Chapter 14
Cardiac Resynchronization Therapy

Michael Glikson and Stefan Bogdan

Introduction

Since for the first case by Cazeau in 1994 showing the beneficial effects of four-chamber pacing in a 54-year old dilated cardiomyopathy patient [1], cardiac resynchronization therapy (CRT) has come a long way. Targeting cardiac dyssynchrony correction, it has become a well-established treatment for symptomatic heart failure patients with severe left ventricular systolic dysfunction and wide QRS (>120 ms). Evidence from large randomized trials have shown the clinical (symptoms improvement; mortality reduction) as well as structural (left ventricular reverse remodeling with ejection fraction increase and mitral regurgitation reduction) benefits of CRT and represent the basis for current guidelines [2]. Unfortunately, not all patients with LV dysfunction and wide QRS respond to CRT. Understanding nonresponse and predicting response has to do with understanding the interrelationship between electrical and mechanical dyssynchrony. Current efforts focus on better patient selection and improving CRT delivery using clinical, electrocardiographic and imaging techniques.

M. Glikson (✉)
Davidai Arrhythmia Center, Leviev Cardiovascular Center,
Sheba Medical Center, Tel Hashomer, Israel
e-mail: Michael.glikson@sheba.health.gov.il

S. Bogdan
Clinical Electrophysiology and Cardiac Pacing Laboratory – Cardiology Department,
Emergency Clinical Hospital of Bucharest, "Carol Davila" University of Medicine and
Pharmacy, Bucharest, Romania

M. Dorobanţu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_14

Pathophysiology of Cardiac Dyssynchrony. Dyssynchrony Assessment

Cardiac mechanical dyssynchrony refers to a difference in the contraction/relaxation timing (lack of synchrony) between different areas of the heart, that usually occurs in the setting of electrical conduction disease (electrical dyssynchrony). Large differences in contraction timing can result in reduced cardiac efficiency and are correlated to heart failure [3]. Cardiac imaging and advanced echocardiography in particular play an important role in mechanical dyssynchrony assessment. Other imaging techniques, including cardiac magnetic resonance and radionuclide imaging, are under development for cardiac dyssynchrony evaluation.

There are three main types of dyssynchrony that can be corrected by CRT: atrioventricular, interventricular and intraventricular (Table 14.1).

Atrioventricular dyssynchrony occurs because of a loss of timing between atrial and ventricular contractions, in the presence of prolonged PR interval, QRS widening or both [4]. The hemodynamic consequence is an impairment of the left ventricular (LV) filling secondary to a shortening of the diastole. Using pulsed-wave Doppler echocardiography, atrioventricular dyssynchrony can be evaluated by measuring the LV filling time from transmitral flow recordings. In the presence of 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 [4]. 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 into one wave) [5, 6].

Inter-ventricular dyssynchrony occurs because of a delay between right ventricular and left ventricular contractions, in the setting of 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 [4]. 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 [7].

Table 14.1 Cardiac dyssynchrony: types, setting, consequence

Dyssynchrony	Electric disease	Consequence
Atrioventricular	Prolonged PR and/or wide QRS	Diastolic impairment
Inter-ventricular	Wide QRS	Systolic impairment
Intra-ventricular LV	Wide QRS	Systolic and diastolic impairment Mitral regurgitation

Wide QRS QRS duration >120 ms, *LV* left ventricle

Intra-ventricular dyssynchrony of the left ventricle (LV dyssynchrony) occurs because of delayed contraction of certain LV segments (usually the postero-lateral wall that is last to contract while the inter-ventricular septum contracts first). This phenomenon is associated 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 and reduced stroke volume. 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. Dis-coordinated papillary muscle function can also cause or further aggravate the mitral regurgitation. These dyssynchrony related changes promote adverse LV remodeling [8].

Imaging in Cardiac Resynchronization Therapy

Imaging in CRT is crucial and serves several roles – to select patients with predicted response, to help define the location for the LV lead at the best area of LV in order to maximize response, and to follow the response. Lead location is the most complex element, which combines identification of the latest contracting segment as well as localization of scars that should be avoided as pacing in a scar area is associated with poor response [9].

It is mainly LV dyssynchrony that has been shown in several milestone studies to be an independent predictor of response to CRT in HF patients following CRT. Many years ago Pitzalis et al. introduced a reliable, easy-to-use and reproducible M-mode echocardiography parameter for LV dyssynchrony measurement [10]. Using parasternal short-axis LV view, the operator measures the time difference between the maximal systolic inward movement of the septum and posterior wall resulting in the septal-to-posterior-wall-motion-delay (SPWMD). A SPWMD $\geq$130 ms is correlated with significant LV dyssynchrony [10]. This initial approach was limited due to the non-uniform pattern of contraction in different segments of the LV, and the limited imaging by M-mode. Several other echocardiographic parameters have since been used for LV dyssynchrony evaluation besides M-mode, including tissue Doppler imaging, speckle tracking that is commonly used as it is considered superior to conventional echo Doppler techniques [11] and more recently 3D echocardiography (Table 14.2). It is conceivable that a technique that includes scar imaging in addition to dyssynchrony in the same test has an advantage in site selection of the LV lead.

Special attention has been given recently to the assessment of rotational dyssynchrony. Left ventricular fibers have a helical configuration: right-hand orientation from the base toward the apex in the endocardial layers and left-hand orientation in the epicardial layers [20]. This spiral architecture of the cardiac fibers causes the LV to make a wringing motion as a result of the opposite rotation of the LV apex and base (counterclockwise and clockwise, respectively, when viewed from the LV apex) [21]. Twist, that is the difference in rotation between apex and base, contributes

Table 14.2 Echocardiographic measurement of intra-ventricular LV dyssynchrony

Parameter	Echo technique	Cut-off
Septal to posterior wall motion delay [10]	M-mode	≥130 ms
Septal flash	M-mode	Non quantifiable[a]
Apical rocking	2D apical 4 chambers	Non quantifiable[b]
Basal septal to lateral Ts delay [12]	Tissue Dopple imaging	≥60 ms
Max delay in Ts in 4 basal LV segments [13]	Tissue Doppler imaging	>65 ms
SD of Ts of 6 basal LV segments [14]	Tissue Doppler imaging	≥34.4 ms
Max delay in Ts in 12 basal and mid LV segments [15]	Tissue Doppler imaging	≥100 ms
SD of Ts in 12 basal and mid LV segments (Dyssynchrony Index; Yu index) [16]	Tissue Doppler imaging	≥32.6 ms
SD of time-to peak longitudinal strain in 12 basal and mid LV segments [17]	Tissue Doppler imaging	>60 ms
Antero-septal to posterior time to peak strain difference (radial strain) [18]	2D speckle tracking	≥130 ms
SD of time to minimum systolic volume of 16 LV segments (systolic dyssynchrony index) [19]	3D echocardiography	>5.6 %

Ts time-to-peak systolic velocity, *SD* standard deviation, *LV* left ventricular, *2D* two dimensional, *3D* three dimensional

[a]Septal flash = early septal systolic thickening and thinning resulting in a short inward motion of the septum

[b]Apical rocking = the initial septal systolic thickening that causes the apex to move septally is followed by delayed activation of lateral wall that pulls the apex laterally while stretching the septum, resulting in a typical motion pattern of the apex defined as "apical rocking"

to LV systolic function [22] and in patients with heart failure it has been shown to be reduced [23]. Two-dimensional speckle tracking can assess the LV rotational motion and has demonstrated that twist can be affected by right ventricular pacing (the experimental model of LBBB) [24, 25]. While LV twist is the net difference at isochronal time points between apex and base in the rotation angle along LV longitudinal axis, LV torsion represents the LV twist indexed to the distance between the LV apex and the LV base (LV length) [20, 21]. LV torsion can be assessed in a standardized way by using three-dimensional speckle tracking echocardiography [26]. The use of two-dimensional speckle tracking echocardiography has proven its clinical utility in the field of CRT [27].

