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## CHAPTER 1

# Cardiac Resynchronization Therapy

*Behzad Pavri, & Arthur M. Feldman*

Jefferson Medical College, Philadelphia, PA, USA

## History of cardiac resynchronization

Cardiac resynchronization therapy (CRT) was first described nearly 25 years ago. In 1983 at the 7th World Symposium on Cardiac Pacing, de Teresa et al. described a series of 4 patients with left bundle branch block (LBBB) who underwent aortic valve replacement [1]. An epicardial left ventricular (LV) lead was placed and attached to the ventricular port of a dual chamber pacemaker along with a right atrial lead. The atrioventricular (AV) delay was adjusted to allow for fusion between native conduction and LV pacing. There was a 25% increase in ejection fraction (EF) and improvement in dyssynchrony based on angioscintigraphy. The importance of these observations was unappreciated, and this report remained largely unnoticed for almost a decade.

Also the 1980s and early 1990s saw reports of echocardiography and angioscintigraphy in patients with widened QRS from either bundle branch block or pacing, which demonstrated dyssynchronous contraction [2,3]. However, little was known about the hemodynamic effects of such dyssynchronous contraction. Several investigators performed animal experiments involving pacing-induced models of dyssynchrony. Burkhoff et al. paced 8 dogs at several sites, including the epicardial atrium, LV apex, LV and RV free walls, and endocardial RV apex [4]. LV pressure was highest

with atrial pacing and lowest with RV free wall pacing. They reported that LV pressure was negatively correlated with QRS width ( $r = 0.971$ ). Park et al. paced dogs in the RV and demonstrated a rightward shift in LV end-systolic pressure–volume relation, with increasing QRS width indicating poorer LV pump function [5]. Lattuca et al. were the first to report experience with biventricular pacing [6]. Three dogs were paced in the RV, LV, or both. Marked improvement was seen in QRS duration, cardiac output, aortic pressure, and right atrial pressure when paced in both ventricles.

Further human experience with pacing therapy for heart failure did not occur until the early 1990s. Initial efforts were focused toward resynchronization of AV timing for heart failure. One initial study demonstrated benefit of AV sequential pacing [7] but subsequent studies either failed to duplicate success or demonstrated worsening outcomes [8–11]. Other studies examined the potential of alternative pacing sites in the RV for improvement in dyssynchrony [12–14].

The first report of CRT in heart failure was in 1994. Cazeau et al. reported a single patient with alcohol-induced dilated cardiomyopathy with LBBB, prolonged PR interval of 200 milliseconds, and New York Heart Association (NYHA) class IV congestive heart failure (CHF) symptoms who was clinically deteriorating despite maximal medical therapy [15]. M-mode echocardiography demonstrated significant delay between septal and posterior wall contraction. In an attempt to correct his conduction abnormalities, the authors implanted a four-chamber pacemaker. An epicardial LV lead

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was placed in addition to transvenously placed right atrial, right ventricular, and left atrial leads. Interestingly, the left atrial lead was placed in the distal coronary sinus. Both atrial leads and both ventricular leads were Y-adapted and connected to a dual chamber pacemaker. The patient experienced acute improvements in pulmonary capillary wedge pressure, cardiac output, and QRS duration. Six weeks after implantation the patient exhibited NYHA class II symptoms. In their conclusion, the authors predicted that resynchronization therapy might be beneficial in the short term but doubted that any long-term benefit would be realized. Shortly after this report, several other groups reported small case reports of the acute benefits of resynchronization [16–18]. All these initial reports involved epicardial lead placement. Transvenous insertion of an LV lead into a branch of the coronary sinus was first described in 1998 by Daubert et al. [19].

These initial small reports were the foundation for the larger clinical trials that followed. Initial feasibility studies were followed by prospective multicenter randomized trials. As a result of these efforts, in 2001 the Food and Drug Administration approved the Medtronic InSync Biventricular pacemaker for treating CHF. As clinical trials continued to report both acute and chronic improvement with resynchronization therapy with most recent trials demonstrating mortality benefits, the ACC/AHA guidelines include a class I recommendation for CRT for patients with  $EF \leq 35\%$ , sinus rhythm, NYHA class III or IV symptoms despite optimal medical therapy with dyssynchrony, and QRS width  $> 120$  milliseconds [20]. CRT was incorporated into defibrillators, thereby increasing the therapeutic potential of these devices. We now recognize CRT as state-of-the-art treatment for selected patients with heart failure, and continued advancements are being reported in device technology, newer LV lead designs, coronary sinus delivery systems, ability to alter V–V timing, tools to track CHF, and imaging modalities to assist in patient identification and therapy titration.

