed below in



No. at Risk (Probability of Survival)					
ICD only	731	621 (0.89)	379 (0.78)	173 (0.71)	43 (0.63)
CRT–ICD	1089	985 (0.92)	651 (0.86)	279 (0.80)	58 (0.73)

Fig. 4.1 Heart failure or death events in mild HF patients with CRT-D vs. ICD-only in MADIT-CRT

Table 4.1, including the respective frequencies of non-LBBB patients, when information was available. As it is evident from this table, the frequency of non-LBBB was often not reported or analyzed in the early CRT studies; these studies focused on the effects of CRT in wide QRS patients primarily presenting with LBBB. The first large randomized trials evaluating the effect of CRT on all-cause mortality, Cardiac Resynchronization-Heart Failure (CARE-HF) and Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION), enrolled 6% and 29% of their patients with non-LBBB, respectively. The REVERSE study, on the other hand, enrolled 38% of patients with non-LBBB, a very high percentage, while MADIT-CRT enrolled 30% [16]. These trials also reported specific outcomes of patients with non-LBBB, allowing us to better understand differences in CRT benefit by baseline ECG morphology.

Pathophysiology of Non-LBBB

Electrical activation of the ventricles in patients with RBBB (non-LBBB) has been described by Fantoni et al. [17]. Patients with RBBB typically showed a single RV breakthrough site in the septum, as compared to LBBB with multiple breakthroughs. Following activation through the septal breakthrough site, activation then slowly spread toward the anterior region with the latest activated regions being the right

Table 4.1 Randomized controlled trials of cardiac resynchronization therapy by LBBB

Clinical trial	Patients (n)	Primary end points	Secondary end points	LVEF (%)	QRS (ms)	Non-LBBB (%)
MUSTIC-SR	58	6MWT	NYHA, QOL, peak VO2, MR, LV, hospitalizations, mortality	23 ± 7	174	13%
MUSTIC-AF	64	6MWT	NYHA, QOL, peak VO2, hospitalizations, mortality	26 ± 0	206	n.a.
PATH-CHF 2	41	6MWT, peak VO2	NHYA class, QOL, hospitalizations	21 ± 7	175	n.a.
PATH-CHF-II (Europe)	86	6MWT, peak VO2	NHYA class, QOL, hospitalizations	21 ± 7	175	n.a.
MIRACLE	453	6MWT, NHYA, QOL	Peak VO2, LVEF, LVEDD, MR, clinical response	22 ± 6	166	n.a.
MIRACLE ICD	555	6MWT, NYHA, QOL	Peak VO2, LVEF, LV volumes, MR, clinical response	24 ± 6	164	13%
COMPANION	1520	All-cause mortality or hospitalization	All-cause mortality and cardiac mortality	21	159	29%
CARE-HF	814	All-cause mortality	NYHA, QOL, LVEF, LVESV, hospitalization for heart failure	25	160	6%
REVERSE	610	HF clinical composite score	LVESVI	27 ± 7	153	38%
MADIT-CRT	1820	HF or death	LVESV, LVEDV change, multiple HF events	24 ± 5	162	30%
RAFT	1798	All-cause mortality or HF hospitalization	All-cause mortality, cardiac mortality, HF hospitalization	23 ± 5	158	20%

6MWT 6-min walk test, *CARE-HF* Cardiac Resynchronization-Heart Failure, *COMPANION* Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure, *HF* heart failure, *LV* left ventricular, *LVEDD* left ventricular end-diastolic dimension, *LVEF* left ventricular ejection fraction, *LVESV* left ventricular end-systolic volume, *MADIT-CRT* Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy, *MIRACLE* Multicenter InSync Randomized Clinical Evaluation, *MIRACLE ICD* Multicenter InSync Randomized Clinical Evaluation Implantable Cardioverter Defibrillator trial, *MR* mitral regurgitation, *MUSTIC* Multisite Simulation in Cardiomyopathies, *NYHA* New York Heart Association, *PATH-CHF* Pacing Therapies in Congestive Heart Failure trial, *QOL* quality-of-life score, *RAFT* Resynchronization-Defibrillation for Ambulatory Heart Failure Trial, *REVERSE* Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction, *VO2* volume of oxygen

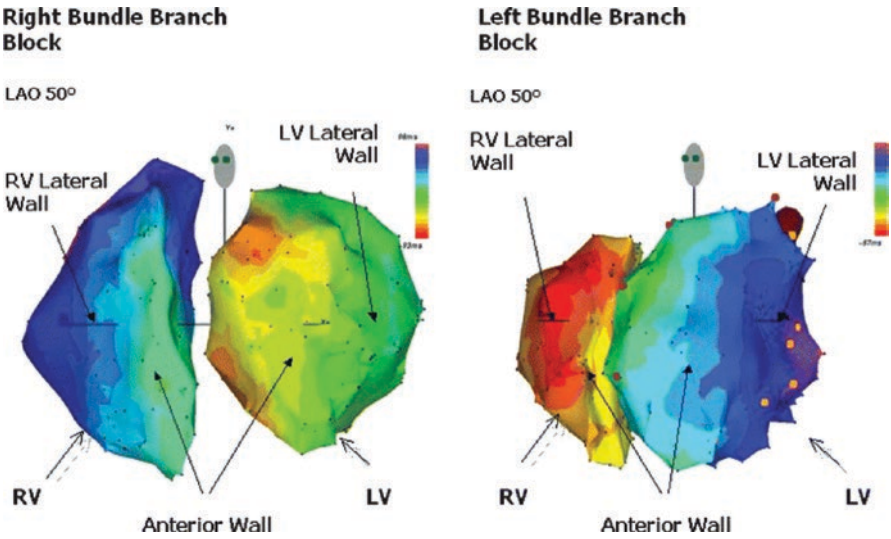


Fig. 4.2 Electrical activation of the left and right ventricle in patients with right bundle branch block and left bundle branch block

lateral wall and the outflow tract. Transseptal activation time, activation time of the RV, and total activation time were significantly longer in RBBB group compared to LBBB. In both patients with RBBB and LBBB, LV activation spread slowly, from the septal or anterior breakthrough site toward apical and lateral regions, with the posterolateral basal region being the latest activated LV area in both groups, suggesting the rationale for CRT in both patients with LBBB and RBBB (non-LBBB); however RBBB patients presented with more severe manifestation of conduction disturbances (Fig. 4.2).