With the advent of cardiac magnetic resonance (CMR), several CMR derived dyssynchrony parameters [28] – such as regional vector variance (RVV), cross-correlation delay, uniformity of strain, time to maximum strain and standard deviation of time to maximum strain, have been analyzed in the setting of HF with low left ventricular ejection fraction (LVEF) and wide QRS. Some, such as RVV, may provide an additive value for the prediction of response to CRT [29]. Cardiac magnetic resonance has the potential to become an alternative to echocardiography for assessing cardiac dyssynchrony. Image acquisition is less operator dependent and it has the advantages of high spatial resolution, highly reproducible wall motion tracking and the capability to assess LV scar, volumes, systolic function, velocity,

strain, and torsion [30]. Current limitation is the fact that MRI derived dyssynchrony parameters have been investigated only in small sample size population and cutoff values for derived indices have yet to be established. Also its use in patients with existing devices is limited by safety issues as well as by the quality of imaging that may be distorted by the device.

Phase analysis of gated single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) has been used for evaluating LV dyssynchrony using radionuclide imaging [31]. Phase analysis is based on the partial volume effect, which indicates that LV regional maximal counts in SPECT MPI images are proportional to the regional wall thickness. Phase analysis approximates the variation of regional maximal counts over the cardiac cycle with the first Fourier harmonic function to measure the onset of mechanical contraction [31]. Quantitative gated SPECT-derived phased analysis on gated myocardial perfusion SPECT was able to detect left ventricular dyssynchrony (strong correlation with tissue Doppler imaging dyssynchrony parameters) and was able to accurately predict response to CRT [32]. Phase analysis of SPECT MPI has several advantages over other imaging techniques such as automated calculation, better reproducibility, and the ability to simultaneously assess myocardial scar location and severity for CRT optimization. The limitations include reduced availability and the small number of centers with clinical experience on relatively small sample size populations [30].

Clinical Evidence in Cardiac Resynchronization Therapy and Current Guidelines.

Randomized multi-center trials have provided solid evidence concerning the benefits of CRT in heart failure treatment.

The initial trials including limited numbers of severe HF failure patients (NYHA III-IV; QRS duration ≥150 ms; LVEF ≤35 %) only showed symptomatic benefit [33, 34]. In 2004, COMPANION was the first randomized trial to show a survival benefit following CRT in HF patients [35]. It included 1520 HF patients, NYHA class III-IV with QRS ≥ 120 ms and LVEF ≤35 %, that were randomized to either CRT or optimal medical treatment (OMT). Patients with pacemaker CRT (CRT-P) had the risk of combined end point of death or hospitalization for HF reduced by 34 % ($p < 0.002$), while in those with defibrillator CRT (CRT-D) the risk was reduced by 40 % ($p < 0.001$). These results were confirmed a year later by the CARE-HF trial [7].

The COMPANION and CARE-HF trials were followed by three cornerstone trials addressing less severe HF patients (NYHA class I-II), with low LVEF and wide QRS: the REVERSE [36], RAFT [37] and MADIT-CRT trials [38].

The REVERSE trial demonstrated in 610 patients with NYHA class I or II HF, wide QRS ≥ 120 ms and low LVEF ≤40 %, that CRT in combination with OMT (±defibrillator) reduces the risk for HF hospitalization and improves ventricular structure (LV end systolic volume reduction), with no effect however on mortality [36].

The RAFT trial randomized 1798 patients suffering from NYHA class II-III HF with wide or paced QRS and LVEF ≤30 %, to CRT with defibrillator (CRT-D) versus implantable cardioverter defibrillator alone (ICD). The trial showed a significant mortality reduction of 25 % ($p = 0.003$) and a reduction of 32 % for HF hospitalization ($p < 0.001$) in the CRT group, at the cost of more peri-procedural adverse events [37].

The MADIT-CRT trial included 1820 patients with NYHA class I-II HF, wide QRS ≥ 130 ms and reduced LVEF ≤ 30 %, that were randomized into CRT-D versus ICD alone. The initial results, published in 2009, 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 however on mortality [38].

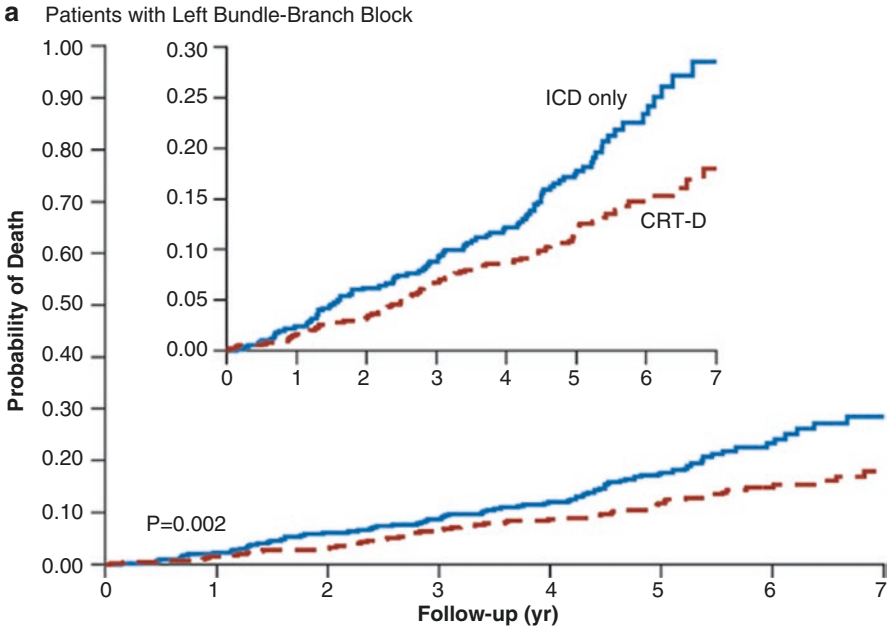
Recently, in 2014, the long-term follow-up of the MADIT-CRT trial has been published. At 7 years of follow-up, among the 1818 patients enrolled in the post-trial registries, CRT-D was associated with significant mortality reduction in LBBB patients (hazard ratio (HR): 0.59; 95 % confidence interval (CI) 0.43–0.80; $p < 0.001$). In contrast, CRT-D was not associated with any clinical benefit, and proved potentially harmful in patients without LBBB (HR: 1.57; 95% CI 1.03–2.39; $p = 0.04$) (Fig. 14.1) [39].

