Abstract

A variety of medical therapies are clinically proven to improve symptoms and mortality in heart failure patients. However, some patients remain symptomatic despite optimal medical therapy. A subset of these patients may demonstrate electrical dyssynchrony which may contribute to hemodynamic and clinical deterioration. This chapter reviews the pathophysiology and clinical assessment of dyssynchrony, the clinical indications for cardiac resynchronization therapy, and a description of the devices and programming features currently available to heart failure patients.

Key Words: Heart failure; Dyssynchrony; Resynchronization; Implantable defibrillator.
Heart failure (HF) affects nearly 5 million patients in the United States and over 500,000 new diagnoses are made each year. Over the past decade, the rate of hospitalizations for heart failure has increased by over 150% and mortality can be as high as 40% at 1 year with severely symptomatic heart failure (1, 2). Medicare spends more dollars for HF diagnosis and management than any other condition. Though multiple causes exist, the most common causes include coronary artery disease, hypertension, and idiopathic dilated cardiomyopathy (2–4).

A variety of medical therapies have been introduced to optimize chamber loading, neurohormonal activation, and correct cellular abnormalities. These therapies, which include angiotensin-converting-enzyme (ACE) inhibitors (5, 6), angiotensin-receptor antagonists (7–9), beta-blockers (10–15), spironolactone (16), and coronary bypass surgery (17, 18) have been shown in multiple, large, randomized controlled clinical trials to improve functional class and survival (Fig. 1). In addition to myocardial abnormalities, electrical abnormalities occur in patients with cardiomyopathies and may contribute to hemodynamic and clinical deterioration.
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Approximately one third of patients with a low LV ejection fraction and New York Heart Association Class III to IV HF manifest a QRS duration greater than 120 ms (2). Furthermore, the presence of a left bundle branch block (LBBB) has been associated with increased mortality in patients with HF (19).

1.2. Electrical Timing

Under normal circumstances, the LV contracts synchronously with less than 40 ms difference between timing of contraction of the various walls (20). This synchrony is important to maximize LV work performance. A segment of myocardium stimulated early is inefficient for chamber pumping function because little if any ejection of blood from the ventricle occurs with one segment contracting early. Late stimulation is wasted work as well because ejection will be compromised by the surrounding increased tension against which this contraction occurs and may affect other segments that are relaxing by exaggerating stretch (20, 21). Such may be the case with bundle branch block or single-site pacing (e.g., RV apical pacing). Interventricular dyssynchrony may involve similar mechanisms by its effects on the interventricular septum (22). Finally, atrioventricular coordination may contribute to sub-optimal ejection because of abnormal chamber filling and exacerbation of mitral regurgitation (20). The role then of cardiac resynchronization therapy (CRT) may include optimization of these three areas of mechanical abnormalities: atrioventricular delay, interventricular dyssynchrony, and intra-left ventricular dyssynchrony (Table 1).

Small studies have evaluated different programmed AV delays on various hemodynamic parameters (Fig. 2). While positive effects have been shown in some (23), including minimization of diastolic mitral regurgitation, other studies have failed to show any changes (24). One explanation for the lack of benefit was the obligate right ventricular pacing during programmed AV delays shorter than the patients’ baseline values.

<table>
<thead>
<tr>
<th>Dyssynchrony location</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrioventricular</td>
<td>Too short or too long an interval results in sub-optimal chamber filling and contributes to mitral regurgitation</td>
</tr>
<tr>
<td>Interventricular (RV/LV)</td>
<td>Part of the CRT response has been thought to be due to improvement in interventricular synchrony; QRS has been considered a marker</td>
</tr>
<tr>
<td>Intraventricular (LV septal/posterior)</td>
<td>Not all patients with wide QRS respond to CRT; dyssynchronous stimulation (e.g., LBBB or RV pacing) creates regions of early and late contraction</td>
</tr>
</tbody>
</table>
Correction of interventricular dyssynchrony has been considered to contribute to the response to CRT. The QRS duration has been identified as a marker of this abnormality and has been used to select patients for CRT (22). However, when LV dyssynchrony is assessed by tissue Doppler echocardiography, QRS duration may correlate poorly. In one study, the relation between QRS duration and LV dyssynchrony (assessed by tissue Doppler imaging [TDI] in 90 patients with severe HF and LVEF <35%) revealed that LV dyssynchrony on TDI in patients with QRS durations of <120 ms, 120–150 ms, or >150 ms was present in 27%, 60%, and 70% of patients, respectively (25). These results suggest that QRS duration as the sole measure of dyssynchrony would include patients who will not respond to therapy and exclude patients who might respond.

Nonetheless, the QRS duration is a marker of spatially dispersed mechanical activation and combining QRS information with imaging analysis of LV dyssynchrony (e.g., tissue Doppler echocardiography) may improve the ability to predict response to CRT (26).

1.3. CRT Compared with Other Methods of Increasing Cardiac Output (Inotropes)

Patients who do respond to CRT have improved systolic performance. A concern that has been raised is the long-term effect of such a therapy compared with other therapies that alter hemodynamic parameters in a similar manner, notably pressors and inotropes. While agents such as milrinone (27) have been shown to acutely improve systolic performance, long-term efficacy and safety may be compromised by the increased metabolic demands of such therapies. In a hemodynamic study comparing the effects of dobutamine and LV pacing on ventricular and aortic pressure and myocardial oxygen consumption investigators found that systolic function rose
substantially in both groups from LV pacing (43% and 37% increase in $dP/dt_{(max)}$ with LV pacing and dobutamine, respectively) (28). However, myocardial oxygen consumption was significantly different among the groups with a decline of 8% in the pacing group and an increase of 22% in the dobutamine group ($P < 0.05$).

### 1.4. Mitral Regurgitation

Patients being considered for CRT have dilated ventricles and reduced systolic function. Mitral regurgitation (MR) is commonly associated. Often the MR is a functional problem related to one or more of at least three mechanisms: annular dilation, altered tethering and contractile forces, and atrioventricular delay (20, 29–31). Though not considered a requirement for benefit from CRT, reduction of mitral regurgitation is an additional hemodynamic and clinical advantage.