Electrocardiographic Parameters to Identify Response to CRT in Non-LBBB Patients

QRS Morphology and QRS Duration

QRS duration reflects ventricular activation time. Hence QRS prolongation has great utility in informing the clinician about electrical activation delay and about regionally delayed ventricular excitation. A LBBB ECG pattern in HF patients has been related to electromechanical ventricular dyssynchrony and subsequently promotes favorable CRT effects on the failing myocardium [18], although various definitions of LBBB were associated with differences in CRT outcomes [19]. In the absence of LBBB, wide QRS may be caused by right bundle branch block (RBBB), left anterior fascicular block (LAFB), or atypical patterns of ventricular conduction

delay that are frequently caused by localized myocardial scar. But in the absence of LBBB, the sole presence of ventricular conduction delay does not imply that the compromised ventricular electromechanical performance can be improved by atrio-biventricular pacing.

While the beneficial effects of CRT have been widely accepted and CRT therapy had been incorporated in all major electrophysiology guidelines worldwide [20, 21], there have been several secondary analyses reporting a suboptimal response to CRT based on the underlying ECG pattern at baseline, before CRT implantation. Specifically, patients with a left bundle branch block (LBBB) ECG pattern before device implantation have been suggested to derive a significant benefit from CRT-D, while those with non-LBBB ECG pattern were shown to have either no benefit or even a potential exposure to harm [22]. In MADIT-CRT, patients with LBBB had a significant, 53% reduction in the risk of HF or death with CRT-D versus an ICD-only (Fig. 4.3), while non-LBBB patients had a nonsignificant, 24% higher rate of HF/death with CRT-D versus an ICD-only (Fig. 4.4).

These findings have been subsequently confirmed in the REVERSE trial which found an independent relationship between QRS duration and outcomes [23]. Data from RAFT also showed a link between QRS morphology, QRS duration, and outcomes in LBBB, and similarly to our study, they did not reveal any benefit in non-LBBB patients [24]. In alignment with these findings, the National Cardiovascular Database Registry (NCDR) ICD Registry sub-study assessing CRT outcomes by QRS morphology and QRS duration confirmed that LBBB patients had better outcomes with CRT-D as compared to non-LBBB [25]. On the other hand, Cleland et al. [26] performed an individual patient-level meta-analysis combining five

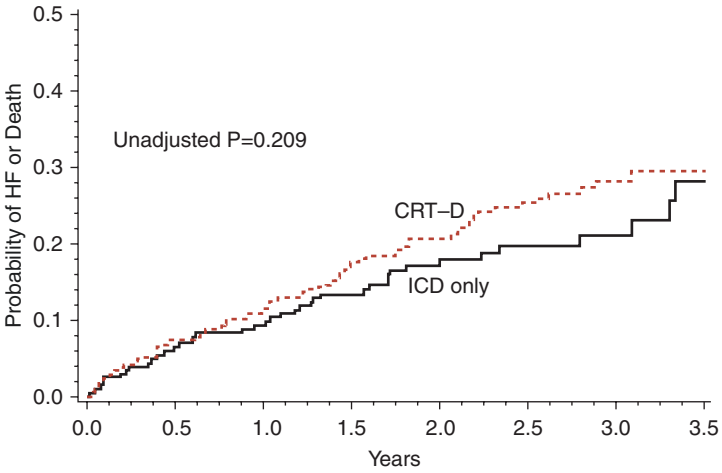


Fig. 4.3 Heart failure or death in patients with LBBB [22]

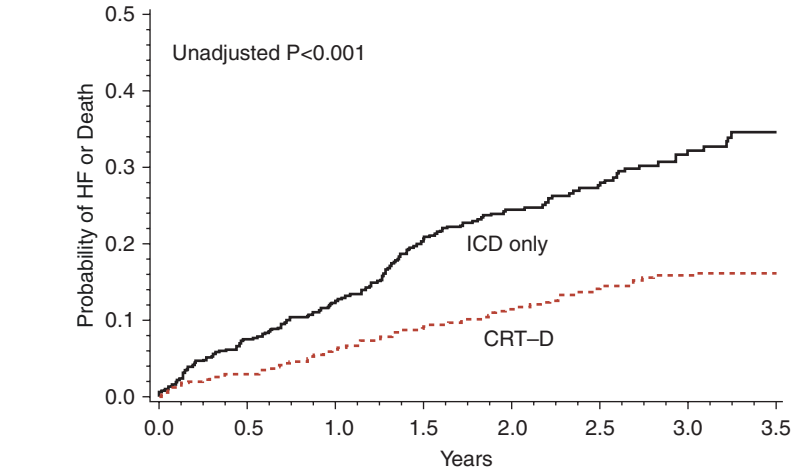


Fig. 4.4 Heart failure or death in patients with Non-LBBB [22]

randomized trials and concluded that QRS duration, but not QRS morphology, was a predictor of CRT outcomes.