While all the main randomized trials addressed the issue of mechanical dyssynchrony correction in the presence of electrical dyssynchrony (defined mainly as wide QRS of at least 120 ms), the EchoCRT trial looked into the potential benefit of CRT in HF patients with narrow QRS. The trial enrolled 809 patients suffering for NYHA class III-IV HF, with narrow QRS <130 ms and low LVEF ≤ 35 %, in whom there was echocardiographic evidence of LV dyssynchrony (defined using color-coded tissue Doppler imaging as an opposing-wall delay in the peak systolic velocity of 80 ms or more in apical four-chamber or apical long-axis views, or by means of speckle-tracking radial strain as a delay in the anteroseptal-to-posterior wall of 130 ms or more in the mid-left ventricular short-axis view). All patients had a CRT device implanted and were randomized to have CRT capability turned on or off. After a mean follow-up of 19 months, the trial was prematurely stopped because of increased mortality in the CRT ON group (11.1 % vs. 6.4 %; HR: 1.81; 95 % CI 1.11–2.93; $p = 0.02$) [40].

The EchoCRT trial demonstrated that in HF patients with narrow QRS <130 ms, CRT does not reduce the rate of death or HF hospitalization and may increase mortality.

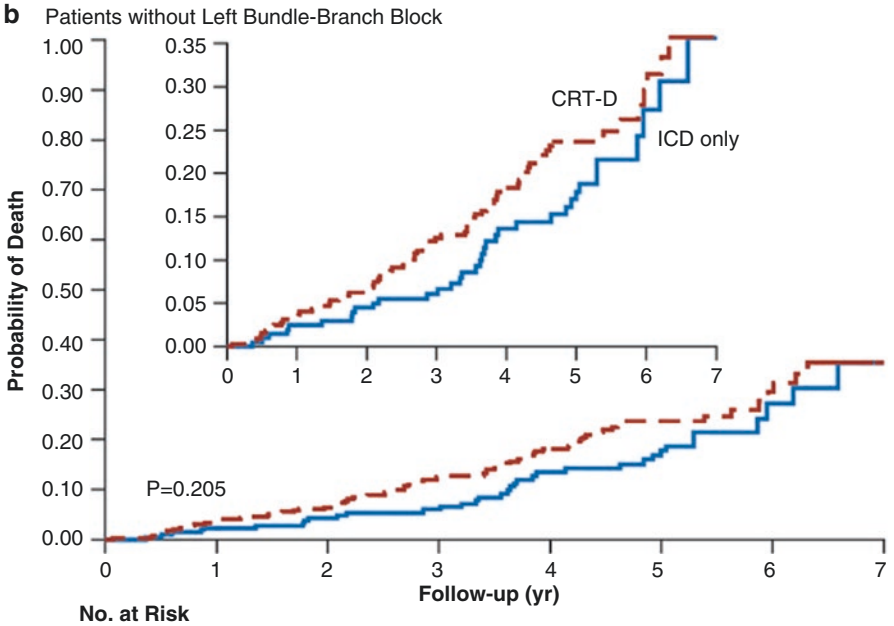
All the major evidence regarding CRT have been integrated into recently updated guidelines, where CRT is recommended in HF patients (NYHA class II-IV) with wide QRS ≥ 130 ms and reduced LVEF ≤ 35 % (Table 14.3) [41]. The American Guidelines dating 2012 are similar to the European ones from 2013, still retaining a

Fig. 14.1 Kaplan–Meier Estimates of the Cumulative Probability of Death from Any Cause among Patients with and Those without Left Bundle-Branch Block. *CRT-D* denotes cardiac-resynchronization therapy with defibrillator, *ICD* implantable cardioverter–defibrillator. The insets show the same data on an enlarged y axis (Goldenberg et al. from the long term follow-up of the MADIT-CRT trial [39])



No. at Risk

ICD only	520	488	463	40	326	254	94	41
CRT-D	761	734	714	636	527	425	157	70



No. at Risk

ICD only	209	197	189	156	115	95	24	10
CRT-D	328	312	292	240	182	136	39	13

CRT indication for QRS between 120 and 130 ms, with only a class IIa recommendation for LBBB 120–149 ms (as opposed to class I in the European guidelines) [2, 42].

Right ventricular apical pacing has been shown to have deleterious effects on LV systolic function, as it is associated with a delayed electrical LV activation, with consequences similar (but not identical) to that seen with LBBB (LV dyssynchrony with reduced LVEF and mitral regurgitation). Clinical consequences include increased risk for atrial fibrillation, HF hospitalization and death [43–45], especially in the setting of pre-existing HF and LV systolic dysfunction (below 40 %) [45].

The BLOCK-HF trial randomized 691 patients with NYHA class I – III HF, LVEF ≤ 50 % and an indication for bradycardia pacing to standard right ventricular pacing or biventricular pacing. The study has shown that patients receiving biventricular pacing had a lower incidence of primary outcome (urgent care visit for HF; death from any cause; progression of HF, defined as significant increase of left ventricular end-systolic volume index). The BLOCK-HF trial supports the use of CRT over standard right ventricular pacing in HF patients with LV systolic dysfunction and atrioventricular block requiring ventricular pacing [46].

Therefore, for patients with an indication for bradycardia pacing, in whom the percentage of ventricular pacing is expected to be high, in the presence of reduced LVEF (although debatable – usually below 40 %), de novo CRT implantation should be considered. In patients with ventricular pacing who develop HF and left ventricular systolic dysfunction (LVEF < 35 %), upgrade to CRT is indicated, as the benefit has been demonstrated by us and other studies [41, 47].

