Indications for Cardiac Resynchronization Therapy

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Clinical Vignette

A 70-year-old man with chronic ischemic cardiomyopathy (New York Heart Association III, left ventricular ejection fraction (LVEF) 20%), percutaneous coronary intervention to left anterior descending artery and right coronary artery one year prior, and hyperlipidemia presents to clinic to discuss cardiac resynchronization therapy (CRT) candidacy. He is currently tolerating maximal doses of carvedilol, lisinopril, and spironolactone. Electrocardiogram shows normal sinus rhythm, left axis deviation, and nonspecific intraventricular conduction delay with QRS duration 140 ms. Repeat echocardiogram shows a severely dilated left atrium and mildly dilated left ventricle with LVEF 20% and global hypokinesis, unchanged in the past year. Is CRT recommended for this patient?

Introduction

Impaired electromechanical coupling is frequently seen in the progression of heart failure (HF), manifesting as prolonged interventricular conduction on the electrocardiogram or a prolonged QRS duration >120 ms (ms). Approximately one-third of patients with heart failure with reduced ejection fraction (HFrEF) have prolongation of the QRS duration. Furthermore, those with a wide QRS with left bundle branch block (LBBB) morphology have increased mortality compared to those with right bundle branch block (RBBB) [1]. Such dyssynchrony can result in further reductions in cardiac output, worsening functional mitral regurgitation,

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adverse left ventricular (LV) remodeling, and ultimately, worse prognosis [2–7]. Cardiac resynchronization therapy (CRT), by allowing simultaneous pacing of the ventricles, has emerged as a therapeutic strategy to promote reverse remodeling and improvement in mitral regurgitation, systolic function, and cardiac chamber dimensions [8, 9]. Robust data from several large randomized control trials (RCTs) have firmly established the clinical benefit of CRT in alleviating symptoms, preventing hospitalizations, and improving mortality in appropriately selected patients [10, 11].

In this chapter, an overview of the current indications for CRT will be discussed with an emphasis on the 2012 American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) Focused Update on Guidelines for Device-Based Therapy and highlighting the landmark trials.

Indications for CRT

Over the last two decades, the use of CRT has rapidly evolved from a last resort in select patients with severe LV systolic dysfunction and LBBB to a standard therapy in heart failure as tested and validated in large randomized controlled trials, as shown in Table 1. Prior to understanding the specifics of the indications, it is important to first understand when to consider a potential candidate for CRT. The appropriate patient has HFrEF as defined as LVEF $\leq$ 35%, on maximally tolerated doses of guideline-directed medical therapy (GDMT) for HF for at least three months, at least 40 days after a myocardial infarction without revascularization or three months after revascularization, and have treated any reversible cause of LV dysfunction [12]. It is also important to avoid implantation in those with significant comorbidities and/or frailty that limits expected survival to less than a year.

1. **Recommendations for Patients in Sinus Rhythm**

The 2012 ACC/AHA/HRS Focused Update on 2008 Guidelines for Device-Based Therapy proposed several key changes in the recommendations for CRT, as seen in Table 2 [12]. First, a Class I indication was limited to patients with NYHA II, III, or ambulatory IV symptoms despite optimal GDMT and QRS duration $\geq$150. Multiple trials and analyses have showed that the benefit of CRT appears dependent on QRS duration, particularly with more favorable outcomes in those with QRS $\geq$150 ms as compared to those with QRS <150 ms [13–16]. A Class II recommendation is given to patients with QRS $\geq$120 to 150 ms who otherwise qualify for CRT. Those with a QRS <120 ms fail to benefit from CRT even with evidence of mechanical dyssynchrony on echocardiogram, thus CRT is a contraindication in these patients in the absence of a need for frequent ventricular pacing [17, 18].

Secondly, the current guidelines also limit the Class I indication to patients with LBBB. In a meta-analysis of four trials including 5,356 patients, CRT significantly