### Pathophysiology of dyssynchrony

#### Mechanical/structural dyssynchrony

As the heart fails, LV remodeling begins. This has been best studied in postinfarction LV dysfunction

but has also been extended to cardiomyopathy due to other causes. There are numerous factors that contribute to the remodeling process. In myocardial infarction, remodeling starts within a few hours after the acute event. Initial events include myocyte slippage due to lengthening of cardiac myocytes, followed by thinning of the ventricular wall, expansion of the infarction, inflammation and necrotic zone resorption, ultimately resulting in scar formation. The infarction zone can expand and lead to LV deformation and dilatation. Unaffected regions of the heart show compensatory hypertrophy. In addition, the extracellular matrix, under the influence of metalloproteases, remodels with collagen accumulation. These changes are mediated by neurohormonal activation, and the remodeling leads to worsening cardiac function through elevated wall stress/hypertrophy, resulting in a vicious cycle leading to progressive decline.

#### Electrical dyssynchrony

In addition to these mechanical changes, the electrical system can develop disease. While conduction delay can occur in all parts of the electrical system, focus has been on the importance of AV synchrony and interventricular synchrony. As will be discussed further below, the loss of electrical synchrony in itself leads to further electrical, structural, physiologic, and molecular remodeling, which in turn contribute to the vicious downward spiral seen in heart failure patients.

#### AV dyssynchrony

AV nodal delay can occur because of intrinsic disease or because of medical therapy. When AV nodal conduction time increases, atrial contraction no longer contributes to late diastolic filling. Rather it occurs during passive early filling. With prolonged AV delays, left atrial pressure can fall below LV pressure late in diastole, leading to “presystolic” mitral regurgitation. Evidence from animal studies suggests that chronic AV block induces mechanical and electrical remodeling.

#### Infra-His dyssynchrony

Widening of the QRS is seen in up to 30% of patients with heart failure, most commonly in an LBBB pattern, and is associated with increased 1-year sudden and total mortality rate [21]. The effect of

pacing-induced LBBB on the LV has been well studied in animals and correlated with humans. Tagged magnetic resonance imaging (MRI) studies in animals reveal that initial activation occurs in the interventricular septum [22]. This early septal activation occurs with lateral wall prestretch and is unable to mount sufficient pressure to effect mitral valve closure. Delayed activation of the lateral wall occurs after the septum has contracted. This contraction occurs against a higher pressure ventricle and a relaxing, noncompliant septum. This leads to paradoxical septal motion, which can worsen mitral regurgitation. Similar patterns have been also demonstrated in humans with dilated cardiomyopathy [23,24]. Tagged MRI studies also demonstrate increased myofiber workload in the late activated lateral wall. Positron emission tomographic scanning reveals differences in regional metabolism, with lateral walls exhibiting twice the septal metabolism, and there is evidence that local myocardial blood flow is altered [25–27]. Such differences in workload can also lead to altered mechanical stretch, which may affect calcium handling with resultant tachyarrhythmias [28].

Clinically, LBBB has been associated with higher event rates in patients with CHF [29] and also has been proposed as a risk factor for developing future CHF in asymptomatic patients [30]. One study suggested that LBBB may be responsible for a reversible form of idiopathic dilated cardiomyopathy [31]. There is animal evidence that electrical dyssynchrony, both within the AV node and with LBBB, can lead to adverse remodeling.

Spragg et al. studied the effects of different types of pacing-induced cardiomyopathy in 11 dogs [32]. Six dogs were paced at over 200 bpm in the right atrium and 5 were paced in the RV at the same rate; 4 dogs served as controls. Dogs were studied with MRI to document dyssynchrony. Both pacing groups resulted in similar degrees of cardiomyopathy. Atrially paced dogs demonstrated uniform LV activation while RV-paced dogs exhibited early septal contraction with concomitant lateral stretch followed by delayed lateral contraction and septal stretch. Western blot analysis of the RV-paced hearts revealed both transmural and interventricular gradients in myocardial protein expression, but these gradients were not seen in the atrial-paced or control groups. Thus, it appears that mechanical

dyssynchrony rather than cardiomyopathy contributed to molecular remodeling. Prinzen et al. reported their studies in 8 dogs that underwent radiofrequency (RF) ablation of the left bundle [33]. After 16 weeks, there was a decrease in EF and an increase in LV cavity volume and LV mass. Both the septum and lateral walls demonstrated hypertrophy, but with an altered ratio. Spragg et al. reported experience with 9 dogs that underwent RF ablation of the left bundle [34]. One month later, tissue was examined from both early-activated anterior segments and late-activated lateral LV myocardial segments. They noted that the conduction velocity, action potential duration and refractory periods of late-activated lateral segments were significantly reduced compared to anterior segments. The distribution of connexin 43 was altered from intercalated disks to lateral myocyte membranes. In addition, the normal gradient in conduction velocity from epicardium to endocardium was reversed. In a pressure overload heart failure model of mice reported by Wang et al., failing hearts exhibited a loss of the normal transmural gradient in the action potential duration and prolongation of epicardial action potential duration [35]. The morphology of the action potential was also altered, with a significantly elevated plateau potential. In addition, increased pacing rates led to increased action potential duration and decreased critical conductance required to propagate the action potential. Wiegand et al. used a computer simulation in their rabbit model of pressure–volume overload heart failure [36]. They discovered that conduction velocity of the myocardium increased, but that myocardial cell size increased to a greater degree, leading to a widened QRS. Thus, there is evidence that AV block and LBBB lead to electrical remodeling.