In summary, QRS morphology and QRS duration appear to determine the treatment success of CRT, but prolonged QRS duration alone is questionable as a prerequisite for CRT. Accordingly, current guidelines [20] define a class I or class IIa indication for CRT in symptomatic HF patients with LBBB ≥120 ms, but non-LBBB patients do not receive a class I indication and have a class IIa indication only at a QRS duration ≥150 ms and a weaker class IIb indication at a QRS duration of 120–149 ms. HF patients with a *narrow QRS* complex <120 ms are not indicated for CRT regardless of ventricular dyssynchrony assessment, unless they require frequent ventricular pacing (>40%) to treat bradycardia [27].

QRS area assessed from the vectorcardiogram in patients with wide QRS reflects three-dimensional electrical force within the heart and has been shown to identify delayed LV lateral wall activation [28]. Therefore, QRS area has been proposed to prospectively identify CRT responders. Respective further studies to confirm this finding are under way.

Prolonged PR-Interval

A prolonged PR interval may result in atrioventricular dromopathy with compromised transmitral left ventricular filling and possible serious adverse clinical consequences [29]. A prolonged PR interval in patients without HF has been shown to be associated with an increased risk of atrial fibrillation [30], LV dysfunction, HF

hospitalization, and all-cause mortality, as compared to normal PR interval [31]. This could be especially relevant in patients with established HF and conduction abnormalities, since a delay in atrioventricular conduction could further lower the cardiac output exacerbating HF symptoms [32]. Accordingly, the correction of AV coupling by CRT in HF patients with long PR interval can be hypothesized to improve the performance of the failing heart.

In line with this hypothesis, we have previously shown in a secondary analysis of MADIT-CRT that HF patients with non-LBBB ECG pattern and a prolonged PR-interval (PR ≥230 ms) derived clinical benefit from CRT-D with a 32% absolute risk reduction in HF or death at 4 years as compared to ICD (Fig. 4.4) [32]. This corresponds to a 73% relative risk reduction in HF or death and a remarkable, 81% risk reduction in all-cause mortality in this subgroup. Non-LBBB patients with a normal PR interval <230 ms derived no clinical benefit. On the contrary, patients with non-LBBB and a normal PR interval had a nonsignificantly higher risk of HF or death and more than twofold increase in the risk of death with CRT-D when compared to an ICD-only (interaction p-value<0.001) [32] (Fig. 4.5).

Such a strong bidirectional interaction with CRT-D treatment suggests that in the absence of LBBB, correction of LV dyssynchrony might not be the principal mechanism of action by CRT. It is more likely that the restoration of the physiological atrioventricular (AV) conduction by shortening the PR interval (AV delay) plays a role in the benefit from CRT-D in this cohort.

These findings were subsequently confirmed in the MADIT-CRT long-term follow-up sub-study, demonstrating sustained benefit in this cohort for up to 7 years [33]. In this follow-up study, we have also established that the benefit of CRT-D in

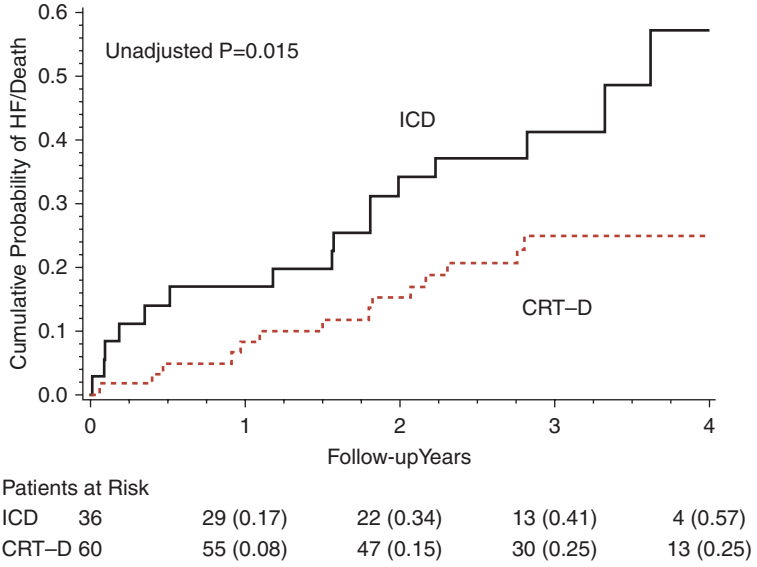


Fig. 4.5 HF or death for non-LBBB and PR ≥230 ms with CRT-D vs. ICD-only [32]

non-LBBB patients was uniformly seen for both patients with QRS <150 ms and QRS ≥150 ms. Previous studies suggested similar association with a prolonged PR interval in more advanced HF patients [34], although more recent analyses from the NCDR ICD Registry challenged these findings in a retrospective cohort study using a matched control group instead of randomization or a prospective design [35]. Therefore, these findings remain an area of controversy at this point.

The pathophysiology of a prolonged PR interval in the presence of conduction abnormalities is depicted above in Fig. 4.6. In patients with an abnormally prolonged PR interval, atrial systole (A) occurs early in diastole, and therefore, it is superimposed on the early left ventricular filling phase (E). This results in the fusion of the diastolic E and A waves, a significantly shorter effective diastolic LV filling time, and a lower cardiac output. Occurrence of an early atrial systole uncouples the mitral valve closure from LV systole resulting in diastolic presystolic mitral regurgitation, and a decreased preload and forward stroke volume, further worsening LV function. Following CRT implantation, the shortening of the PR interval to normal ranges restores the physiologic AV sequence (right panel), completely abolishes E and A fusion, and reduces or eliminates diastolic presystolic mitral regurgitation.