Remodeling of the LV is a dynamic process which includes myocyte hypertrophy, fibrosis and deposition of extracellular matrix, and cellular necrosis and apoptosis. On the macroscopic level, LV dilation occurs and the chamber becomes more spherical. The remodeling process, which is an adaptation to preserve stroke volume, however, over time, causes loss of contractility and secondary MR (32). Among the clinical and hemodynamic benefits of CRT, a reverse of this remodeling process has been observed with an 8–15% reduction in LV end-diastolic dimension and a 4–7% increase in LV ejection fraction (1, 33).

Separate from improving chamber geometry, functional mitral regurgitation has been shown to be reduced by CRT in patients with HF and LBBB by altering contractile forces. By directly increasing the left ventricular $dP/dt$ and thus the transmitral pressure gradient, the mitral valve effective regurgitant orifice area is reduced (31).

Too short or too long of an AV interval can contribute to MR. During long AV intervals, the mitral valve may attain an open configuration in late diastole, which may lead to regurgitation early in systole (34). Optimizing the AV interval may mitigate this risk.

### 1.5. LV vs. BiV Pacing

Biventricular (BiV) and LV pacing result in different electrical activation and may provide different results in hemodynamic and clinical end points. Various investigators have tested the hypothesis that LV pacing alone confers the same benefit as BiV pacing despite the different electrical activation patterns. While larger clinical trials are ongoing, several of these studies have suggested that mechanical synchronization can be achieved equally with either approach (35–37).
2. IMAGING MODALITIES TO IDENTIFY PATIENTS

2.1. Echocardiography

Echocardiography is the most often used tool to evaluate dyssynchrony, and various echocardiographic techniques can be used for this purpose (38). Using M-mode echocardiography, time to peak contraction can be evaluated separately for the septal and posterior walls when the left ventricle is imaged in the parasternal short axis. The difference in timing has been used to identify intraventricular dyssynchrony. A septal to posterior difference of >130 ms has been proposed as a discriminator (39). However, this value has not been validated in other studies (40). Two-dimensional echocardiography has been evaluated to assess for dyssynchrony, but use of this technique has been largely supplanted by tissue Doppler imaging.

Tissue Doppler imaging (TDI) measures the velocity of contracting myocardial segments and allows relative timing of different left ventricular segments to be compared to the QRS and to each other. The necessary software is available in most echocardiographic packages. Specialized training is often required. Frequently, the time to peak systolic velocity is assessed. In one study, when the time to peak velocity was measured in the basal septal and lateral walls, a delay of ≥60 ms was considered predictive of a response to CRT (41). In a four-segment model (septal, lateral, inferior, and anterior) ≥65 ms delay was shown to predict response to CRT (42). Tissue synchronization imaging is a color-coded method to detect peak velocity and time to peak velocity based on tissue Doppler information. This technique tracks left ventricular segments from the time of aortic valve opening to the echocardiographic E wave.

The Predictors of Response to CRT (PROSPECT) trial evaluated 12 different echocardiographic parameters of dyssynchrony at 53 centers in 498 patients (43). The ability of the 12 echocardiographic parameters to predict clinical response varied widely with sensitivity of the parameters ranging from 6% to 74% and the specificity ranging from 35% to 91%. There was large variability in the analysis of the dyssynchrony parameters and it was concluded that no single echocardiographic measure of dyssynchrony may be recommended to improve patient selection for CRT beyond current guidelines.

2.2. Other Imaging Techniques

Other imaging modalities have been used to support echocardiographic findings and add additional information. Nuclear and magnetic resonance imaging can be used for identification of non-viable myocardium (scar) that may be unsuitable for pacing. Computed tomographic and magnetic resonance angiography has been used to define coronary sinus anatomy prior to implantation procedures (Fig. 3). A summary of various imaging modalities is presented in Table 2.
Fig. 3. Panels a–d demonstrate coronary sinus (CS) anatomy including posterior (PostV) and lateral (LatV) branches. The right coronary artery (RCA) is shown as well.

3. CLINICAL EVIDENCE

3.1. Trials

Based on the results of smaller CRT studies that evaluated hemodynamic and echocardiographic end points, a number of large randomized, clinical trials in CRT have been reported (44–52). These trials have evaluated both functional and hard end points such as mortality and hospitalization for HF and form the basis for selecting candidates for CRT.

The Multisite Stimulation in Cardiomyopathy (MUSTIC) was a single-blinded randomized trial to examine CRT in HF (47). In this study, 67 patients with sinus rhythm, a QRS duration greater than 150 ms, and New York Heart Association Class III HF due to left ventricular systolic dysfunction (LV ejection fraction < 0.35 and end-diastolic diameter > 6.0 cm) had BiV pacemakers implanted. The study was a single-blind, randomized,
controlled crossover study and compared patient responses during 3 months of inactive pacing with 3 months biventricular pacing. The primary end point was the distance walked in 6 min and secondary end points included quality of life, peak oxygen consumption, hospitalizations for HF, and mortality rate. Of the 48 patients who completed both study phases, the mean distance walked in 6 min was 23% greater with active pacing, quality of life improved, peak oxygen uptake increased by 8%, and hospitalizations decreased by two thirds. Active pacing was preferred by 85% of the patients.

The Pacing Therapies in Congestive Heart Failure (PATH-CHF) study enrolled 41 patients with New York Heart Association Class III or IV symptoms for >6 months prior to enrollment, dilated cardiomyopathy of any etiology, sinus rhythm ≥55 beats/min, a QRS ≥120 ms, and a PR interval ≥150 ms. These patients received two pacemakers. The first was attached to a right atrial and right ventricular lead (both placed transvenously) and the second was attached to a right atrial lead (placed transvenously) and an LV epicardial lead (via thoracotomy). At implantation, hemodynamic testing was performed to select the optimal univentricular stimulation (LV or RV) and to determine the best AV delay as determined by the maximum rate of change in LV pressure and aortic pulse pressure. Patients were randomized to 4 weeks of univentricular or biventricular stimulation followed by 4 weeks of no treatment and then the opposite stimulation for another 4 weeks. The primary end points were measurements of exercise capacity. In 36 of 41, the LV was the optimal univentricular pacing site. The investigators found
an improvement in 6 min walking distance and peak oxygen uptake over the course of the study and noted that clinical differences between hemodynamically optimized biventricular and univentricular (predominantly LV) resynchronization methods were not significant.