## Review of major CRT trials

The short-term clinical response to resynchronization therapy has been examined in numerous studies [37–40]. Consistently, these studies have shown that resynchronization therapy dramatically improves symptoms and functional capacity in patients with severe heart failure symptoms (NYHA class III–IV), LVEF < 35%, and widened QRS (see Table 1.1) [1–43].

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**Table 1.1** Major cardiac resynchronization therapy trials.

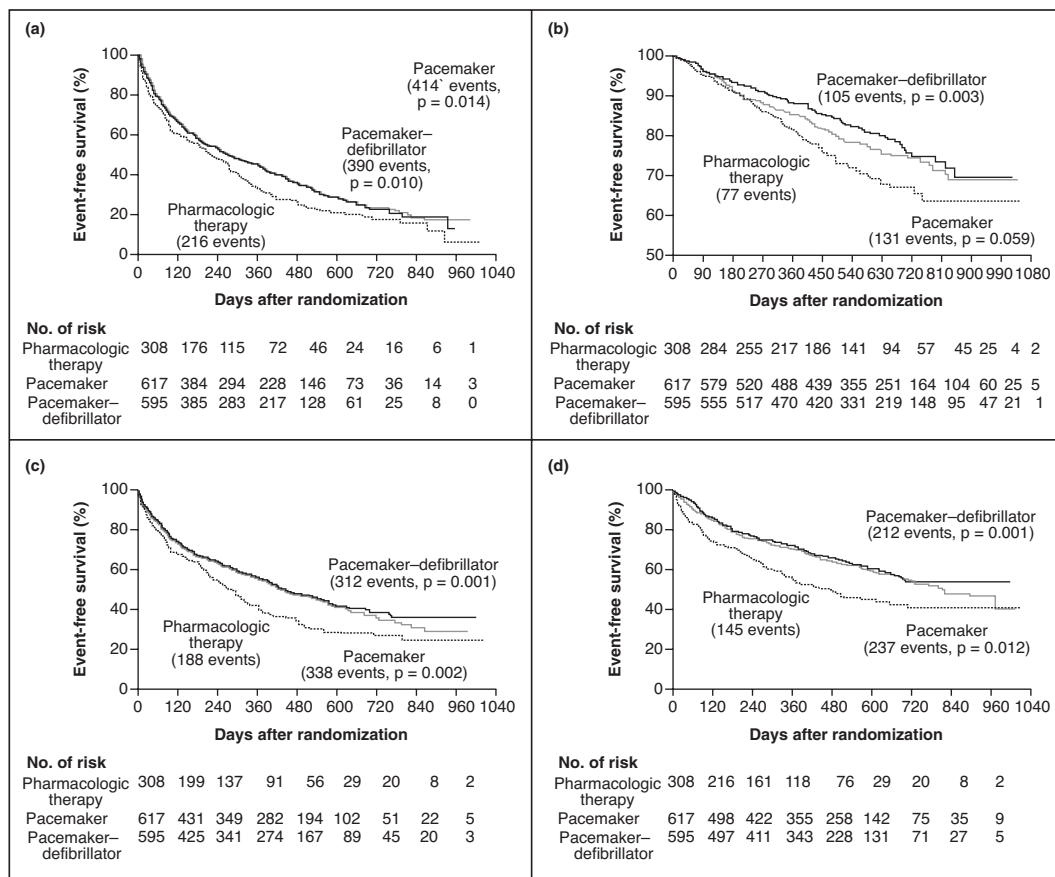
<i>Trial design</i>	<i>Number of patients</i>	<i>Age (years)</i>	<i>Follow up</i>	<i>NYHA class</i>	<i>QRS width</i>	<i>Significant endpoints (all <math>p &lt; 0.05</math>)</i>
<i>Clinical improvement</i>						
CONTAK CD [37]	490	66	3–6 mo	II–IV	158	Composite of all-cause mortality, heart failure hospitalization, and ventricular tachycardia requiring ICD intervention
InSync ICD [38]	554	66	6 mo	II–IV	165	QoL score, NYHA functional class, and 6-min hall walk distance
MUSTIC [39]	58	63	6 mo	III	176	Improved 6-min walk, QoL score, and $Vo_2$ max
MIRACLE [40]	532	64	3–6 mo	III–IV	166	Improved 6-min walk, QoL score, and NYHA functional class
<i>Mortality</i>						
Meta-analysis [41]	1634	63–66	3–6 mo	II–IV	158–176	OR 0.49, death from CHF (95% CI 0.25–0.93) OR 0.71, overall mortality (95% CI 0.51–1.18)
COMPANION [42]	1520	65	12 mo	III–IV	158	OR 0.66, death or CHF hospitalization (95% CI 0.53–0.87) OR 0.76, overall mortality (95% CI 0.58–1.01)
CARE-HF [43]	813	66	29.4 mo	III–IV	160	HR 0.54, death or CHF hospitalization (95% CI 0.43–0.68) HR 0.64, overall mortality (95% CI 0.48–0.85)

CHF, congestive heart failure; ICD, implantable cardioverter-defibrillator; QoL, quality of life scores (Minnesota Living with Heart Failure questionnaire); OR, odds ratios; HR, hazard ratios.