The underlying concept for the benefit of physiologic, AV sequential pacing in HF patients with a prolonged PR interval is well known. Previously reported case series on right ventricular (RV) DDD pacing with shorter AV delay in HF patients and low ejection fraction in the 1990s reported an improvement in HF symptoms [36]. However, in a subsequent sub-study from the DAVID trial, outcome with DDD versus VVI pacing was similarly unfavorable in HF patients with low LVEF and a prolonged PR interval (>200 ms), suggesting that dyssynchronous RV pacing in HF patients potentially outweighs the benefit of the restoration of AV synchrony [37]. We are therefore proposing that in MADIT-CRT, the presence of LV pacing (CRT) by eliminating iatrogenic dyssynchronous RV pacing while shortening the AV delay could be responsible for the above seen beneficial effects. It has also been shown

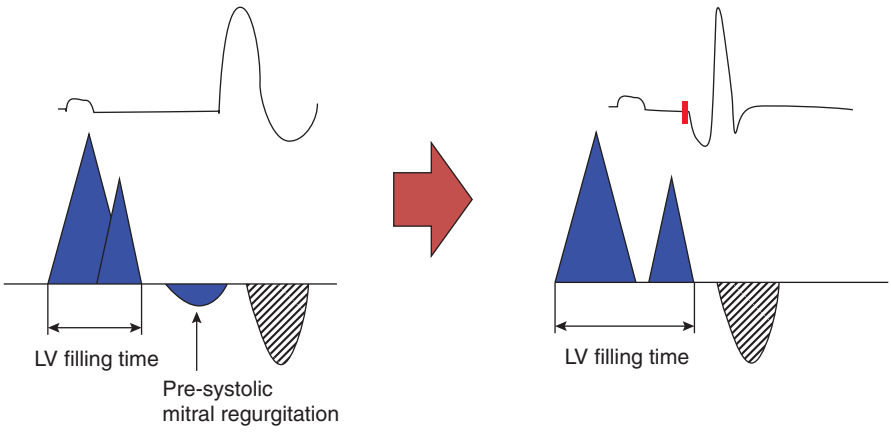


Fig. 4.6 Pathophysiology in non-LBBB with prolonged PR interval (left panel) and normalization with CRT-D and shorter AV-delay (right panel) (Kutyifa and Stockburger 2013)

that patients with first degree AV block without a pacing indication are three times more likely to develop a need for pacing during follow-up [32]. This further signifies the need for a more physiological pacing modality in this cohort, such as LV pacing. Newer techniques, such as His bundle pacing, could also be considered in this cohort, and initial studies have shown acute hemodynamic benefit in this population [38]. A larger, randomized study in patients with non-LBBB and a prolonged PR-interval applying His bundle pacing vs. no pacing is currently underway (HOPE-HF, https://clinicaltrials.gov/ct2/show/NCT02671903).

Further Electrocardiographic Parameters

A prolonged P wave duration with delayed left atrial activation may attenuate the adverse effect of a long PR on left ventricular filling. From a practical standpoint, the appraisal of the pulsed wave transmitral Doppler flow pattern may be of additional value to establish (in case of short filling and E/A fusion, Fig. 4.7a) or to disaffirm (in case of preserved E/A separation, Fig. 4.7b) a CRT pacing indication based on first-degree AV block in HF patients. Guidelines suggest a possible pacing indication in patients with a PR of at least 300 ms.

Right ventricular (RV) pacing in patients with reduced left ventricular ejection fraction has been demonstrated to adversely affect clinical outcome [39, 40]. Biventricular pacing has been demonstrated to be superior to RV pacing in AV block and impaired ventricular function [41, 42]. *Second- or third-degree AV block* with an expected ventricular pacing rate of at least 40% therefore constitutes an accepted (class IIa) indication for CRT.

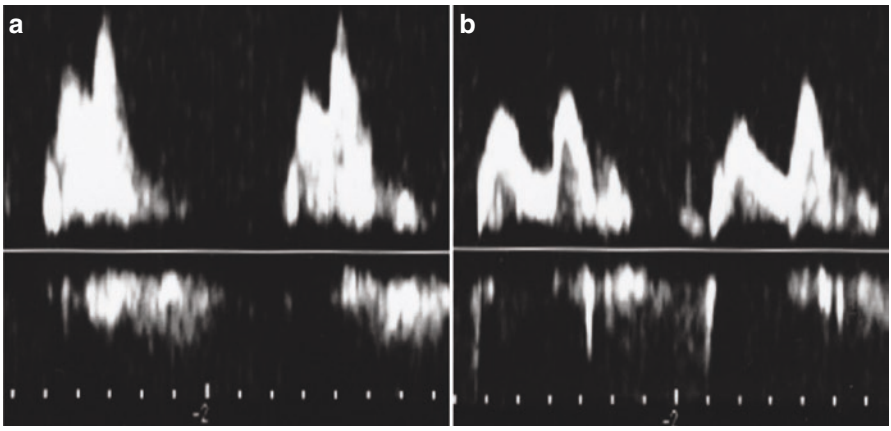


Fig. 4.7 Shortened transmitral left ventricular filling time with partial fusion of E and A waves in a patient with severe systolic heart failure, wide QRS, and long PR (panel **a**). Preserved separation of E and A waves in a patient with severe systolic heart failure, wide QRS, and normal PR interval (panel **b**)

Imaging Modalities to Identify Response to CRT in Non-LBBB Patients

It has been suggested that ventricular dyssynchrony measured during cardiac imaging could provide a mechanistically plausible and non ECG-based rationale for the application of cardiac resynchronization. Echocardiography is the most easily accessible imaging method and provides different possibly helpful variables mirroring dyssynchrony.