The Pacing Therapies in Congestive Heart Failure II (PATH-CHF II) study evaluated single-site LV pacing compared with no pacing and focused on the impact of baseline conduction delay. This trial enrolled 86 patients with New York Heart Association Class II CHF or worse, an LV ejection fraction of <0.3, sinus rhythm, and a QRS $\geq 120$ ms. Investigators stratified patients by the baseline QRS interval into long (QRS >150 ms) and short (QRS 120–150 ms) groups. The groups were either paced or unpaced for 3 months and then crossed over to the other group for 3 months. The primary end point included peak oxygen consumption and distance walked in 6 min. The short QRS group did not improve in any end point with active pacing, while the long QRS group had an increase in peak oxygen consumption and distance walked in 6 min. This trial helped establish that patients with a longer QRS (i.e., >150 ms) derived the most benefit from LV pacing.

The Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial was a prospective, randomized, double-blind trial that evaluated 453 patients with moderate-to-severe symptoms of heart failure who had a LV ejection fraction <0.35 and a QRS interval of $\geq 130$ ms (44). All of the patients who had a successful biventricular pacemaker implantation (92%) were then randomized to CRT or to optimal medical therapy for 6 months. The primary end points were New York Heart Association functional class, quality of life, and the distance walked in 6 min. The patients in the CRT group had a significant improvement in the 6-min walk test (+39 m vs. +10 m), in functional class and quality of life, and in LV ejection fraction (+4.6% vs. –0.2%). A secondary end point was hospitalization for HF, and fewer patients in the CRT group required hospitalization (8% vs. 15%). Of note, 6 patients had major complications including death, refractory hypotension, bradycardia, and perforation of the coronary sinus requiring pericardiocentesis. Based on this study, the Medtronic InSync system was approved by the US Food and Drug Administration (FDA).

The Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE-ICD) trial was a prospective, randomized, double-blind trial designed similarly to the MIRACLE trial and included 369 patients with an indication for an ICD including cardiac arrest due to a ventricular tachyarrhythmia or to a spontaneous or induced sustained ventricular tachyarrhythmia. In both groups, the ICD was programmed on, but CRT was assigned randomly. Though functional class improved in the CRT group, there was no difference in the 6-min walk test between the groups nor was there a difference in LV ejection fraction, hospitalization for HF, survival, or proarrhythmia. Based on this study, the FDA approved the CRT–ICD device from this study.
The Cardiac Resynchronization Therapy for the Treatment of Heart Failure in Patients with Intraventricular Conduction Delay and Malignant Ventricular Tachyarrhythmias (CONTAK CD) trial randomized 490 patients with New York Heart Association Class II to IV HF, an LV ejection fraction ≤0.35, QRS interval ≥120 ms, and an indication for an ICD to CRT therapy programmed on or off for 6 months (51). Patients were excluded if they had atrial tachyarrhythmias or had an indication for a permanent pacemaker. The primary end point was HF progression (defined as all-cause mortality, HF hospitalization, or ventricular tachyarrhythmias requiring device intervention). The study’s secondary end points included peak oxygen consumption, distance walked in 6 min, New York Heart Association class, and quality of life. Though the primary end point was not statistically significantly different (approximately 15% lower in both groups), 6-min walk improved, LV ejection fraction improved, and LV dimension reduction occurred in the CRT-treated patients. The patients with Class III–IV HF had improvement in all of the functional end points.

The Cardiac Resynchronization Therapy with or without an Implantable Defibrillator in Advanced Chronic Heart Failure (COMPANION) trial tested the hypothesis that CRT with or without a defibrillator would reduce the risk of death and hospitalization among patients with advanced HF and intraventricular conduction delays (49). Patients included had New York Heart Association Class III or IV heart failure resulting from either infarct-related or nonischemic causes, were hospitalized in the preceding 12 months, had an LV ejection fraction of ≤0.35, a QRS ≥120 ms, a PR interval ≥150 ms, sinus rhythm, and no clinical indication for a pacemaker or implantable defibrillator. In a 1:2:2 ratio, 1520 patients were assigned to medical therapy only, CRT with an ICD and CRT without an ICD. The primary end point was death or hospitalization for any cause. Implantation was successful in 87% of the patients in the pacemaker group and 91% of the patients in the ICD group. Both CRT groups had an approximately 20% reduction in annual risk of the primary end point. The 1-year mortality rate in the pharmacologic therapy group was 19%. In the CRT group without an ICD there was a 24% reduction (P = 0.06) and in the CRT group with an ICD there was a 36% reduction (P = 0.003). This large trial showed that CRT with or without an ICD reduced death or hospitalization.

The Effect of Cardiac Resynchronization on Morbidity and Mortality in Heart Failure (CARE-HF) study was designed to evaluate the effect of CRT without an ICD on morbidity and mortality in patients with New York Heart Association Class III or IV HF despite optimal medical therapy, with an LV ejection fraction ≤0.35, with an LV end-diastolic dimension ≥3.0 cm (indexed to height), and with a QRS ≥120 ms (46). A unique feature of this trial was that patients with a QRS 120–149 ms were required to meet two of three additional echocardiographic criteria for dyssynchrony. These criteria were an aortic prejection delay of >140 ms, an interventricular mechanical delay of >40 ms, and delayed activation of the posterolateral
LV wall. The primary end point was death from any cause or hospitalization for a cardiovascular event. Death from any cause was a secondary end point. Patients were followed for an average of 29.4 months. Among the 813 patients enrolled, 55% in the medical therapy arm reached the primary end point while 36% reached it in the CRT arm ($P < 0.001$). There was a 30% mortality rate in the medical therapy arm and a 20% mortality rate in the CRT arm ($P < 0.002$). Of note, CRT reduced the end-systolic volume index and mitral regurgitant volume and increased the LV ejection fraction. A summary of the patient characteristics, QRS findings, and principle results are noted in Tables 3, 4, and 5.