The MIRACLE study was the first large randomized, double-blinded study comparing optimal medical management and resynchronization therapy in 453 patients. Over a 6-month follow-up, the MIRACLE investigators found significant improvement in NYHA functional class, 6-minute walk distances, and quality of life scores in patients randomized to CRT. Furthermore, patients randomized to CRT had significantly greater improvement in EF, increase in measured  $Vo_2$ max, decrease in mitral regurgitant jet area, and decrease in LV end-diastolic dimensions. These responses to CRT were seen as early as 1-month postimplant in the majority of patients, and were maintained at 6-month and 1-year follow-up.

While earlier studies were underpowered to detect changes in mortality over their relatively short

follow-up periods, the COMPANION [42] and CARE-HF [43] trials were designed specifically for this purpose. The largest study to date, COMPANION, randomized 1520 patients with severe heart failure and wide QRS to CRT (biventricular pacing only), CRT-D (defibrillator with biventricular pacing capability), and optimal medical management [42]. Over a follow-up period of approximately 12 months, both the CRT and CRT-D arms showed a comparable and statistically significant improvement in the primary endpoint, a composite of death or hospitalization for any cause. While CRT alone did not reach a statistically significant reduction in death ( $p = 0.06$ ), the addition of defibrillation therapy achieved an incremental and significant improvement, likely due to reduction in sudden death events. Kaplan–Meier curves for the primary and



**Figure 1.1** Kaplan-Meier estimates of the time to (a) the primary endpoint of death from or hospitalization for any cause, (b) the time to the secondary endpoint of death from any cause, (c) the time to death from or hospitalization for cardiovascular causes and (d) the time to death from or hospitalization for heart failure. (Reproduced with permission from [42]. Copyright © 2004 Massachusetts Medical Society. All Rights Reserved.)

secondary endpoints separated early and continued to diverge throughout the 12-month follow-up (see Figure 1.1).

The recently published CARE-HF trial [43] compared CRT (biventricular pacing without a defibrillator) and optimal medical management in 813 patients for a mean duration of 29.4 months. CARE-HF was the first trial to demonstrate a significant reduction of death of 36% ( $p = 0.003$ ) with CRT compared with medical management. Furthermore, this study supported and extended the findings of COMPANION with regard to reduction in hospitalization for cardiac causes over an extended period of follow-up. Both COMPANION and CARE-HF reproduced prior study findings of a significant improvement in clinical symptoms and

evidence of the ability of resynchronization to cause reverse remodeling.

## Effects of CRT

Improvements in cardiac hemodynamics are often seen shortly after the initiation of CRT. Several studies in which invasive hemodynamic monitoring was performed during CRT device implantation have demonstrated acute improvements in systolic blood pressure, cardiac output, peak  $dP/dT$ , EF, accompanied by a decline in pulmonary capillary wedge pressures [44–49].

Proposed mechanisms for this abrupt improvement in cardiac function include changes in loading conditions, reduced mitral regurgitation, and

enhanced contractile function. Coordinated contraction of the septum and the LV free wall improve ejection efficiency, which can be seen in pressure-volume tracings by an increase in stroke volume and stroke work and decrease in end-systolic volume [49]. These changes occur without an increase in myocardial oxygen consumption, suggesting improved cardiac efficiency as the predominant acute effect of cardiac resynchronization [50].

Numerous studies have reported decreases in functional mitral regurgitation with the initiation of resynchronization therapy [39,40,43,51]. Breithardt et al. have shown that the change in LV  $dP/dT$  after initiation of CRT directly correlated with the reduction in effective regurgitant orifice area, suggesting that improved contractile function resulted in an increase in the transmitral pressure gradient and earlier mitral valve closure [52]. Subsequent studies have suggested that the restoration of coordinated papillary muscle activation is another beneficial response to CRT that contributes to reduced regurgitant volumes. Late improvements in mitral regurgitation may occur due to the effects of delayed LV remodeling, associated with a decrease in the sphericity index and reduction in mitral annular dilatation [52–54]. However, patient with significant mitral regurgitation (regurgitant orifice area  $\geq 0.20 \text{ cm}^2$ ) prior to CRT may not show improvement [55]. An important benefit may be the observation that CRT attenuates the worsening of functional mitral regurgitation during exercise [56].

While many patients demonstrate improvements in noninvasive indices of diastolic function after CRT initiation, a direct effect on ventricular relaxation has been more difficult to prove. In patients with elevated filling pressures and a “pseudonormalized” mitral filling pattern, the E wave/Em septal and E/FP ratios have been noted to improve shortly following resynchronization [57]. However, in patients with normal baseline filling patterns, acute effects of CRT fail to improve these noninvasive diastolic indices. This absence of effect suggests that measured changes in LV diastolic filling are caused primarily by a reduction in ventricular volumes and are not in fact due to fundamental changes in myocardial lusitropic properties [57]. Similarly, recent studies have reported a beneficial effect on atrial systolic function, atrial compliance, and atrial dimensions [58].