Table 14.3 The 2016 updated indications for cardiac resynchronization therapy in HF patients [41]

Patients characteristics	Rhythm	QRS morph.	QRS dur. (ms)	Class	Evid.
Ambulatory NYHA II-IV LVEF ≤ 35 %	Sinus	LBBB	>150 ms	I	A
			130–150 ms	I	B
		Non-LBBB	>150 ms	IIa	B
			130–150 ms	IIb	B
HF patients	Sinus	Regardless	<130 ms	III	A
HF patients (regardless NYHA) High degree AV block Reduced LVEF[a]	Sinus/AF	Regardless	Regardless	I	A
Worsening HF Previous PM/ICD High proportion of RV pacing Reduced LVEF[a]	Sinus/AF	RV pacing	(Wide)	IIb	B
NYHA III-IV LVEF≤35 %	AF	Regardless	≥130	IIa	B

AF atrial fibrillation, *HF* heart failure, *ICD* implantable cardioverter defibrillator, *LVEF* left ventricular ejection fraction, *LBBB* left bundle branch block, *NYHA* New York Heart Association heart failure class, *PM* pacemaker

[a]The 2016 guidelines do not define a clear cut-off for reduced LVEF in this scenario (usually considered <40 %)

Most patients included in large CRT randomized trials were in sinus rhythm. In one prospective study for HF patients with permanent AF, reduced LVEF ≤ 35 % and wide QRS > 120 ms, the per-protocol analysis including patients with biventricular pacing percentage >85 % showed a slight but significant symptomatic improvement at 6 months and 1 year follow-up [48]. A meta-analysis by Wilton et al. that included 7495 CRT recipients, 25 % with atrial fibrillation, from 23 observational studies, with a mean follow-up of 33 months, demonstrated an attenuated improvement of symptoms and LV end systolic volume, in the presence of AF, but not for the LVEF [49]. Current guidelines recommend CRT for AF patients with ambulatory NYHA class III-IV, wide QRS ≥ 130 ms and reduced LVEF ≤ 35 %, provided a high percentage a biventricular pacing (ideally 100 %) can be achieved – a target for which atrioventricular junction ablation should be taken into consideration [41].

Response to CRT: Patient Selection and Improving CRT Delivery

Response to CRT can be evaluated from a clinical and structural perspective (Table 14.4), using individual or composite parameters (such as "functional response" [50]).

Depending upon the definition of response, the rate of non-response to CRT varies between 20 and 40 % [51]. Patient's characteristics (underlying heart disease, comorbidities and arrhythmias; type and severity of conduction disorder; presence and degree of dyssynchrony; presence and extent of scar tissue; functional myocardial reserve) as well as CRT related aspects (electrical and anatomical positioning of LV lead; programming mode and percentage of effective bi-ventricular pacing) have been shown to influence the response to CRT [9, 51–54].

Diagnosing dyssynchrony is crucial for patient selection in view of successful cardiac resynchronization therapy. Despite remarkable cardiac imaging advancements in the evaluation and understanding of mechanical dyssynchrony, electrical dyssynchrony (i.e.: wide QRS) remains the guidelines criterion for CRT recommendation.

Table 14.4 Response to cardiac resynchronization therapy evaluation

Clinical		Structural	
Parameter	***Responder***	***Parameter***	***Responder***
NYHA	Reduction ≥1 class	LVEF	Absolute increase ≥5–6 %
6MWT	Increase ≥10–20 %	LVESV	Decrease ≥10–15 %
VO_2 max	Increase ≥10–15 %	Mitral regurgitation reduction	
Hospitalization rate	Decrease >25–30 %		
QOL	Decrease ≥8–10 points		

6MWT 6-minute walk test, *LVEF* left ventricular ejection fraction, *LVESV* left ventricular end-systolic volume, *NYHA* New York Heart Association heart failure class, *QOL* quality of life questionnaire, *VO_2 max* maximal oxygen consumption

The role of LV dyssynchrony assessment to predict response in CRT patients remains controversial to date. The PROSPECT trial investigated the predictive value of several echocardiographic dyssynchrony parameters (Doppler, M-mode, tissue Doppler imaging and delayed longitudinal contraction) on LV reverse remodeling and a composite clinical score. The conclusion was that given the modest sensitivity and specificity in this multicenter setting despite training and central analysis, no single echocardiographic measure of dyssynchrony may be recommended to improve patient selection for CRT beyond current guidelines [53]. More recently, the EchoCRT trial has shown that mechanical dyssynchrony detected by echocardiography is not a good target for CRT correction, in the absence of electrical dyssynchrony (i.e.: QRS < 130 ms) [40]. Still, other trials have shown that the amount of LV dyssynchrony at baseline and the remainder of LV dyssynchrony following CRT are correlated with clinical outcomes and response to CRT [10, 55].

Interestingly, the recently published PREDICT-CRT trial by Stankovic et al. has shown that the presence of apical rocking and septal flash – two subjectively measured echocardiographic dyssynchrony parameters (Table 14.2), is associated with more favorable long-term survival after CRT. Both apical rocking and septal flash were also indicators of an effective therapy [56]. Current guidelines recommend the use of echocardiography only for CRT optimization in case of non-response, but the results of PREDICT-CRT may impact the use of echo for patient selection in the future.

The type of electric disease is important for CRT response. LBBB morphology and a QRS duration >150 ms are associated with the best response following CRT. The question remains in patients with wide QRS of right bundle branch (RBBB) or intraventricular conduction delay (IVCD) morphology. The long-term MADIT-CRT follow-up has shown the absence of mortality benefit of CRT-D versus ICD alone in mild-to-moderate HF with reduced LVEF ≤ 30 %, who presented with RBBB or IVCD at baseline [39] (Fig. 14.1, Section B). Specific subgroup analysis from MADIT-CRT demonstrated that the use of CRT-D in non-LBBB patients with prolonged PR ≥230 ms was associated with a 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 [57]. In the absence of prolonged PR, pure RBBB morphology should probably disqualify a patient for CRT. The Canadian Guidelines already consider RBBB with 120–150 ms duration not to be an indication for CRT [58], while European guidelines are more permissive, giving it a IIb recommendation [2].

The underlying heart condition and co-morbidities influence the overall prognostic and response to CRT. Although LV reverse remodeling after CRT is not affected by the duration of HF, clinical outcomes are better in patients implanted earlier in their disease course [59]. Atrial fibrillation, by comparison to sinus rhythm, is associated with increased risk of non-response to CRT (34.5 % vs 26.7 %; pooled relative risk 1.32; 95 % CI 1.12–1.55; P = 0.001), as demonstrated by Wilton's

meta-analysis [49]. In ischemic heart disease the benefit of CRT exists but is attenuated by comparison to non-ischemic heart disease, as shown in the MIRACLE trial [60]. Focal scar burden detected by late-Gadolinium enhancement on cardiac magnetic resonance was shown to correlate with poorer CRT response [61] as did lead localization in scar areas. Co-morbidities such as renal failure may also affect CRT. Interestingly, we have recently shown that functional response to CRT at 1 year did not differ significantly between patients with or without chronic kidney disease and was shown to be an independent predictor of improved long-term survival in patients with renal dysfunction (eGFR <60 ml/min/1.73m^2) [50]. Although data regarding CRT response in severe renal failure patients is scarce, we have recently shown that dialysis does not significantly modify the adverse outcomes associated with severe renal dysfunction (eGFR < 30 ml/min/1.73 m^2) following ICD/CRT-D implantation [62].

In order to ensure CRT response, *optimal LV lead placement is essential*. Ideally, it should be placed in the utmost late contracting segment of the left ventricle [63]. The area of delayed contraction can be previously detected by using echocardiography (tissue Doppler imaging and two-dimensional speckle tracking being considered the most sensitive) [63, 64]. Cardiac magnetic resonance and SPECT MPI may also detect it, with the advantage of offering supplemental information concerning its viability.