Table 3  
Patient characteristics in selected cardiac resynchronization trials

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Number of patients</th>
<th>NYHA class</th>
<th>LVEF</th>
<th>LVEDD (cm)</th>
<th>Cardiomyopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUSTIC (2001)</td>
<td>67</td>
<td>III</td>
<td>0.23</td>
<td>7.3</td>
<td>n/a</td>
</tr>
<tr>
<td>MIRACLE (2002)</td>
<td>453</td>
<td>III, IV</td>
<td>0.22</td>
<td>6.9</td>
<td>IRC: 50–58%</td>
</tr>
<tr>
<td>PATH-CHF (2002)</td>
<td>42</td>
<td>III, IV</td>
<td>0.21</td>
<td>7.3</td>
<td>IRC: 29%</td>
</tr>
<tr>
<td>CONTAK-CD (2003)</td>
<td>490</td>
<td>II, III, IV</td>
<td>0.21</td>
<td>7.1</td>
<td>IRC: 67–71%</td>
</tr>
<tr>
<td>MIRACLE-ICD (2003)</td>
<td>369</td>
<td>III, IV</td>
<td>0.24</td>
<td>7.6</td>
<td>IRC: 64–74%</td>
</tr>
<tr>
<td>PATH-CHF II (2003)</td>
<td>101</td>
<td>II, III, IV</td>
<td>0.23</td>
<td>n/a</td>
<td>CAD: 24–44%</td>
</tr>
<tr>
<td>COMPANION (2004)</td>
<td>1520</td>
<td>III, IV</td>
<td>0.22</td>
<td>6.7</td>
<td>IRC: 55–59%</td>
</tr>
<tr>
<td>CARE-HF (2005)</td>
<td>813</td>
<td>III, IV</td>
<td>0.25</td>
<td>n/a</td>
<td>IRC: 43–48%</td>
</tr>
</tbody>
</table>

IRC, infarct-related cardiomyopathy; DCM, dilated cardiomyopathy; CAD, coronary artery disease

3.2. Patient Characteristics/Subsets

Notable characteristics of patients enrolled in CRT trials include LV ejection fractions substantially lower than 0.35, enlarged LV end-diastolic dimensions (frequently $> 6.0$ cm), similar benefits in patients with infarct-related and dilated cardiomyopathies, and QRS durations considerably longer than 120 ms (frequently $> 160$ ms and predominantly LBBB).

Within the CARE-HF population, age, sex, cause of cardiomyopathy, and LV ejection fraction did not discriminate responders from non-responders. However, patients with New York Heart Association Class III HF, a QRS $\geq 160$ ms, an echocardiographic interventricular mechanical delay
Table 4
QRS morphology in selected cardiac resynchronization trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean QRS (ms)</th>
<th>Morphology</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUSTIC</td>
<td>175</td>
<td>87% LBBB</td>
</tr>
<tr>
<td>MIRACLE</td>
<td>165</td>
<td>Not stated</td>
</tr>
<tr>
<td>PATH-CHF</td>
<td>175</td>
<td>93% LBBB, 7% RBBB</td>
</tr>
<tr>
<td>CONTAK-CD</td>
<td>160</td>
<td>54% LBBB, 32% IVCD, 14% RBBB</td>
</tr>
<tr>
<td>MIRACLE-ICD</td>
<td>165</td>
<td>13% RBBB</td>
</tr>
<tr>
<td>PATH-CHF II</td>
<td>155</td>
<td>88% LBBB</td>
</tr>
<tr>
<td>COMPANION</td>
<td>160</td>
<td>70% LBBB, 10% RBBB</td>
</tr>
<tr>
<td>CARE-HF</td>
<td>160</td>
<td>Not stated</td>
</tr>
</tbody>
</table>

LBBB = left bundle branch block; RBBB = right bundle branch block; IVCD = intraventricular conduction delay

≥ 49.2 ms, and/or a mitral regurgitation area ≥0.22 had statistically significant benefit from CRT when these cutoffs were used (46). In the COMPANION study, patients with NYHA Class IV HF had a significant reduction in death rate compared with NYHA Class III patients. The same was true for those with LV ejection fractions ≤ 0.2 (compared with > 0.2), QRS ≥148 ms (compared with < 147 ms), and LBBB (compared with other conduction delays) (49).