Two-dimensional echo (apical four-chamber view) in patients with LBBB frequently shows a typical apical left ventricular rocking movement (predominantly with counterclockwise orientation), in many patients combined with an initial septal deviation of the apex caused by early septal contraction ("septal flash"). The simple visually assessed apical rocking phenomenon has been found to predict reverse LV remodeling and a lower clinical event rate during follow-up in patients with HF and predominantly LBBB [43, 44]. The presence of apical rocking and a septal flash movement before CRT has been confirmed to predict response to CRT by a large multicenter registry [45]. However, information on the usefulness of these visual 2D echo-derived parameters in patients without LBBB is scarce.

Pulsed-wave Doppler echocardiography also adds predictive information while reliably reflecting left ventricular pre-ejection period (LVPEP) and right ventricular pre-ejection period (RVPEP) [46]. LVPEP and RVPEP are calculated as the time elapsed from QRS onset to the beginning of transaortic and transpulmonary PW Doppler flow, respectively. The interventricular mechanical delay (IVMD) is defined by the difference of LVPEP and RVPEP (Fig. 4.8).

LVPEP can be seen as a measure of global LV electromechanical performance. Baseline LVPEP prolongation of at least 140 ms and an IVMD of 40 ms or more have been shown to predict CRT response in HF patients with LBBB with high sensitivity, but limited specificity [17]. The predictive value of these parameters to predict CRT effectiveness in patients with non-LBBB HF has also been demonstrated [47]. Considering these results, Doppler echo parameters of ventricular dyssynchrony may contribute to patient-centered decision-making in the presence of HF accompanied by non-LBBB wide QRS. In addition, Doppler-derived characterization of transmitral LV inflow and atrioventricular coupling helps to anticipate possible benefit from CRT to correct the sequelae of a long PR interval.

Tissue Doppler imaging (TDI) delineates the velocity and timing of the regional myocardial wall motion in the left ventricular wall segments. Patients with LBBB usually exhibit a visually considerably dyssynchronous regional LV TDI pattern (Fig. 4.9), but numerical measures of TDI dyssynchrony were poorly reproducible and failed to identify CRT response in the Predictors of Response to CRT (PROSPECT) trial [48]. Similarly, this is true for non-LBBB.

Hence TDI-derived parameters may illustrate LV dyssynchrony, but cannot guide the decision whether to implant a CRT device in a patient with HF, but without LBBB. TDI is not able to discriminate regional myocardial contraction from passive wall motion of a scarred segment.

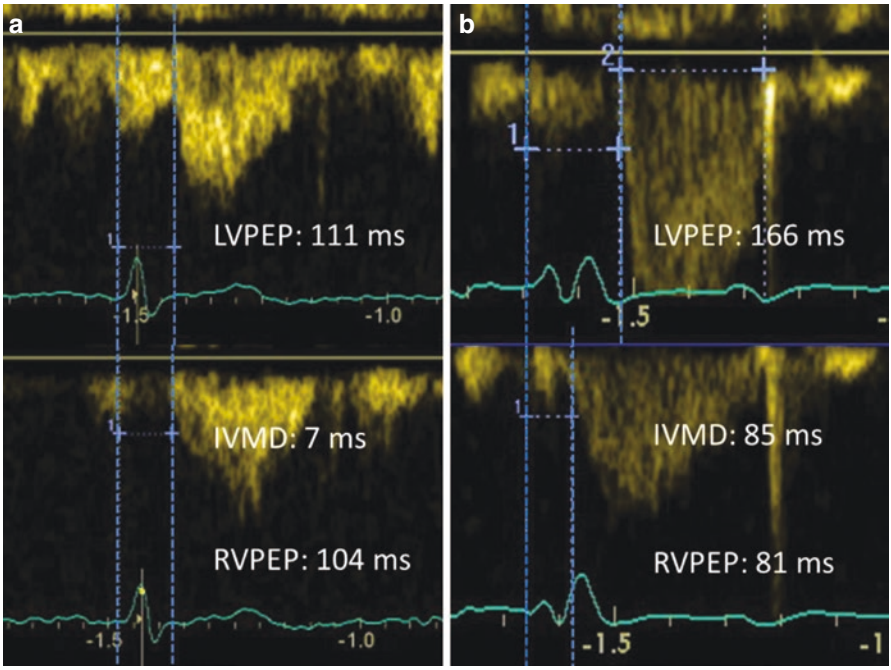


Fig. 4.8 Pulsed-wave Doppler representation of pulmonary valve and transaortic valve flow with indication of left ventricular pre-ejection period (LVPEP), right ventricular pre-ejection period (RVPEP), and interventricular mechanical delay (IVMD) from a healthy individual (panel **a**) and a patient with severe systolic heart failure and QRS prolongation (panel **b**)