Reaching the target area for the LV lead is largely dependent upon the venous anatomy. Non-invasive pre-procedural visualization of the cardiac venous system can be performed using 64-slice computed tomography, which may offer important information concerning the existence of a potential target vein [65].

Hybrid methods for defining venous and myocardial anatomy are under development. Recently, a tool kit has been developed to reconstruct the three-dimensional LV venous anatomy from dual-view fluoroscopic venograms and to fuse it with LV epicardial surface on SPECT myocardial perfusion images. It is technically accurate for guiding LV lead placement by the 17-segment model and is feasible for clinical use in the catheterization laboratory [66].

Sometimes the target vein is difficult to access due to tortuosity or stenosis. For overcoming anatomical obstacles, the operator has now several tools and techniques, including telescopic delivering systems [67], performing venoplasty and the use of Lasso snaring techniques [68]. Once the target vein has been reached, electrical problems can arise such as local high pacing thresholds or phrenic capture. Currently, the introduction of quadripolar LV leads has significantly reduced these issues (Fig. 14.2) [69, 70]. Furthermore, the possibility to pace from multiple sites from the quadripolar LV lead has improved response to CRT [71]. When the target vein is unreachable or the patient has no target vein, the LV lead can still be implanted either using a transeptal approach [72] or surgically [73]. Finally, the LV lead should not be placed in an apical position but left in a basal or mid-ventricular segment [74].

Following implantation, in order to deliver optimal cardiac resynchronization therapy, the device has to be programmed in order to reach an ideal of 100 % biventricular pacing [75]. Further efforts should be performed in order to maxi-

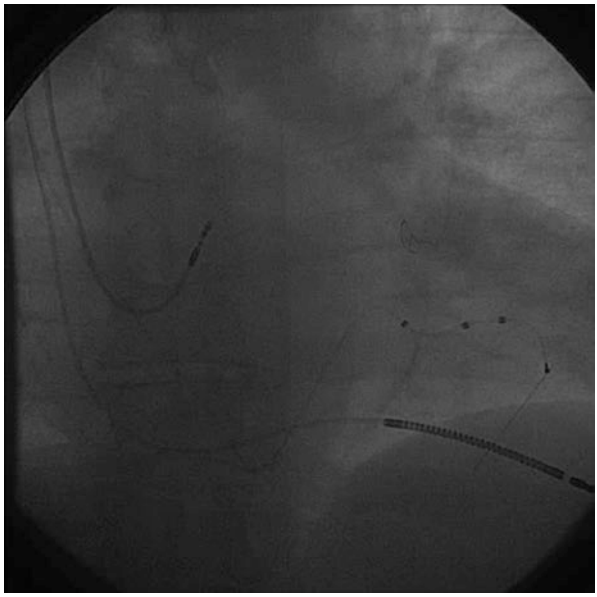


Fig. 14.2 A CRT-D system using a quadripolar LV lead

mize the percentage of biventricular pacing (very strict AF rate control – including atrio-ventricular node ablation if needed; ventricular premature beats elimination [76]).

Thus, preventing non-response should include:

- Prior dyssynchrony documentation and myocardial scar burden assessment
- Optimal LV lead positioning (preferably quadripolar lead)
- Obtaining consistent biventricular pacing (as close to 100 % of the time as possible)

In case of non-response, a protocol-driven approach for CRT optimization involving HF physician, electrophysiologist, and focused echocardiography has been shown to improve response rates [77].

Conclusion

Cardiac resynchronization therapy has become part of the standard of care for heart failure patients with reduced left ventricular ejection fraction and wide QRS. Despite its role in evaluating and understanding cardiac dyssynchrony, echocardiography was unable to top the classic ECG criteria (QRS morphology and duration) for patient selection. Future imaging techniques, such as cardiac magnetic resonance or SPECT myocardial perfusion imaging may provide better dyssynchrony assessment. Improved technology and better knowledge concerning therapy optimization will most likely improve CRT response in the near future.

Future Directions

- Improved dyssynchrony and myocardial scar assessment (3D echo; CMR; SPECT MPI)
- Better CRT delivery (quadripolar LV lead; multi-site LV pacing)
- Alternative biventricular pacing for non-responders (LV endocardial pacing)

References

1. Cazeau S, Ritter P, Bakdach S, Lazarus A, Limousin M, Henao L, Mundler O, Daubert JC, Mugica J. Four chamber pacing in dilated cardiomyopathy. Pacing Clin Electrophysiol. 1994;17(11 Pt 2):1974–9.
2. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE, ESC Committee for Practice Guidelines (CPG), Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Document R, Kirchhof P, Blomstrom-Lundqvist C, Badano LP, Aliyev F, Bänsch D, Baumgartner H, Bsata W, Buser P, Charron P, Daubert JC, Dobreanu D, Faerestrand S, Hasdai D, Hoes AW, Le Heuzey JY, Mavrakis H, McDonagh T, Merino JL, Nawar MM, Nielsen JC, Pieske B, Poposka L, Ruschitzka F, Tendera M, Van Gelder IC, Wilson CM. 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.
3. Nagueh SF. Mechanical dyssynchrony in congestive heart failure: diagnostic and therapeutic implications. J Am Coll Cardiol. 2008;51(1):18–22.
4. Cazeau S, Bordachar P, Jauvert G, Lazarus A, Alonso C, Vandrell MC, Mugica J, Ritter P. Echocardiographic modeling of cardiac dyssynchrony before and during multisite stimulation: a prospective study. Pacing Clin Electrophysiol. 2003;26(1 Pt 2):137–43.
5. Ritter P, Silvestre J. AV delay optimisation by peak endocardial acceleration in cardiac resynchronisation therapy: comparison with standard echocardiographic procedure (abstract). Europace. 2004;6(Suppl 1):209.
6. León AR, Abraham WT, Brozena S, Daubert JP, Fisher WG, Gurley JC, Liang CS, Wong G; InSync III Clinical Study Investigators. Cardiac resynchronization with sequential biventricular pacing for the treatment of moderate-to-severe heart failure. J Am Coll Cardiol. 2005;46(12):2298–304.
7. Cleland JF, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L; Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005; 352(15):1539–49.
8. Nof E, Glikson M, Bar-Lev D, Gurevitz O, Luria D, Eldar M, Schwammenthal E. Mechanism of diastolic mitral regurgitation in candidates for cardiac resynchronization therapy. Am J Cardiol. 2006;97(11):1611–4.
9. Delgado V, van Bommel RJ, Bertini M, Borleffs CJW, Marsan NA, Arnold CT, Nucifora G, van de Veire NRL, Ypenburg C, Boersma E, Holman ER, Schalij MJ, Bax JJ. Relative merits of left ventricular dyssynchrony, left ventricular lead position, and myocardial scar to predict