3.3. QRS Morphology

The majority, but not the entirety, of patients included in the major clinical CRT trials had LBBB. While no trials have prospectively compared non-LBBB QRS morphology with LBBB morphology, retrospective analysis has been performed on patients with RBBB. In an analysis of the patients with RBBB in the MIRACLE and CONTAK CD trials, there were trends toward improvement in 6-min walk distance, quality-of-life scores, and norepinephrine levels, but they were not statistically significant (53). These investigators did note an improvement in NYHA HF, however, control patients also showed significant improvement in NYHA class. These researchers concluded that CRT therapy in patients with RBBB was not
<table>
<thead>
<tr>
<th>Study</th>
<th>Findings</th>
<th>All-cause mortality or HF hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUSTIC</td>
<td>Improved 6-min walk with CRT</td>
<td>N/A</td>
</tr>
<tr>
<td>MIRACLE</td>
<td>Improved quality of life, NYHA class, and 6-min walk</td>
<td>20% Med Rx</td>
</tr>
<tr>
<td>PATH-CHF</td>
<td>No significant differences between hemodynamically optimized biventricular</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>and univentricular (predominantly LV) resynchronization</td>
<td></td>
</tr>
<tr>
<td>CONTAK-CD</td>
<td>Improved 6-min walk with CRT but no difference in NYHA class or peak</td>
<td>38% Med Rx</td>
</tr>
<tr>
<td></td>
<td>oxygen consumption</td>
<td>32% CRT-D</td>
</tr>
<tr>
<td>MIRACLE-ICD</td>
<td>Improved quality of life, NYHA class, and peak oxygen consumption with</td>
<td>26% Med Rx</td>
</tr>
<tr>
<td></td>
<td>CRT-D</td>
<td>26% CRT-D</td>
</tr>
<tr>
<td>PATH-CHF II</td>
<td>QRS &gt;150 ms group (but not QRS 120–150 ms group) had an increase in peak</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>oxygen consumption and 6-min walk compared to no pacing</td>
<td></td>
</tr>
<tr>
<td>COMPANION</td>
<td>Both CRT-P and CRT-D had significant reduction in all-cause mortality and</td>
<td>45% Med Rx</td>
</tr>
<tr>
<td></td>
<td>hospitalization compared to Med Rx (improved survival only seen in CRT-D)</td>
<td>31% CRT-P</td>
</tr>
<tr>
<td></td>
<td></td>
<td>29% CRT-D</td>
</tr>
<tr>
<td>CARE-HF</td>
<td>Improved survival in CRT group and improved LVEF, chamber dimensions, and</td>
<td>33% Med Rx</td>
</tr>
<tr>
<td></td>
<td>quality of life compared to Med Rx</td>
<td>18% CRT-P</td>
</tr>
</tbody>
</table>

HF = heart failure; CRT = cardiac resynchronization therapy; N/A = not available; NYHA = New York Heart Association Classification; Med Rx = medical treatment; CRT-P = cardiac resynchronization therapy with pacing only; CRT-D = cardiac resynchronization therapy with defibrillation.

supported by available data. Others have postulated that echocardiographic evaluation is superior to QRS duration in selecting patients for CRT (54–56). In small studies, patients with narrow QRS duration (<120 ms) with echocardiographic dyssynchrony were found to derive equal benefit from CRT as their counterparts with similar echocardiographic dyssynchrony but prolonged QRS duration. The Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS (RethinQ) study was a double-blind clinical trial evaluating the efficacy of CRT in patients with a standard indication for an ICD (ischemic or nonischemic cardiomyopathy and an ejection fraction of 35% or less), NYHA Class III heart failure, a QRS interval of less than 130 ms, and evidence of mechanical dyssynchrony as measured.
on echocardiography (57). In a prespecified subgroup with a QRS interval of 120 ms or more, the peak oxygen consumption increased in the CRT group \((P = 0.02)\), but it was unchanged in a subgroup with a QRS interval of less than 120 ms \((P = 0.45)\). There were 24 heart failure events requiring intravenous therapy in 14 patients in the CRT group (16.1%) and 41 events in 19 patients in the control group (22.3%), but the difference was not significant. The study authors concluded that CRT did not improve peak oxygen consumption in patients with moderate-to-severe heart failure, providing evidence that patients with heart failure and narrow QRS intervals may not benefit from CRT.

### 3.4. Atrial Fibrillation

Although most clinical trials have excluded patients with atrial fibrillation, atrial fibrillation is a common arrhythmia in patients with heart failure occurring in up to 50% of patients with advanced HF (58). Small studies have examined the use of CRT in this patient population and have reported functional benefit (59–61). Concomitant performance of an atrioventricular junctional ablation to ensure >85% biventricular pacing may improve results compared to use of CRT in patients with native conduction (59).

### 3.5. Cost-Effectiveness

While device implantation is expensive, improved survival and functional improvement may offset these costs. A cost-effective analysis was performed on the COMPANION patient population. Investigators noted that the incremental cost of CRT therapy with or without an ICD was within accepted benchmarks cost-effectiveness (62). However, when comparing CRT without a defibrillator to CRT with an ICD, the additional cost may be substantial (63). In the absence of a head-to-head trial, the true cost-effectiveness cannot be determined.

The American Heart Association issued a science advisory based on the published clinical trials incorporating the results into a statement about patient selection for CRT (Table 6) (64).

### 4. HARDWARE

#### 4.1. Leads and Delivery Systems

Essential to transvenous placement of a lead for left ventricular pacing is cannulation of the coronary sinus. A variety of techniques and aids have been developed to facilitate gaining access to the coronary sinus including the use of guidewires, guiding sheaths, sub-selective sheaths (used within the guiding sheath to direct the guidewire into the coronary sinus), and steerable catheters/sheaths.
Table 6
Patient selection for cardiac resynchronization therapy

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus rhythm</td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>≤0.35</td>
</tr>
<tr>
<td>Infarct-related or idiopathic dilated cardiomyopathy</td>
<td></td>
</tr>
<tr>
<td>QRS duration</td>
<td>≥120 ms</td>
</tr>
<tr>
<td>NYHA functional Class III or IV</td>
<td></td>
</tr>
<tr>
<td>Maximal pharmacologic therapy for CHF</td>
<td></td>
</tr>
</tbody>
</table>

Each major CRT device manufacturer has accessories designed to facilitate LV lead placement (Fig. 4). Medtronic Attain™ system includes preformed shaped catheters that can be integrated with soft-tipped subselective telescoping catheters to engage the coronary sinus and its branches. The Boston Scientific system (Guidant RAPIDO™) contains an outer guide catheter that is used to cannulate the coronary sinus, while inner catheters may be used to facilitate branch vessel selection. The St. Jude Medical lead delivery system offers various different preformed shaped catheters to account for variable cardiac and coronary sinus anatomy.

4.2. Technical Considerations

Once in place, occlusive coronary sinus venography is frequently performed to identify potential target branches. A variety of leads are available to match branch anatomy and increase the chance of acute successful placement and secure longevity. Specific considerations include size, lead delivery, lead shape, fixation, and pacing electrode polarity (Table 7).