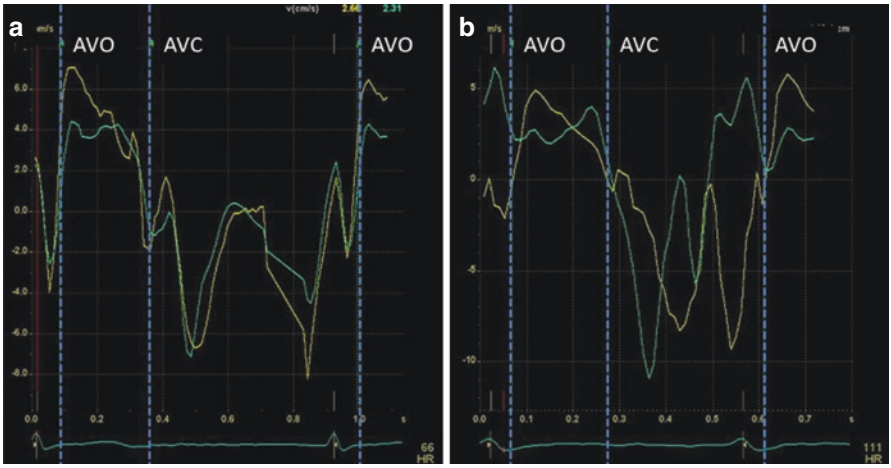


Fig. 4.9 Tissue Doppler velocity tracings with representation of basal septal and basal lateral left ventricular wall segments from a healthy individual (panel **a**) and a patient with severe systolic heart failure and QRS prolongation (panel **b**). *AVO* aortic valve opening, *AVC* aortic valve closure

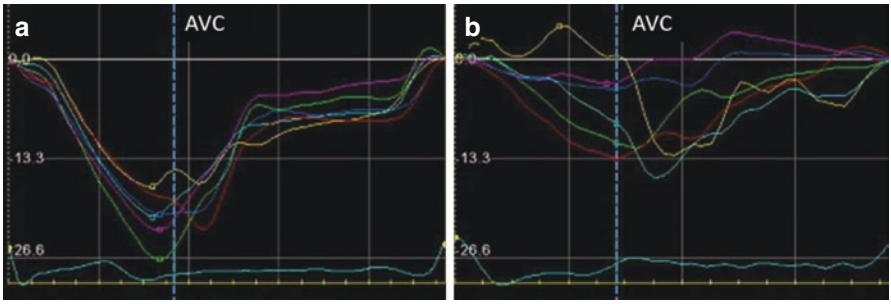


Fig. 4.10 Regional left ventricular deformation pattern assessed by two-dimensional strain imaging (speckle tracking) from a healthy individual (panel **a**) and a patient with severe systolic heart failure and QRS prolongation (panel **b**). *AVC* aortic valve closure

This methodological disadvantage is eliminated by myocardial deformation imaging modalities. Such method is two-dimensional strain echocardiography (speckle tracking). Initially, characterization of time dispersion of peak regional LV myocardial shortening (Fig. 4.10) by two-dimensional strain echocardiography (speckle tracking) showed encouraging results [49], and a derived index appeared to accurately and prospectively separate responders from nonresponders to CRT in patients with a wide QRS and heart failure. These findings were paralleled by a MADIT-CRT sub-analysis that found improving dyssynchrony and increasing global longitudinal strain to be correlated with favorable LV reverse remodeling and fewer adverse clinical events [21]. The subsequent ECHO-CRT study however did not find benefit from CRT-D versus an ICD in patients with HF, normal QRS width, and ventricular dyssynchrony derived from TDI or speckle tracking. Thus we can conclude that myocardial deformation imaging by speckle tracking can be useful to identify future CRT responders among patients with HF and a wide QRS (LBBB and non-LBBB), but probably much less so in those with normal QRS duration.

Cardiac magnetic resonance imaging (cMRI) is a promising new imaging modality that can also provide information on delayed LV ejection and abnormal apical and septal LV movement in LBBB [50] and, in addition, allows evaluating cardiac myocardial deformation [51]. However, all of these parameters can be more easily be obtained by echocardiography with sufficient reliability. The cMRI has however the most important role to localize and quantify myocardial scar, and the amount and distribution of scar may predict ventricular arrhythmias. In addition, LV pacing in scar areas should be avoided, since this could potentially contribute to ventricular arrhythmia events [52]. Therefore, cMRI can inform decision-making before CRT implantation, and it could also potentially guide LV lead placement in both patients with LBBB and non-LBBB. Image-guided CRT implantation has been shown to improve CRT outcomes in multiple trials and in meta-analysis [53]. However, it is not currently applied in standard clinical practice probably due to its time-consuming nature and its need to form multidisciplinary teams. However, further studies are warranted in this field.

Conclusions

In summary, cardiac resynchronization therapy in patients with non-LBBB has been shown to improve outcomes to a lesser degree than in patients with LBBB before CRT implantation. Additional ECG parameters, such as PR interval, QRS area, as well as imaging techniques to identify dyssynchrony, and the latest activated left ventricular segment, could be potentially relevant in this cohort to increase response rate. Alternative pacing techniques, such as His bundle pacing, are emerging to provide physiologic pacing in this high-risk population. Further studies are nevertheless warranted to better understand the pathomechanism of cardiomyopathies in patients with HF and non-LBBB, to evaluate the role of current and new treatment modalities with or without CRT, and to further improve outcomes.

Dedication The authors would like to dedicate this work to Dr. Arthur J. Moss, a true giant in cardiology, who graciously and open-mindedly allowed the authors of this book chapter to test a new hypothesis in MADIT-CRT, namely, the bidirectional relationship between PR interval and CRT-D outcomes in patients with non-LBBB. Without high-integrity leaders like Dr. Arthur J. Moss advocating for scientific curiosity freely available to anyone in the world irrespective of country, gender, sex, or age, our world would be less of many discoveries that truly advanced medicine. The legacy of Dr. Arthur J. Moss is these very discoveries and his "many sons and daughters," who will pay it forward for generations to come. We are grateful for having known him and had this opportunity.