long-term survival of ischemic heart failure patients undergoing cardiac resynchronization therapy. Circulation. 2011;123(1):70–8.
10. Pitzalis MV, Iacoviello M, Romito R, Massari F, Rizzon B, Luzzi G, Guida P, Andriani A, Mastropasqua F, Rizzon P. Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony. J Am Coll Cardiol. 2002;40(9):1615–22.
11. Khan SG, Klettas D, Kapetanakis S, Monaghan MJ. Clinical utility of speckle-tracking echocardiography in cardiac resynchronisation therapy. Echo Res Pract. 2016;3(1):R1–R11.
12. Bax JJ, Marwick TH, Molhoek SG, Bleeker GB, van Erven L, Boersma E, Steendijk P, van der Wall EE, Schalij MJ. Left ventricular dyssynchrony predicts benefit of cardiac resynchronization therapy in patients with end-stage heart failure before pacemaker implantation. Am J Cardiol. 2003;92(10):1238–40.
13. Bax JJ, Bleeker GB, Marwick TH, Molhoek SG, Boersma E, Steendijk P, van der Wall EE, Schalij MJ. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. J Am Coll Cardiol. 2004;44(9):1834–40.
14. Notabartolo D, Merlino JD, Smith AL, DeLurgio DB, Vera FV, Easley KA, Martin RP, León AR. Usefulness of the peak velocity difference by tissue Doppler imaging technique as an effective predictor of response to cardiac resynchronization therapy. Am J Cardiol. 2004;94(6):817–20.
15. Van de Veire NR, Bleeker GB, Ypenburg C, De Sutter J, Ajmone Marsan N, Holman ER, van der Wall EE, Schalij MJ, Bax JJ. Usefulness of triplane tissue Doppler imaging to predict acute response to cardiac resynchronization therapy. Am J Cardiol. 2007;100(3):476–82.
16. Yu CM, Fung WH, Lin H, Zhang Q, Sanderson JE, Lau CP. Predictors of left ventricular reverse remodeling after cardiac resynchronization therapy for heart failure secondary to idiopathic dilated or ischemic cardiomyopathy. Am J Cardiol. 2003;91(6):684–8.
17. Mele D, Pasanisi G, Capasso F, De Simone A, Morales MA, Poggio D, Capucci A, Tabacchi G, Sallusti L, Ferrari R. Left intraventricular myocardial deformation dyssynchrony identifies responders to cardiac resynchronization therapy in patients with heart failure. Eur Heart J. 2006;27(9):1070–8.
18. Suffoletto MS, Dohi K, Cannesson M, Saba S, Gorcsan J. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. Circulation. 2006;113(7):960–8.
19. Marsan NA, Bleeker GB, Ypenburg C, Ghio S, van de Veire NR, Holman ER, van der Wall EE, Tavazzi L, Schalij MJ, Bax JJ. Real-time three-dimensional echocardiography permits quantification of left ventricular mechanical dyssynchrony and predicts acute response to cardiac resynchronization therapy. J Cardiovasc Electrophysiol. 2008;19(4):392–9.
20. Sengupta PP, Korinek J, Belohlavek M, Narula J, Vannan MA, Jahangir A, Khandheria BK. Left ventricular structure and function: basic science for cardiac imaging. J Am Coll Cardiol. 2006;48(10):1988–2001.
21. Torrent-Guasp F, Kocica MJ, Corno AF, Komeda M, Carreras-Costa F, Flotats A, Cosin-Aguillar J, Wen H. Towards new understanding of the heart structure and function. Eur J Cardiothorac Surg Off J Eur Assoc Cardiothorac Surg. 2005;27(2):191–201.
22. Notomi Y, Lysyansky P, Setser RM, Shiota T, Popović ZB, Martin-Miklovic MG, Weaver JA, Oryszak SJ, Greenberg NL, White RD, Thomas JD. Measurement of ventricular torsion by two-dimensional ultrasound speckle tracking imaging. J Am Coll Cardiol. 2005;45(12):2034–41.
23. Fuchs E, Müller MF, Oswald H, Thöny H, Mohacsi P, Hess OM. Cardiac rotation and relaxation in patients with chronic heart failure. Eur J Heart Fail. 2004;6(6):715–22.
24. Matsuoka K, Nishino M, Kato H, Egami Y, Shutta R, Yamaguchi H, Tanaka K, Tanouchi J, Yamada Y. Right ventricular apical pacing impairs left ventricular twist as well as synchrony: acute effects of right ventricular apical pacing. J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr. 2009;22(8):914–9. quiz 970–1
25. Hara M, Nishino M, Taniike M, Makino N, Kato H, Egami Y, Shutta R, Yamaguchi H, Tanouchi J, Yamada Y. Chronic effect of right ventricular pacing on left ventricular rotational synchrony in patients with complete atrioventricular block. Echocardiogr Mt Kisco N. 2011;28(1):69–75.

26. Lee Y, Mori N, Nakamura D, Yoshimura T, Taniike M, Makino N, Kato H, Egami Y, Shutta R, Tanouchi J, Yamada Y, Nishino M. New approach for rotational dyssynchrony using three-dimensional speckle tracking echocardiography. Echocardiogr Mt Kisco N. 2014;31(4): 492–8.
27. Norisada K, Kawai H, Tanaka H, Tatsumi K, Onishi T, Fukuzawa K, Yoshida A, Hirata K. Myocardial contractile function in the region of the left ventricular pacing lead predicts the response to cardiac resynchronization therapy assessed by two-dimensional speckle tracking echocardiography. J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr. 2010;23(2): 181–9.
28. Hor KN, Wansapura JP, Al-Khalidi HR, Gottliebson WM, Taylor MD, Czosek RJ, Nagueh SF, Akula N, Chung ES, Benson WD, Mazur W. Presence of mechanical dyssynchrony in Duchenne muscular dystrophy. J Cardiovasc Magn Reson Off J Soc Cardiovasc Magn Reson. 2011;13:12.
29. Petryka J, Miśko J, Przybylski A, Śpiewak M, Małek ŁA, Werys K, Mazurkiewicz Ł, Gepner K, Croisille P, Demkow M, Rużyłło W. Magnetic resonance imaging assessment of intraventricular dyssynchrony and delayed enhancement as predictors of response to cardiac resynchronization therapy in patients with heart failure of ischaemic and non-ischaemic etiologies. Eur J Radiol. 2012;81(10):2639–47.
30. Chan YH, Wang CL, Kuo CT, Yeh YH, Wu CT, Wu LS. Clinical assessment and implication of left ventricular mechanical dyssynchrony in patients with heart failure. Acta Cardiol Sin. 2013;29(6):505–14.
31. Chen J, Garcia EV, Bax JJ, Iskandrian AE, Borges-Neto S, Soman P. SPECT myocardial perfusion imaging for the assessment of left ventricular mechanical dyssynchrony. J Nucl Cardiol Off Publ Am Soc Nucl Cardiol. 2011;18(4):685–94.
32. Boogers MM, Van Kriekinge SD, Henneman MM, Ypenburg C, Van Bommel RJ, Boersma E, Dibbets-Schneider P, Stokkel MP, Schalij MJ, Berman DS, Germano G, Bax JJ. Quantitative gated SPECT-derived phase analysis on gated myocardial perfusion SPECT detects left ventricular dyssynchrony and predicts response to cardiac resynchronization therapy. J Nucl Med Off Publ Soc Nucl Med. 2009;50(5):718–25.
33. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, Garrigue S, Kappenberger L, Haywood GA, Santini M, Bailleul C, Daubert JC; Multisite Stimulation in Cardiomyopathies (MUSTIC) Study Investigators. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med. 2001;344(12):873–80.
34. Auricchio A, Stellbrink C, Butter C, Sack S, Vogt J, Misier AR, Böcker D, Block M, Kirkels JH, Kramer A, Huvelle E; Pacing Therapies in Congestive Heart Failure II Study Group, and Guidant Heart Failure Research Group. Clinical efficacy of cardiac resynchronization therapy using left ventricular pacing in heart failure patients stratified by severity of ventricular conduction delay. J Am Coll Cardiol. 2003;42(12):2109–16.
35. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM; Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004;350(21):2140–50.
36. Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C; REVERSE (REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction) Study Group. 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.
37. Tang ASL, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL; Resynchronization-Defibrillation for Ambulatory Heart Failure Trial Investigators. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med. 2010;363(25):2385–95.
38. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NAM, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W; MADIT-CRT Trial

Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med. 2009;361(14):1329–38.
39. Goldenberg I, Kutyifa V, Klein HU, Cannom DS, Brown MW, Dan A, Daubert JP, Estes NAM, Foster E, Greenberg H, Kautzner J, Klempfner R, Kuniss M, Merkely B, Pfeffer MA, Quesada A, Viskin S, McNitt S, Polonsky B, Ghanem A, Solomon SD, Wilber D, Zareba W, Moss AJ. Survival with cardiac-resynchronization therapy in mild heart failure. N Engl J Med. 2014;370(18):1694–701.
40. Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, Dickstein K, Ford I, Gorcsan J, Gras D, Krum H, Sogaard P, Holzmeister J; EchoCRT Study Group. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. N Engl J Med. 2013;369(15):1395–405.
41. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2015: ehw128.
42. Tracy CM, Epstein AE, Darbar D, DiMarco JP, Dunbar SB, Estes NAM, Ferguson TB, Hammill SC, Karasik PE, Link MS, Marine JE, Schoenfeld MH, Shanker AJ, Silka MJ, Stevenson LW, Stevenson WG, Varosy PD. 2012 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. J Am Coll Cardiol. 2012;60(14):1297–313.
43. Sweeney MO, Hellkamp AS, Ellenbogen KA, Greenspon AJ, Freedman RA, Lee KL, Lamas GA; MOde Selection Trial Investigators. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation. 2003;107(23):2932–37.
44. Connolly SJ, Kerr CR, Gent M, Roberts RS, Yusuf S, Gillis AM, Sami MH, Talajic M, Tang AS, Klein GJ, Lau C, Newman DM. Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. Canadian Trial of Physiologic Pacing Investigators. N Engl J Med. 2000;342(19):1385–91.
45. Wilkoff BL, Cook JR, Epstein AE, Greene HL, Hallstrom AP, Hsia H, Kutalek SP, Sharma A, Chamber D, Implantable Defibrillator Trial Investigators VVI. 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.
46. Curtis AB, Worley SJ, Adamson PB, Chung ES, Niazi I, Sherfesee L, Shinn T, Sutton MSJ; Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK HF) Trial Investigators. Biventricular pacing for atrioventricular block and systolic dysfunction. N Engl J Med. 2013;368(17):1585–93.
47. Marai I, Gurevitz O, Carasso S, Nof E, Bar-Lev D, Luria D, Arbel Y, Freimark D, Feinberg MS, Eldar M, Glikson M. Improvement of congestive heart failure by upgrading of conventional to resynchronization pacemakers. Pacing Clin Electrophysiol. 2006;29(8):880–4.
48. Linde C, Leclercq C, Rex S, Garrigue S, Lavergne T, Cazeau S, McKenna W, Fitzgerald M, Deharo JC, Alonso C, Walker S, Braunschweig F, Bailleul C, Daubert JC. Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STimulation in cardiomyopathy (MUSTIC) study. J Am Coll Cardiol. 2002;40(1):111–8.
49. Wilton SB, Leung AA, Ghali WA, Faris P, Exner DV. Outcomes of cardiac resynchronization therapy in patients with versus those without atrial fibrillation: a systematic review and meta-analysis. Heart Rhythm Off J Heart Rhythm Soc. 2011;8(7):1088–94.
50. Bogdan S, Klempfner R, Sabbag A, Luria D, Gurevitz O, Bar-Lev D, Lipchenca I, Nof E, Kuperstein R, Goldenberg I, Eldar M, Glikson M, Beinart R. Functional response to cardiac resynchronization therapy in patients with renal dysfunction and subsequent long-term mortality. J Cardiovasc Electrophysiol. 2014;25(11):1188–95.
51. Yu CM, Sanderson JE, Gorcsan J. Echocardiography, dyssynchrony, and the response to cardiac resynchronization therapy. Eur Heart J. 2010;31(19):2326–37.