Choosing the appropriate lead requires knowledge of the target vessel size and matching the vessel size with the pacing electrode. Unipolar leads tend to be narrower in diameter. A number of over-the-wire leads are available for CS pacing (Table 8).

Initially, LV leads were placed via stylet-driven systems. The development of LV pacing leads that could be placed via an over-the-wire technique facilitated lead placement and improved rates of successful LV lead placement. The technique uses a guiding wire (ranging from softer to stiffer compositions depending on the clinical need) to cannulate a target vein and serve as the guide for advancement of the pacing electrode.

Lead shape is often an additional consideration to ensure stability and appropriate lead orientation (Fig. 5). Leads with varying tip angulation and preformed curves (S curve and corkscrew configurations) are available. Generally, large veins require larger curved leads and smaller, tortuous veins may require smaller caliber leads for stability. Because LV pacing electrodes sit within vein branches and not directly on atrial or ventricular endocardium, fixation is passive. Some leads, however, do contain tines to increase stability by wedging within the target vessel.
Fig. 4. A variety of sheaths and LV lead delivery systems are displayed. (A) Medtronic Attain Select Guide Catheters; (B) Medtronic Attain Deflectable Catheter Delivery System; (C) Medtronic Prevail Steerable Catheter; (D) Boston Scientific (Guidant) Rapido Dual-Catheter System; (E) St. Jude Medical Cardiac Positioning System.

Inability to successfully place a lead in the desired coronary sinus branch occurs occasionally and lead dislodgement may occur in up to 12% of patients despite initial successful placement (38, 44, 46, 47). When biventricular pacing is desired but transvenous lead placement is unattainable, surgical LV lead placement remains an option. Epicardial leads are
Table 7
LV Lead selection factors

<table>
<thead>
<tr>
<th>Size</th>
<th>Lead delivery</th>
<th>Lead shape</th>
<th>Fixation</th>
<th>Pacing electrode polarity</th>
<th>Coronary sinus anatomy</th>
</tr>
</thead>
</table>

available in unipolar or bipolar configurations and attach by active fixation. These leads are typically implanted in pairs to ensure pacing if one fails.

4.3. Devices

4.3.1. Pacing Configurations

Pacemakers and ICDs designed to deliver biventricular pacing offer a multitude of programming options to support optimal delivery of therapy. Programmable parameters include pacing polarity, algorithms to maximize biventricular pacing, and functions to assure pacing with an adequate pacing threshold.

Not all devices offer all possible pacing configurations. In addition, choices may be limited by the LV lead implanted (unipolar vs. bipolar, for example) or by the patient’s anatomy (for example, if the tip electrode paces adequately but the proximal ring electrode of a bipolar lead has a high threshold or does not capture due to cardiac scar). In general, most modern CRT devices offer a variety of pacing configurations. The advantage of this is the potential to minimize pacing threshold to conserve battery life and avoid diaphragmatic capture. For example, some CRT-D devices offer three LV pacing polarities when a bipolar lead is implanted: LV tip to RV coil, LV tip to LV ring, and LV ring to RV coil. In many cases, the RV–LV timing is adjustable such that pacing one chamber can be programmed to precede the other by up to 80 ms (see below). Many devices also include algorithms to automatically optimize A-V and V-V intervals, based on data extracted from clinical trials and echo-guided substudies.

4.3.2. Maximizing LV Pacing

At its most basic, CRT devices sense the intrinsic atrial depolarization and then deliver timed signals to the right and left ventricles resulting in coordinated, atrial synchronous biventricular pacing. A variety of arrhythmias can undermine the devices ability to perform in this manner, including atrial fibrillation and ventricular ectopic beats. Because these arrhythmias often
Table 8
Selected over-the-wire leads available for coronary sinus pacing

<table>
<thead>
<tr>
<th>Lead</th>
<th>Connector/polarity</th>
<th>Maximum body and tip diameter (French)</th>
<th>Length (cm)</th>
<th>Insulation</th>
<th>Fixation/shape</th>
</tr>
</thead>
<tbody>
<tr>
<td>4193 Attain (Medtronic)</td>
<td>IS-1 Unipolar</td>
<td>(tip 5.4)</td>
<td>78, 88, 103</td>
<td>Polyurethane (55D)</td>
<td>Canted tip</td>
</tr>
<tr>
<td>4194 Attain (Medtronic)</td>
<td>IS-1 Bipolar</td>
<td>6.0 (tip 5.4)</td>
<td>78, 88</td>
<td>Polyurethane (55D)</td>
<td>Canted tip</td>
</tr>
<tr>
<td>1056 K Quicksite (St. Jude Medical)</td>
<td>IS-1 Unipolar</td>
<td>6.0 (tip 5.0)</td>
<td>75, 86</td>
<td>Polyurethane, Silicone</td>
<td>Blunt tip 8 mm S-curve</td>
</tr>
<tr>
<td>1056T Quicksite (St. Jude Medical)</td>
<td>IS-1 Bipolar</td>
<td>6.0 (tip 5.0)</td>
<td>75, 86</td>
<td>Polyurethane, Silicone</td>
<td>Blunt tip 8 mm S-curve</td>
</tr>
<tr>
<td>1058T Quicksite (St. Jude Medical)</td>
<td>IS-1 Bipolar</td>
<td>6.0 (tip 5.0)</td>
<td>75, 86</td>
<td>Polyurethane, Silicone</td>
<td>Blunt tip 16 mm S-curve</td>
</tr>
<tr>
<td>4510, 4511, 4512, 4513 Easytrak</td>
<td>LV-1 Unipolar</td>
<td>6.0 (tip 4.8)</td>
<td>65, 72, 80, 90</td>
<td>Polyurethane</td>
<td>Tined</td>
</tr>
<tr>
<td>4537, 4538 Easytrak (Boston Scientific)</td>
<td>IS-1 Unipolar</td>
<td>6.0 (tip 4.8)</td>
<td>80, 90</td>
<td>Polyurethane, Silicone</td>
<td></td>
</tr>
<tr>
<td>4515, 4517, 4518, 4520 Easytrak2</td>
<td>LV-1 Bipolar</td>
<td>6.0 (tip 5.7)</td>
<td>65, 80, 90, 100</td>
<td>Polyurethane, Silicone</td>
<td>Tined</td>
</tr>
<tr>
<td>4542, 4543, 4544 Easytrak2 (Boston Scientific)</td>
<td>IS-1 Bipolar</td>
<td>6.0 (tip 5.7)</td>
<td>80, 90, 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4522, 4524, 4525, 4527 Easytrak3</td>
<td>LV-1 Bipolar</td>
<td>6.0 (tip 5.8)</td>
<td>65, 80, 90, 100</td>
<td>Polyurethane, Silicone</td>
<td>Pigtail</td>
</tr>
<tr>
<td>4548, 4549, 4550 Easytrak3 (Boston Scientific)</td>
<td>IS-1 Bipolar</td>
<td></td>
<td>80, 90, 100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
occur in patients with heart failure, algorithms have been designed to maximize the frequency of biventricular pacing in order to deliver the greatest therapeutic benefit to patients.