References

1. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. Nat Rev Cardiol. 2011;8(1):30–41.
2. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2013;61(3):e6–75.
3. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J. 2013;34(29):2281–329.
4. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005;352(15):1539–49.
5. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004;350(21):2140–50.
6. Breithardt OA, Sinha AM, Schwammenthal E, Bidaoui N, Markus KU, Franke A, et al. Acute effects of cardiac resynchronization therapy on functional mitral regurgitation in advanced systolic heart failure. J Am Coll Cardiol. 2003;41(5):765–70.

7. Auricchio A, Stellbrink C, Sack S, Block M, Vogt J, Bakker P, 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(12):2026–33.
8. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med. 2001;344(12):873–80.
9. Solomon SD, Foster E, Bourgoun M, Shah A, Viloria E, Brown MW, et al. Effect of cardiac resynchronization therapy on reverse remodeling and relation to outcome: multicenter automatic defibrillator implantation trial: cardiac resynchronization therapy. Circulation. 2010;122(10):985–92.
10. Young JB, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD trial. JAMA J Am Med Assoc. 2003;289(20):2685–94.
11. Rivero-Ayerza M, Theuns DA, Garcia-Garcia HM, Boersma E, Simoons M, Jordaens LJ. Effects of cardiac resynchronization therapy on overall mortality and mode of death: a meta-analysis of randomized controlled trials. Eur Heart J. 2006;27(22):2682–8.
12. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med. 2010;363(25):2385–95.
13. Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. J Am Coll Cardiol. 2008;52(23):1834–43.
14. Goldenberg I, Kutyifa V, Moss AJ. Survival with cardiac-resynchronization therapy. N Engl J Med. 2014;371(5):477–8.
15. Linde C, Gold MR, Abraham WT, St John Sutton M, Ghio S, Cerkvenik J, et al. Long-term impact of cardiac resynchronization therapy in mild heart failure: 5-year results from the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study. Eur Heart J. 2013;34(33):2592–9.
16. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med. 2009;361(14):1329–38.
17. Fantoni C, Kawabata M, Massaro R, Regoli F, Raffa S, Arora V, et al. Right and left ventricular activation sequence in patients with heart failure and right bundle branch block: a detailed analysis using three-dimensional non-fluoroscopic electroanatomic mapping system. J Cardiovasc Electrophysiol. 2005;16(2):112–9; discussion 20–1.
18. Goldenberg I, Kutyifa V, Klein HU, Cannom DS, Brown MW, Dan A, et al. Survival with cardiac-resynchronization therapy in mild heart failure. N Engl J Med. 2014;370(18):1694–701.
19. Jastrzebski M, Kukla P, Kisiel R, Fijorek K, Moskal P, Czarnecka D. Comparison of four LBBB definitions for predicting mortality in patients receiving cardiac resynchronization therapy. Ann Noninvasive Electrocardiol. 2018;23(5):e12563.
20. Tracy CM, Epstein AE, Darbar D, Dimarco JP, Dunbar SB, Estes NA 3rd, et al. ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Heart Rhythm. 2012;9(10):1737–53.
21. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, et al. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. 2015;36(41):2793–867.
22. Zareba W, Klein H, Cygankiewicz I, Hall WJ, McNitt S, Brown M, et al. Effectiveness of cardiac resynchronization therapy by QRS morphology in the Multicenter Automatic Defibrillator

Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). Circulation. 2011;123(10):1061–72.
23. Gold MR, Thebault C, Linde C, Abraham WT, Gerritse B, Ghio S, et al. Effect of QRS duration and morphology on cardiac resynchronization therapy outcomes in mild heart failure: results from the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study. Circulation. 2012;126(7):822–9.
24. Birnie DH, Ha A, Higginson L, Sidhu K, Green M, Philippon F, et al. Impact of QRS morphology and duration on outcomes after cardiac resynchronization therapy: results from the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT). Circ Heart Fail. 2013;6(6):1190–8.
25. Peterson PN, Greiner MA, Qualls LG, Al-Khatib SM, Curtis JP, Fonarow GC, et al. QRS duration, bundle-branch block morphology, and outcomes among older patients with heart failure receiving cardiac resynchronization therapy. JAMA. 2013;310(6):617–26.
26. Cleland JG, Abraham WT, Linde C, Gold MR, Young JB, Claude Daubert J, et al. An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure. Eur Heart J. 2013;34(46):3547–56.
27. Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, et al. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. N Engl J Med. 2013;369(15):1395–405.
28. van Stipdonk AMW, Ter Horst I, Kloosterman M, Engels EB, Rienstra M, Crijns H, et al. QRS area is a strong determinant of outcome in cardiac resynchronization therapy. Circ Arrhythm Electrophysiol. 2018;11(12):e006497.
29. Salden F, Kutyifa V, Stockburger M, Prinzen FW, Vernooy K. Atrioventricular dromotropathy: evidence for a distinctive entity in heart failure with prolonged PR interval? Europace. 2018;20(7):1067–77.
30. Cheng S, Keyes MJ, Larson MG, McCabe EL, Newton-Cheh C, Levy D, et al. Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. JAMA. 2009;301(24):2571–7.
31. Crisel RK, Farzaneh-Far R, Na B, Whooley MA. First-degree atrioventricular block is associated with heart failure and death in persons with stable coronary artery disease: data from the Heart and Soul Study. Eur Heart J. 2011;32(15):1875–80.
32. Kutyifa V, Stockburger M, Daubert JP, Holmqvist F, Olshansky B, Schuger C, et al. PR interval identifies clinical response in patients with non-left bundle branch block: a Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy substudy. Circ Arrhythm Electrophysiol. 2014;7(4):645–51.
33. Stockburger M, Moss AJ, Klein HU, Zareba W, Goldenberg I, Biton Y, et al. Sustained clinical benefit of cardiac resynchronization therapy in non-LBBB patients with prolonged PR-interval: MADIT-CRT long-term follow-up. Clin Res Cardiol. 2016;105(11):944–52.
34. Olshansky B, Day JD, Sullivan RM, Yong P, Galle E, Steinberg JS. Does cardiac resynchronization therapy provide unrecognized benefit in patients with prolonged PR intervals? The impact of restoring atrioventricular synchrony: an analysis from the COMPANION trial. Heart Rhythm. 2012;9(1):34–9.
35. Friedman DJ, Bao H, Spatz ES, Curtis JP, Daubert JP, Al-Khatib SM. Association between a prolonged PR interval and outcomes of cardiac resynchronization therapy: a report from the National Cardiovascular Data Registry. Circulation. 2016;134(21):1617–28.
36. Hochleitner M, Hortnagl H, Ng CK, Gschnitzer F, Zechmann W. Usefulness of physiologic dual-chamber pacing in drug-resistant idiopathic dilated cardiomyopathy. Am J Cardiol. 1990;66(2):198–202.
37. Kutalek SP, Sharma AD, McWilliams MJ, Wilkoff BL, Leonen A, Hallstrom AP, et al. Effect of pacing for soft indications on mortality and heart failure in the dual chamber and VVI implantable defibrillator (DAVID) trial. Pacing Clin Electrophysiol (PACE). 2008;31(7):828–37.