Cardiac resynchronization also has been shown to have significant effects on the maladaptive neurohormonal responses seen in CHF. Early studies failed to show significant reduction in norepinephrine, dopamine, endothelin, and brain natriuretic peptide levels, possibly due to their small size, short follow-up periods, or methodological limitations [59]. More recently, data have emerged to suggest that sympathetic nerve activity is reduced with CRT, above and beyond the effects of optimal pharmacologic treatment [60]. Furthermore, CARE-HF demonstrated a large reduction in N-terminal BNP, which was not evident until the end of the follow-up period [43]. CRT is associated with long-term improvements in cardiac sympathetic nerve activity, as reflected by improvements in cardiac  $^{123}\text{I}$ -MIBG uptake [61]. Several studies have also shown significant improvement in heart rate variability and heart rate profiles after initiation of CRT, which further supports the hypothesis that the neurohormonal balance is shifted away from the sympathetic excess that is ubiquitous in CHF [62].

The application of CRT to a growing population of patients with CHF has also lead to numerous observations beyond improvement in LV systolic function. In particular, improvements in sleep disordered breathing [63], pulmonary hypertension [64], RV function and tricuspid regurgitation [65,66], and the frequency of atrial fibrillation (AF) events [67] are examples of the global cardiac benefit due to the elimination of ventricular dyssynchrony. Occasional case reports of increased ventricular tachycardia burden (proarrhythmia) have been described [68,69], and proximity of LV pacing site to the culprit reentrant circuit has been postulated as the possible explanation.

### Patient selection—responders and nonresponders

The cumulative results of the above-referenced trials have lead to CRT receiving a class IIa indication in the 2002 ACC/AHA/NASPE guidelines for cardiac pacing [70], and a class I indication in the 2005 HFSA guidelines [71] for patients with NYHA class III–IV CHF, EF  $< 35\%$ , and QRS width  $> 120$  milliseconds. Despite the impressive results of these studies, it has become clear that the benefits of CRT are not uniform within this patient population.

**Table 1.2** Causes for failure of or “nonresponse” to cardiac resynchronization therapy.

<i>Factors related to patient selection</i>
Absence of dyssynchrony
Posterolateral wall scarred or hibernating
<i>Factors related to individual patient</i>
Atrial anatomic distortion leading to nonengageable coronary sinus
Lack of suitable posterolateral venous branch (anatomy, diaphragm stimulation), leading to nonplacement of LV lead or placement in suboptimal location
High LV pacing threshold leading to loss of consistent LV capture
High burden of AF with rapid ventricular response
Conduction delay from LV pacing site (marked latency)
<i>Factors related to device programming</i>
Failure to adjust AV delay to optimize AV blood flow
Failure to adjust V–V timers (when available) to compensate for suboptimal lead LV location
Failure to adjust LV output to accommodate high LV capture threshold

AF, atrial fibrillation; AV, atrioventricular; LV, left ventricular.

Table 1.2 lists potential reasons for the lack of response to CRT.

As many as one-third of patients receiving CRT are considered “nonresponders.” The definition of a “nonresponder” has not been uniform in the multitude of studies published to date, which adds to the confusion regarding what endpoints ought to be considered appropriate measures of treatment success. There are three primary categories of responses: *hemodynamic* (both acute and chronic measurements), *clinical* (includes quality of life scores, 6-min walk times, and functional classification), and *volumetric* (changes in ventricular volumes or EF). More strict definitions of response, such as improvement in volumetric changes, increase the percentage of nonresponders to 36–43%; accurate recognition of patients who will benefit most from CRT continues to be a primary goal [72].

Measurement of the hemodynamic responses to CRT requires invasive monitoring and is not practical for long-term follow-up. Defining responders by clinical measures is confounded by the strong placebo effect seen in the large clinical studies such as MIRACLE, where 39% of the control arm were considered to have improved by one or more clinical endpoints [40]. Yu et al. recently have shown that a reduction in LV end-systolic volume by >10% predicted a significant decrease in morbidity and mortality, while standard clinical measures of response failed to do so. In light of this information it appears that volumetric response may be a more robust measure of success [73].

Current practice involves patient selection on the basis of QRS width and morphology, using both as indirect markers of ventricular dyssynchrony. However, the degree of mechanical dyssynchrony is not always reflected in the QRS width, and this may explain some of the observed variability in response to CRT. In patients with severe heart failure, as many as one-third of patients who meet standard criteria for CRT implant may have little or no demonstrable dyssynchrony, while in one-third of patients with RBBB or narrow QRS, significant dyssynchrony may be present [74,75]. As a treatment modality aimed at restoring ventricular synchrony, it is not surprising to note that the strongest independent predictor of response to CRT is the presence of dyssynchrony at baseline. Neither baseline QRS width nor morphology was accurate predictors of response, in keeping with the growing recognition that QRS duration is a poor surrogate for the presence or absence of mechanical dyssynchrony [76]. Achilli et al. have shown that in patients with significant dyssynchrony, clinical and volumetric responses were seen to an equal degree in patients with both wide and narrow QRS morphologies [77]. Under current guidelines, however, CRT would not be offered to patients with LV dyssynchrony and narrow QRS complexes. It should be noted that there is some controversy about the importance of mechanical dyssynchrony as a predictor of response, and some have correctly pointed out that randomized trials need to be conducted before current guidelines can be changed [78].