For example, patients who develop atrial fibrillation may stop LV pacing due to an intrinsic conducted ventricular rate greater than the lower programmed pacing rate of the device. This would result in the absence of LV pacing and loss of therapeutic benefit. Many devices now may be programmed to trigger LV pacing upon sensing of an intrinsic RV signal. This can restore (at least partially) resynchronization of the RV and LV pacing and may be utilized during atrial fibrillation or periods of ventricular ectopy. It should be noted, however, that in some patients LV pacing may be proarrhythmic and increase the frequency of ventricular events.

4.3.3. Other Diagnostics

Several additional diagnostic options have been incorporated into many modern CRT devices in an effort to better monitor heart failure status. While the precise methodology and function of these additional features varies from manufacturer to manufacturer and device to device, each attempts to provide some physiologic measurement of the patient’s clinical status. For example, Medtronic’s OptiVol system measures intrathoracic impedance using an electrical impulse vector between the RV lead and the CRT generator, which has been shown to correlate with the patient’s overall volume status. Some Boston Scientific devices offer an autonomic balance monitor, heart rate variability counter, and an activity log to assist in patient clinical
4.4. CRT Defibrillators vs. CRT Pacemakers

Because most patients who meet guideline criteria for CRT devices also meet criteria for implanted defibrillators, CRT devices without defibrillation capability (CRT-P) are implanted much less often. The most common reasons for selection of a CRT-P rather than a CRT-D device are (1) patient and physician preference to avoid defibrillator shocks and (2) the desire to improve quality but not necessarily quantity of life. That being said, well-conducted clinical trials suggest that resynchronization therapy, even in the absence of defibrillation improves survival in appropriately selected patients. Each of the major device manufacturers that offers CRT-D also offer devices that deliver CRT-P with defibrillation.

5. TROUBLESHOOTING/OPTIMIZATION

Hemodynamic and clinical changes can be anticipated in patients implanted with CRT devices. Hemodynamic changes include increased cardiac output, increased systolic blood pressure, decreased pulmonary capillary wedge pressure, and decreased chamber size (65, 66). Clinical changes include improvement in New York Heart Association Heart Failure class, improved 6-min walk tests, fewer hospitalizations, and improved survival (44, 46). Some patients notice improvement within a few days, others feel improvement after several months, and still others notice no change or progression of symptoms. When HF symptoms persist, however, a series of troubleshooting steps should be employed to optimize the device function (Fig. 6).

Routine follow-up is required for every patient with an implantable device, and a number of specific issues should be addressed in patients with CRT devices. The patient’s symptoms, volume status, heart rhythm, comorbidities, and medications should be evaluated (66). When ischemia, a volume abnormality (i.e., fluid overload or hypovolemia), supraventricular tachycardia, or other important clinical developments are noted, these conditions merit specific and often immediate attention.

5.1. ECG Patterns

A 12-lead electrocardiogram (ECG) is a simple, inexpensive test that can assess the presence or absence of appropriate biventricular pacing. In patients with an R/S ratio $\geq 1$ in lead VI and an R/S ratio $\leq 1$ in lead I, biventricular pacing can be confirmed with a sensitivity of 94% and a specificity of 93% (Fig. 7) (67). Confirming ECG findings with device interroga-
Fig. 6. An algorithm for the approach to clinical management of patients with cardiac resynchronization devices (CRT) is shown. For patients that respond well to therapy, routine follow-up are advised. Further clinical assessment and additional testing or device optimization may be warranted for non-responders (44).

5.2. AV Optimization

When patients continue to have clinical HF symptoms despite adequate device function, pacing parameters should be reviewed for optimal programming (66). In particular, atrioventricular (AV) and interventricular (VV) timing should be carefully reviewed. Lack of atrioventricular coordination may contribute to sub-optimal ejection due to abnormal chamber filling and exacerbation of mitral regurgitation (21). Several techniques to adjust AV delay to maximize left ventricular performance have been described (Table 9)
Fig. 7. Twelve-lead electrocardiograms (ECG) are shown for a single patient during (a) RV only pacing, (b) RV and LV simultaneous pacing, and (C) LV only pacing. If an R/S ratio ≥ 1 is present in lead VI and an R/S ratio ≤ 1 is present in lead I, then biventricular pacing can be confirmed with a sensitivity of 94% and a specificity of 93%.