38. Sohaib SMA, Wright I, Lim E, Moore P, Lim PB, Koawing M, et al. Atrioventricular optimized direct his bundle pacing improves acute hemodynamic function in patients with heart failure and PR interval prolongation without left bundle branch block. JACC Clin Electrophysiol. 2015;1(6):582–91.
39. Steinberg JS, Fischer A, Wang P, Schuger C, Daubert J, McNitt S, et al. The clinical implications of cumulative right ventricular pacing in the multicenter automatic defibrillator trial II. J Cardiovasc Electrophysiol. 2005;16(4):359–65.
40. Wilkoff BL, Cook JR, Epstein AE, Greene HL, Hallstrom AP, Hsia H, et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial. JAMA. 2002;288(24):3115–23.
41. Curtis AB, Worley SJ, Adamson PB, Chung ES, Niazi I, Sherfesee L, et al. Biventricular pacing for atrioventricular block and systolic dysfunction. N Engl J Med. 2013;368(17):1585–93.
42. Kindermann M, Hennen B, Jung J, Geisel J, Bohm M, Frohlig G. Biventricular versus conventional right ventricular stimulation for patients with standard pacing indication and left ventricular dysfunction: the Homburg Biventricular Pacing Evaluation (HOBIPACE). J Am Coll Cardiol. 2006;47(10):1927–37.
43. Ghani A, Delnoy PP, Ottervanger JP, Ramdat Misier AR, Smit JJ, Adiyaman A, et al. Association of apical rocking with long-term major adverse cardiac events in patients undergoing cardiac resynchronization therapy. Eur Heart J Cardiovasc Imaging. 2016;17(2):146–53.
44. Ghani A, Delnoy PP, Ottervanger JP, Misier AR, Smit JJ, Adiyaman A, et al. Apical rocking is predictive of response to cardiac resynchronization therapy. Int J Cardiovasc Imaging. 2015;31(4):717–25.
45. Beela AS, Unlu S, Duchenne J, Ciarka A, Daraban AM, Kotrc M, et al. Assessment of mechanical dyssynchrony can improve the prognostic value of guideline-based patient selection for cardiac resynchronization therapy. Eur Heart J Cardiovasc Imaging. 2019;20(1):66–74.
46. Stockburger M, Fateh-Moghadam S, Nitardy A, Celebi O, Krebs A, Habedank D, et al. Baseline Doppler parameters are useful predictors of chronic left ventricular reduction in size by cardiac resynchronization therapy. Europace. 2008;10(1):69–74.
47. Hara H, Oyenuga OA, Tanaka H, Adelstein EC, Onishi T, McNamara DM, et al. The relationship of QRS morphology and mechanical dyssynchrony to long-term outcome following cardiac resynchronization therapy. Eur Heart J. 2012;33(21):2680–91.
48. Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, et al. Results of the predictors of response to CRT (PROSPECT) trial. Circulation. 2008;117(20):2608–16.
49. Lim P, Buakhamsri A, Popovic ZB, Greenberg NL, Patel D, Thomas JD, et al. Longitudinal strain delay index by speckle tracking imaging: a new marker of response to cardiac resynchronization therapy. Circulation. 2008;118(11):1130–7.
50. Revah G, Wu V, Huntjens PR, Piekarski E, Chyou JY, Axel L. Cardiovascular magnetic resonance features of mechanical dyssynchrony in patients with left bundle branch block. Int J Cardiovasc Imaging. 2016;32(9):1427–38.
51. Zweerink A, van Everdingen WM, Nijveldt R, Salden OAE, Meine M, Maass AH, et al. Strain imaging to predict response to cardiac resynchronization therapy: a systematic comparison of strain parameters using multiple imaging techniques. ESC Heart Fail. 2018;5(6):1130–40.
52. Kutyifa V, Zareba W, McNitt S, Singh J, Hall WJ, Polonsky S, et al. Left ventricular lead location and the risk of ventricular arrhythmias in the MADIT-CRT trial. Eur Heart J. 2012;34:184–90.
53. Jin Y, Zhang Q, Mao JL, He B. Image-guided left ventricular lead placement in cardiac resynchronization therapy for patients with heart failure: a meta-analysis. BMC Cardiovasc Disord. 2015;15:36.