Simply stated, the best modality to define dyssynchrony has yet to be validated. Imaging modalities including the echocardiogram, tissue Doppler, tissue strain imaging, speckle tracking, nuclear imaging, and MRI have been employed (Table 1.3). Echocardiography with tissue Doppler imaging is currently the methodology most likely to replace QRS duration [79]. In small studies, each of these methods of defining dyssynchrony has shown promising ability in predicting responders. The PROSPECT study [80] will individually and prospectively evaluate the prognostic accuracy of a variety of echocardiographic and tissue Doppler imaging parameters in an effort to determine the best method to diagnose dyssynchrony.

Demographic factors such as age, sex, baseline EF, or the presence of AF have shown little or no prognostic significance [81]. On the other hand, the etiology of the patient's cardiomyopathy has been shown to predict response [82]. Patients with idiopathic dilated cardiomyopathies seem to have a greater, more homogenous response to CRT than patients with ischemic heart disease. This may be related to the progressive nature of coronary artery disease, or (more likely) due to the presence of scar in the region of the LV targeted for pacing. In this population, the amount of viable myocardium, both globally and in the lateral wall, has been shown to predict response to CRT [83,84]. End-stage heart failure (NYHA class IV), severe mitral regurgitation and LV end-diastolic dimensions greater than 75 mm all were independent predictors of non-response [85]. In the CARE-HF trial [43], the effect of CRT on progression to heart transplantation was not significant. The resynchronization arm of CARE-HF had fewer emergent heart transplants (1 vs 3), but the same number of transplanted patients overall. However, in one report of 34 patients enrolled in the CRT arm of a major clinical study and who met indications for heart transplantation, only 2 still met criteria after 6 months [86]. In these patients being considered for heart transplantation, the duration of response is not known, and concerns remain that CRT may simply delay the need for heart transplantation, ultimately disqualifying some patients from transplant eligibility due to advanced age.

## Special populations

### Patients with AF

AF is a common occurrence with heart failure. However, most of the major clinical trials on cardiac resynchronization excluded patients with AF. Most of the smaller trials on patients with AF included mostly patients who had previously undergone AV node ablation for difficulty in rate control or patients who had combined AF and bradycardia [87,88]. The PAVE trial [89] enrolled patients with chronic (>30 days) AF who had undergone AV junction ablation and pacemaker implantation for rate control, and limited exercise capacity in spite of medical therapy. EF was not an inclusion criteria and the average EF was 46%. CRT resulted in improved 6-minute walk distance and higher LVEF at 6 months, compared to RV pacing. These benefits were limited to patients with  $EF \leq 45\%$  and NYHA class  $\geq II$ . At 6 months of follow-up, patients with CRT had a significantly higher EF than patients with RV leads only (46% vs 41%,  $p = 0.03$ ). There was no significant difference in mortality or in complications.

Few data are available on the effects of resynchronization in patients with AF without a standard pacing indication. In one study, clinical response to CRT was not different in sinus rhythm versus AF [90], about half of whom had undergone AV nodal ablation. It is not the irregularity of R-R intervals but the rapidity of the heart rate in AF that impacts most on LVEF [91]. Therefore, even with the use of cardiac resynchronization in patients with heart failure and AF, rate control remains extremely important. Features available in many CRT devices designed to provide biventricular pacing even during rapid rates in AF (such as "sense assurance," "conducted AF response," and "rate regulation") have not been proven to be of clinical benefit. The positive effects of CRT in patients with AF continue for at least 12 months [92]. Although left atrial remodeling after CRT in patients with chronic AF has been described, it is a small minority of patients who will show spontaneous conversion to sinus rhythm [93].

### Patients with LV dysfunction and standard pacing indications

The detrimental effects of RV pacing-induced dyssynchrony are now firmly established, as



Table 1.3 Criteria for dyssynchrony and response.

Author (year)	N	Definition of responders	Follow-up	Modality	Criteria	Cutoff	Methodology of cutoff	Sensitivity (%)	Specificity (%)
Pitzalis M (2002)	20	↓LLVs index $\geq 15\%$	1 mo	M-mode at short-axis view	Septoposterior delay in systole	130 ms	Derived from ROC curve of study population	100	63
Bax JJ (2003)	25	Absolute $\uparrow EF \geq 5\%$	1 day	TDI	Septolateral delay in Ts (ejection phase)	60 ms	Derived from study population	76	87.5
Yu CM (2003)	30	↓LLVs $> 15\%$	3 mo	TDI	Ts-SD of six basal, six mid-LV segments	32.6 ms	+2 SD from mean of 88 normal controls	100	100
Yu CM (2004)	54	↓LLVs $> 15\%$	3 mo	TDI		31.4 ms	Derived from ROC curve of study population	96	78
Penicka M (2004)	49	Relative $\uparrow EF \geq 25\%$	6 mo	TDI	Ts (onset) of BS, BL, BP, and BRV by summation of inter- and intraventricular delay	102 ms	Derived from study population	96	71
Nortabartolo D (2004)	49	↓LLVs $> 15\%$	3 mo	TDI	Maximal difference in Ts in six basal segments (both ejection phase and postsystolic shortening)	110 ms	Derived from study population	97	55

(Cont.)