A common and practical method uses echocardiography to measure continuous wave Doppler flow across the mitral valve to examine the E and A waves. The AV delay is set as short as possible without truncating the A wave. This method minimizes isovolumic contraction time during which diastolic mitral regurgitation can occur. By allowing full inscription of the A wave, full contribution of atrial contraction to ventricular filling can occur. With any of the described techniques to optimize AV timing, echocardiog-
Table 9
Selected methods of AV optimization

<table>
<thead>
<tr>
<th>Method</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic velocity time integral (VTI) method:</td>
<td>Optimized AV delay may increase in aortic VTI more than mitral inflow method</td>
</tr>
<tr>
<td>Maximum increase aortic VTI using</td>
<td></td>
</tr>
<tr>
<td>continuous wave Doppler</td>
<td></td>
</tr>
<tr>
<td>Mitral inflow method:</td>
<td>Requires visualization of A wave</td>
</tr>
<tr>
<td>Shortest AV delay that does not compromise</td>
<td></td>
</tr>
<tr>
<td>the transmitral A wave using</td>
<td></td>
</tr>
<tr>
<td>continuous wave Doppler</td>
<td></td>
</tr>
<tr>
<td>Left Ventricular dP/dt method:</td>
<td>Requires mitral regurgitation</td>
</tr>
<tr>
<td>Initial downslope of mitral regurgitation</td>
<td></td>
</tr>
<tr>
<td>jet using continuous wave Doppler</td>
<td></td>
</tr>
</tbody>
</table>

raphy (or another mode of hemodynamic monitoring) is requisite. Reports have suggested improvement in the aortic velocity time integral of up to 19% and an increase in LV ejection fraction by up to 5% (69, 70).

5.3. VV Optimization

Because most modern CRT devices permit programming of variable V-V (right ventricular stimulation to left ventricular stimulation) timing, the opportunity exists to optimize an individual patient’s programming. One method measures continuous Doppler flow across the aortic valve at different programmed V-V settings to determine the maximum velocity time integral as a correlate of stroke volume. Some investigators have noted improvement in LV ejection fraction of up to 8% while others have noted no change from empiric simultaneous RV and LV pacing (71, 72). Of note, in one study, 50% of patients benefited from RV pacing prior to LV pacing while the other 50% benefited from the reverse timing (73).

5.4. Additional Evaluation

When HF persists despite optimized volume status, exclusion of arrhythmias and ischemia, adequate device function, and optimized timing settings, repeat evaluation for dyssynchrony can be considered (66). If dyssynchrony is present then LV lead revision may be necessary either via the transvenous or transthoracic approach. When dyssynchrony is not present, other management options for severe HF may be required including transplant evaluation or, in the case of valvular heart disease, valve repair or replacement.

6. GUIDELINES

Published Clinical Guidelines from professional organization including the American Heart Association, the American College of Cardiology, and
the Heart Rhythm Society have categorized recommendations into three classes. Class I includes conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective. Class II includes conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment. The Class II recommendations are further divided into Class IIa and Class IIb. The Class IIa label is applied when the weight of evidence/opinion is in favor of usefulness/efficacy, and the Class IIb distinction is used when usefulness/efficacy is less well established by evidence/opinion. Class III conditions are those for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful. Furthermore, the degree of evidence is

<table>
<thead>
<tr>
<th>Recommendation class</th>
<th>Level of evidence</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>For patients with LVEF ≤35%, QRS duration ≥ 0.12 s, and sinus rhythm, CRT and/or an ICD is indicated for the treatment of NYHA functional Class III or ambulatory Class IV HF symptoms on OMT.</td>
</tr>
<tr>
<td>IIa</td>
<td>B</td>
<td>For patients who have LVEF ≤35%, QRS duration ≥ 0.12 s, and AF, CRT and/or an ICD is reasonable for the treatment of NYHA functional Class III or ambulatory Class IV heart failure symptoms on OMT.</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>For patients with LVEF ≤35% with NYHA functional Class III or ambulatory Class IV symptoms on OMT and who have frequent dependence on ventricular pacing, CRT is reasonable</td>
</tr>
<tr>
<td>IIb</td>
<td>C</td>
<td>For patients with LVEF ≤35% with NYHA functional Class I or II symptoms on OMT and who are undergoing implantation of a permanent pacemaker and/or ICD with anticipated frequent ventricular pacing, CRT may be considered</td>
</tr>
<tr>
<td>III</td>
<td>B</td>
<td>CRT is not indicated for asymptomatic patients with reduced LVEF in the absence of other indications for pacing</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>CRT is not indicated for patients whose functional status and life expectancy are limited predominantly by chronic noncardiac conditions</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation or atrial flutter; CRT = cardiac resynchronization therapy; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; OMT = optimal medical therapy
divided into three levels. Level of Evidence A is data derived from multiple randomized clinical trials or meta-analyses. Level B is data derived from a single randomized trial or nonrandomized studies, and Level C is consensus opinion of experts, case studies, or standard of care in the absence of the above.

In guidelines published that address CRT, prolonged QRS duration, an electrocardiographic representation of abnormal cardiac conduction, has been used to identify patients with left ventricular dyssynchrony (74, 75). To date, no well-established consensus definition of cardiac dyssynchrony (e.g., an echocardiographic description) has been formed.

Generally, guidelines suggest that the use of an ICD in combination with CRT should be based on the indications for ICD therapy while noting that the majority of CRT trials have primarily enrolled patients in normal sinus rhythm, and acknowledging that further investigation of patients with atrial fibrillation, right-bundle branch block, and obligate right ventricular pacing are ongoing.

The ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities categorizes CRT with or without an ICD for patients with a left ventricular ejection fraction $\leq 35\%$, QRS duration $\geq 120$ ms, and NYHA Class III or ambulatory Class IV on optimal medical therapy as Class I for patients in normal sinus rhythm, and Class IIa for patients with atrial fibrillation or for patients who ventricularly pace frequently. Comprehensive recommendations are displayed in Table 1074.

7. CONCLUSIONS

Cardiac resynchronization therapy (CRT) has been well studied and is proven to improve clinical outcomes and quality of life, and reduce mortality, in selected patients with heart failure and reduced ejection fraction. A variety of devices are available to deliver this important therapy to patients. Ongoing investigations will continue to refine the subset of patients most likely to benefit from this important therapy.

REFERENCES

62. Feldman AM, de Llissovoy G, Bristow MR, et al. Cost effectiveness of cardiac resynchronization therapy in the Comparison of Medical Therapy, Pacing, and Defibrilla-