52. McAlister FA, Ezekowitz J, Hooton N, Vandermeer B, Spooner C, Dryden DM, Page RL, Hlatky MA, Rowe BH. Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction: a systematic review. JAMA. 2007;297(22):2502–14.
53. Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, Abraham WT, Ghio S, Leclercq C, Bax JJ, Yu CM, Gorcsan J, St John M, Sutton J, Sutter D, Murillo J. Results of the predictors of response to CRT (PROSPECT) trial. Circulation. 2008;117(20):2608–16.
54. Miyazaki C, Redfield MM, Powell BD, Lin GM, Herges RM, Hodge DO, Olson LJ, Hayes DL, Espinosa RE, Rea RF, Bruce CJ, Nelson SM, Miller FA, Oh JK. Dyssynchrony indices to predict response to cardiac resynchronization therapy: a comprehensive prospective single-center study. Circ Heart Fail. 2010;3(5):565–73.
55. Pitzalis MV, Iacoviello M, Romito R, Guida P, De Tommasi E, Luzzi G, Anaclerio M, Forleo C, Rizzon P. Ventricular asynchrony predicts a better outcome in patients with chronic heart failure receiving cardiac resynchronization therapy. J Am Coll Cardiol. 2005;45(1):65–9.
56. Stankovic I, Prinz C, Ciarka A, Daraban AM, Kotrc M, Aarones M, Szulik M, Winter S, Belmans A, Neskovic AN, Kukulski T, Aakhus S, Willems R, Fehske W, Penicka M, Faber L, Voigt JU. Relationship of visually assessed apical rocking and septal flash to response and long-term survival following cardiac resynchronization therapy (PREDICT-CRT). Eur Heart J Cardiovasc Imaging. 2016;17(3):262–9.
57. Kutyifa V, Stockburger M, Daubert JP, Holmqvist F, Olshansky B, Schuger C, Klein H, Goldenberg I, Brenyo A, McNitt S, Merkely B, Zareba W, Moss AJ. 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.
58. Parkash R, Philippon F, Shanks M, Thibault B, Cox J, Low A, Essebag V, Bashir J, Moe G, Birnie DH, Larose É, Yee R, Swiggum E, Kaul P, Redfearn D, Tang AS, Exner DV. Canadian cardiovascular society guidelines on the use of cardiac resynchronization therapy: implementation. Can J Cardiol. 2013;29(11):1346–60.
59. Verbrugge FH, Dupont M, Vercammen J, Jacobs L, Verhaert D, Vandervoort P, Tang WHW, Mullens W. Time from emerging heart failure symptoms to cardiac resynchronisation therapy: impact on clinical response. Heart Br Card Soc. 2013;99(5):314–9.
60. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J; MIRACLE Study Group. Multicenter InSync Randomized Clinical Evaluation. Cardiac resynchronization in chronic heart failure. N Engl J Med. 2002;346(24):1845–53.
61. Chen Z, Sohal M, Sammut E, Child N, Jackson T, Claridge S, Cooklin M, O'Neill M, Wright M, Gill J, Chiribiri A, Schaeffter T, Carr-White G, Razavi R, Rinaldi CA. Focal but not diffuse myocardial fibrosis burden quantification using cardiac magnetic resonance imaging predicts left ventricular reverse modeling following cardiac resynchronization therapy. J Cardiovasc Electrophysiol. 2016;27(2):203–9.
62. Bogdan S, Nof E, Eisen A, Sela R, Rosenheck S, Freedberg N, Geist M, Ben-Zvi S, Haim M, Glikson M, Goldenberg I, Suleiman M; Israeli working group of pacing and electrophysiology of the Israeli Heart Society Clinical outcomes in patients with severe renal dysfunction including dialysis following defibrillator implantation. Am J Nephrol. 2015;42(4):295–304.
63. Khan FZ, Virdee MS, Palmer CR, Pugh PJ, O'Halloran D, Elsik M, Read PA, Begley D, Fynn SP, Dutka DP. Targeted left ventricular lead placement to guide cardiac resynchronization therapy: the TARGET study: a randomized, controlled trial. J Am Coll Cardiol. 2012;59(17):1509–18.
64. Risum N, Strauss D, Sogaard P, Loring Z, Hansen TF, Bruun NE, Wagner G, Kisslo J. Left bundle-branch block: the relationship between electrocardiogram electrical activation and echocardiography mechanical contraction. Am Heart J. 2013;166(2):340–8.
65. Van de Veire NR, Schuijf JD, De Sutter J, Devos D, Bleeker GB, de Roos A, van der Wall EE, Schalij MJ, Bax JJ. Non-invasive visualization of the cardiac venous system in coronary artery disease patients using 64-slice computed tomography. J Am Coll Cardiol. 2006;48(9):1832–8.

66. Zhou W, Hou X, Piccinelli M, Tang X, Tang L, Cao K, Garcia EV, Zou J, Chen J. 3D fusion of LV venous anatomy on fluoroscopy venograms with epicardial surface on SPECT myocardial perfusion images for guiding CRT LV lead placement. JACC Cardiovasc Imaging. 2014;7(12):1239–48.
67. Worley SJ. CRT delivery systems based on guide support for LV lead placement. Heart Rhythm. 2009;6(9):1383–7.
68. Soga Y, Ando K, Yamada T, Goya M, Shirai S, Sakai K, Iwabuchi M, Yasumoto H, Yokoi H, Nosaka H, Nobuyoshi M. Efficacy of coronary venoplasty for left ventricular lead implantation. Circ J Off J Jpn Circ Soc. 2007;71(9):1442–5.
69. Shetty AK, Duckett SG, Bostock J, Rosenthal E, Rinaldi CA. Use of a quadripolar left ventricular lead to achieve successful implantation in patients with previous failed attempts at cardiac resynchronization therapy. Europace. 2011;13(7):992–6.
70. Ohlow MA, Lauer B, Brunelli M, Daralammouri Y, Geller C. The use of a quadripolar left ventricular lead increases successful implantation rates in patients with phrenic nerve stimulation and/or high pacing thresholds undergoing cardiac resynchronisation therapy with conventional bipolar leads. Indian Pacing Electrophysiol J. 2013;13(2):58–65.
71. Pappone C, Calovic Z, Saviano M, McSpadden LC, Ryu K, Cuko A, Baldi M, Ciaccio C, Giannelli L, Ionescu B, Pappone A, Petretta A, Vitale R, Vicedomini G, Santinelli V. Abstract 13412: cardiac resynchronization therapy with multisite left ventricular pacing improves acute hemodynamic response in patients. Circulation. 2012;126(21 Supplement):A13412.
72. Bracke FA, van Gelder BM, Dekker LRC, Houthuizen P, ter Woorst JF, Teijink JA. Left ventricular endocardial pacing in cardiac resynchronisation therapy: moving from bench to bedside. Neth Heart J. 2012;20(3):118–24.
73. Ailawadi G, LaPar DJ, Swenson BR, Maxwell CD, Girotti ME, Bergin JD, Kern JA, DiMarco JP, Mahapatra S. Surgically placed left ventricular leads provide similar outcomes to percutaneous leads in patients with failed coronary sinus lead placement. Heart Rhythm Off J Heart Rhythm Soc. 2010;7(5):619–25.
74. Singh JP, Klein HU, Huang DT, Reek S, Kuniss M, Quesada A, Barsheshet A, Cannom D, Goldenberg I, McNitt S, Daubert JP, Zareba W, Moss AJ. Left ventricular lead position and clinical outcome in the multicenter automatic defibrillator implantation trial–cardiac resynchronization therapy (MADIT-CRT) trial. Circulation. 2011;123(11):1159–66.
75. Hayes DL, Boehmer JP, Day JD, Gilliam FR, Heidenreich PA, Seth M, Jones PW, Saxon LA. Cardiac resynchronization therapy and the relationship of percent biventricular pacing to symptoms and survival. Heart Rhythm Off J Heart Rhythm Soc. 2011;8(9):1469–75.
76. Lakkireddy D, Di Biase L, Ryschon K, Biria M, Swarup V, Reddy YM, Verma A, Bommana S, Burkhardt D, Dendi R, Dello Russo A, Casella M, Carbucicchio C, Tondo C, Dawn B, Natale A. Radiofrequency ablation of premature ventricular ectopy improves the efficacy of cardiac resynchronization therapy in nonresponders. J Am Coll Cardiol. 2012;60(16):1531–9.
77. Mullens W, Grimm RA, Verga T, Dresing T, Starling RC, Wilkoff BL, Tang WHW. Insights from a cardiac resynchronization optimization clinic as part of a heart failure disease management program. J Am Coll Cardiol. 2009;53(9):765–73.