**Table 1.3 (Continued)**

Author (year)	N	Definition of responders	Follow-up	Modality	Criteria	Cutoff	Methodology of cutoff	Sensitivity (%)	Specificity (%)
Gorcsan J III (2004)	29	↑ Stroke volume $\geq$ 25%	Acute (within 48 h)	TSI	Septoposterior delay (both ejection phase and postsystolic shortening)	65 ms	Derived from 15 pilot patients	87	100
Yu CM (2005)	56	↓ LVVs > 15%	3 mo	TSI	(1) Lateral wall delay (2) Ts-SD of six basal, six mid-LV segments	(1) Qualitative (2) 34.4 ms	(1) Qualitative (2) Derived from ROC curve of study population	47 87	89 81

BS, basal septal; BL, basal lateral; BP, basal posterior; BRV, basal right ventricular; EF, ejection fraction; LV, left ventricular; LVVs, left ventricular end-systolic volume; ROC, receiver operating curve; TDI, tissue Doppler imaging; TSI, tissue synchronization imaging; Ts, time to peak myocardial systolic velocity; Ts(onset), time to onset of myocardial systolic velocity; Ts-SD, standard deviation of time to peak myocardial systolic velocity.  
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reported in the DAVID [94] and other trials. The HOBIPACE trial [95] examined CRT in patients with CHF and standard pacing indications using a randomized, crossover study design. Compared to RV pacing, CRT led to significant improvements in the study's primary (LV end-systolic volume, LVEF, and  $\text{VO}_2\text{max}$ ) and secondary (NT-proBNP, NYHA class, quality of life, and exercise capacity) endpoints.

#### **Patients with class I–II CHF**

Subgroup analysis of CRT trials suggested that in patients with mild heart failure symptoms with a wide QRS complex and an implantable cardioverter-defibrillator (ICD) indication, CRT did not alter exercise capacity but did result in significant improvement in cardiac structure and function and composite clinical response over 6 months [96]. Based on such observations, the role of resynchronization therapy in patients with class I–II CHF is currently being examined with several ongoing clinical trials, most notably the MADIT-CRT trial [97], where patients with NYHA class I or II heart failure are being randomly assigned to treatment with CRT-D versus dual chamber defibrillators.

#### **Patients with narrow QRS**

Recognizing that the QRS duration may be a poor surrogate for mechanical dyssynchrony, data are accumulating from a few studies that have specifically examined the effect of resynchronization therapy on patients with narrow QRS complexes, but with mechanical dyssynchrony by echocardiogram. In one study, there was similar and significant improvement in NYHA class, LVEF, LV end-diastolic volume, mitral regurgitation area, deceleration time, interventricular delay in all patients, irrespective of baseline QRS duration [77]. Similarly, preliminary reports from a multicenter study [98] and other studies [99,100] suggest that about half of the patients with a narrow QRS complex will benefit from CRT, and baseline QRS duration does not predict favorable response.

#### **Patients with RBBB as the qualifying wide QRS**

The majority of patients enrolled in major CRT trials (>85%) had either LBBB or nonspecific intraventricular conduction delay on the initial

echocardiogram. Patients with RBBB, therefore, were clearly underrepresented in these trials, and it would seem intuitively obvious that delayed RV activation with preserved LV activation would be unlikely to benefit from the placement of an LV pacing lead. In keeping with this, a recent meta-analysis suggested that except for NYHA functional class, patients with RBBB as the qualifying wide QRS did not show any improvement in objective measurements ( $\text{VO}_2$ , 6-min walk distance, LVEF, and norepinephrine levels) studied at 3 or 6 months [101]. However, as discussed above, the presence of an RBBB pattern on the echocardiogram does not mean that left bundle conduction is normal and that intraventricular conduction delays are often present in the failing LV. This is why some have argued that until prospective data are available, all patients with wide QRS complexes should be offered CRT according to current guidelines.

### **Limitations and complications**

Clinically, the success rate of transvenous LV lead placement is approximately 90% [102], although distortion of right atrial anatomy and severe tricuspid dilation/regurgitation from long-standing CHF can lead to difficulty in cannulation of the ostium of the coronary sinus (see Table 1.2). Vein branch size, presence of valves, venous tortuosity, or phrenic nerve stimulation may complicate or prevent LV lead deployment. Complications include infection, pneumothorax, bleeding, lead dislodgement, and dissection or perforation of the coronary venous system [103]. Coronary sinus or venous trauma is usually of little consequence, especially in patients with prior open heart surgery where the pericardial space is often obliterated, and usually allows successful completion of the procedure. Tamponade and death are rare [104].

Epicardial LV pacing, by reversing the normal endocardium-to-epicardium depolarization sequence, has raised theoretical concerns about proarrhythmia [105]. The QT interval, dispersion of refractoriness, and ventricular premature depolarization frequency were increased in one study with LV epicardial and biventricular pacing compared to RV pacing [106], and case reports have described torsade de pointes after CRT. However, other studies have demonstrated that

CRT is beneficial in reducing the dispersion of refractoriness compared to LV pacing alone [107]. In addition, analysis of the CONTAK CD and InSync ICD studies demonstrated no increase in polymorphic ventricular tachycardia in CRT patients [108]. Recent data from body surface mapping suggest that CRT improves transmural dispersion of repolarization [109].

### **Cost-effectiveness of CRT**

To understand the cost-effectiveness of resynchronization therapy, intent-to-treat data from the COMPANION trial were modeled to estimate the cost-effectiveness of CRT-D and CRT-P relative to optimal pharmacological therapy over a 7-year base-case treatment episode [110]. Exponential survival curves were derived from trial data and adjusted by quality-of-life trial results to yield quality-adjusted life years (QALYs). For the first 2 years, follow-up hospitalizations were based on trial data. The model assumed equalized hospitalization rates beyond 2 years. Initial implantation and follow-up hospitalization costs were estimated using Medicare data.

Over 2 years, follow-up hospitalization costs were reduced by 29% for CRT-D and 37% for CRT-P. Extending the cost-effectiveness analysis to a 7-year base-case time period, the ICER (incremental cost-effectiveness ratio) for CRT-P was \$19,600 per QALY and the ICER for CRT-D was \$43,000 per QALY relative to optimal pharmacological therapy. These results were slightly lower but consistent with data derived by Sanders et al. looking at eight studies of implantable cardioverter-defibrillation [111].

Thus, the use of CRT-P and CRT-D was associated with a cost-effectiveness ratio below generally accepted benchmarks for therapeutic interventions of \$50,000 per QALY to \$100,000 per QALY. This suggests that the clinical benefits of CRT-P and CRT-D can be achieved at a reasonable cost.

### **Recent advances, future directions, and conclusions**

Newer generations of CRT devices also provide important information regarding a patient's heart failure status. Indices such as average nighttime vs daytime heart rates and heart rate variability offer clues to a patient's clinical status. In addition,

measurement and trending of transthoracic impedance (resistance to current flow between the device and the RV lead) may be reasonably reflective of "lung wetness" [112]. Some devices have proprietary algorithms that may be useful in alerting physicians about impending worsening of heart failure, although preliminary data suggest that unfiltered shock impedance trends may also provide similar information [113].

As many as 40% of patients referred to heart failure and transplant clinicians meet the 2002 ACC/AHA/NASPE guidelines for biventricular pacing [114]. In the past 12 years, CRT has been convincingly shown to improve both the functional and symptomatic consequences of heart failure and also to effect beneficial structural changes in the failing ventricle. The mortality benefit accrued from CRT rivals that from proven pharmacologic interventions such as beta-blockade and ACE-inhibition [59]. The addition of defibrillation therapy provides an incremental improvement in survival, likely due to the reduction in sudden arrhythmic deaths. In the absence of optimal medical management the beneficial effects of resynchronization and defibrillation are blunted, highlighting the importance on continued optimal medical therapy [42]. Better tools are needed to identify which patients with heart failure have significant dyssynchrony. An effective method will allow for the recognition of patients with a "normal" QRS who would also benefit from CRT, and possibly guide electrophysiologists in selecting optimal LV pacing sites, as being studied in the RETHINQ trial [115]. When endovascular choices for lead positioning are limited by patient-specific anatomy, venoplasty or surgical epicardial lead placement remains an effective alternative [116]. Optimization of the AV interval and sequential LV–RV timing may improve the overall rate and degree of response.

The future is likely to see continued broadening of the patient populations selected for resynchronization therapy. It is hoped that QRS duration will be replaced by echocardiographic parameters of dyssynchrony as qualifying criteria for patient selection for resynchronization therapy. Initiation of resynchronization therapy at earlier stages of CHF may, by ending the negative cascade of events caused by electrical and mechanical dyssynchrony, prevent progression of disease.

In conclusion, the assessment of ventricular dyssynchrony should be part of the initial evaluation of patients presenting with systolic LV dysfunction. Patients with dyssynchrony should be offered CRT as an important adjunct to medical management, both for symptomatic improvement and for mortality benefit. Evidence of volumetric response, including improvement in EF and reduction of LV end-systolic volumes by >10%, should be considered as the primary goal of the treatment. With the improvement in operator experience and implantation tools, CRT can be safely performed percutaneously in nearly 95% of patients, and conservative estimates of its cost-effectiveness are on par with other lifesaving medical treatments such as hemodialysis.

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