Table 1 Landmark trials in cardiac resynchronization therapy

Trial, year of publication	N	Patient population	Trial design (follow-up duration)	Endpoints	Findings
Normal Sinus Rhythm and Advanced Heart Failure					
MIRACLE, 2002 [15]	453	• NYHA III-IV • LVEF ≤ 35% • QRS ≥ 130 ms	CRT-P versus OMT (6 mo)	Primary: NYHA class, QOL Secondary: Peak VO_2, LVEDD, clinical composite response	CRT-P ↑ 6MWD (+39 m versus +10 m), ↑ QOL, ↓ NYHA class, ↑ peak VO_2, ↑ LVEF (4.6 vs -0.2%)
COMPANION, 2004 [10]	1520	• NYHA III-IV • LVEF ≤ 35% • QRS ≥ 120 ms	CRT-P/CRT-D versus OMT (15 mo)	Primary: all-cause mortality and hospitalization Secondary: all-cause mortality	↓ primary endpoint for CRT-P and CRT-D (34% and 40%, respectively) versus OMT; ↓ all-cause mortality (CRT-P ↓ 24% [p = 0.06], CRT-D ↓ 36%)
CARE-HF, 2005 [37]	813	• NYHA III-IV • LVEF ≤ 35% • QRS ≥ 120 ms • LVEDD > 30 mm	CRT-P versus OMT (29.4 mo)	Primary: all-cause mortality or CV hospitalization Secondary: all-cause mortality, NYHA, QOL	CRT-P ↓ all-cause mortality or hospitalization; ↓ all-cause mortality; ↑ LV measures and QOL
Normal Sinus Rhythm and Mild Heart Failure					
REVERSE, 2008 [47]	610	• NYHA I-II • LVEF ≤ 40% • QRS ≥ 120 ms • LVEDD > 5.5 cm	CRT-on versus CRT-off (12 mo)	Primary: HF clinical composite score Secondary: LVESV index, HF hospitalizations and all-cause mortality	No improvement in primary endpoint in CRT-on versus CRT-off (16% vs 21%, p = 0.10). CRT-on did have ↓ LVESV, ↑ LVEF, and delay in time-to-first hospitalization (HR: 0.47, p = .03)
MADIT-CRT, 2009 [48]	1820	• NYHA I-II • LVEF ≤ 30% • QRS ≥ 130 ms	CRT-D versus ICD (2.4 years)	Primary: all-cause mortality or HF hospitalizations Secondary: All-cause mortality or LVESV	↓ primary endpoint with CRT-D (17% vs 25% with HR 0.66, p = 0.001) driven by 41% reduction in HF events. ↓ LVSEV. No reduction in all-cause mortality
RAFT, 2010 [11]	1798	• NYHA II-III • LVEF ≤ 30% • QRS ≥ 120 ms	CRT-D versus ICD (40 mo)	Primary: all-cause mortality or HF hospitalizations Secondary: all-cause mortality or cardiovascular death	CRT-D ↓ primary endpoint (33% vs 40%). ↓ mortality (29% vs 35%).

(continued)

Table 1 (continued)

Trial, year of publication	N	Patient population	Trial design (follow-up duration)	Endpoints	Findings
Chronic RV Pacing and Permanent Atrial Fibrillation					
BLOCK-HF, 2013 [32]	918	• NYHA I-III • LVEF ≤ 50% • Indication for pacing with AV block	CRT versus RV pacing (37 mo)	Primary: all-cause mortality, acute HF, increase in LVESV > 15% Secondary: composite of all-cause mortality, acute HF, and hospitalization	CRT ↓ composite outcome (HR 0.74; 95% CI, 0.60–0.90); CRT ↓ secondary outcomes except death
APAF-CRT, 2018 [49]	102	• Permanent atrial fibrillation • Narrow QRS (≤110 ms) • One HF hospitalization in previous year	AV junction ablation and CRT versus OMT (16 mo)	Primary: Death due to HF, HF hospitalization, worsening HF Secondary: All-cause mortality, HF hospitalization, worsening HF.	Ablation + CRT ↓ primary endpoint (20% vs 38%) and ↓ secondary endpoint in ablation + CRT
Narrow QRS					
RethinQ, 2007 [17]	172	• NYHA III • LVEF ≤ 35% • QRS < 130 ms	CRT-D versus ICD (6 mo)	Primary: Peak VO_2	No change in peak VO_2
ECHO-CRT, 2013	1680	• NYHA I-IV • LVEF ≤ 35% • QRS <130 ms • Evidence of echo dyssynchrony	CRT-on versus CRT-off (19 mo)	Primary: all-cause mortality or HF hospitalization Secondary: HF events	Study stopped with significant ↑ in mortality with LVEF ≤ 35% and narrow QRS

Abbreviations: NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; OMT, optimal medical therapy; CRT-P, cardiac resynchronization therapy pacing; CRT-D, cardiac resynchronization therapy defibrillator; QOL, quality of life; LVEDD, left ventricular end diastolic dimension; HR; hazard ratio; CV, cardiovascular; LVESV, left ventricular end systolic volume; ICD, implantable cardiac defibrillator; AV, atrioventricular

reduced the composite adverse clinical events by 36% in those with a LBBB [19]. No benefit was observed in those with right bundle branch block (RBBB) or nonspecific intraventricular conduction delay (NICD). Nonetheless, other studies still suggest a wide QRS duration in patients with advanced HF and non-LBBB morphologies is associated with enhanced reverse remodeling and improved long-term outcomes following CRT [11, 20].

Lastly, perhaps the most significant changes of the updated guidelines include the expansion of Class I recommendation to NYHA class II patients (with QRS $\geq$ 150 ms and LBBB) and the addition of a Class IIb recommendation to patients with NYHA class I patients (with LVEF $\leq$ 30%, ischemic etiology of HF, and LBBB $\geq$ 150 ms). These changes are largely due to the publication of three major trials: REVERSE (Resynchronization Reverses Remodeling in Systolic LV Dysfunction), MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with CRT), and RAFT (Resynchronization-Defibrillation for Ambulatory HF Trial) as described in Table 1.

2. **Recommendations for Patients in Permanent Atrial Fibrillation**

Another update based on the most recent guidelines from 2012 involves a class II recommendation for CRT in patients with permanent AF and LVEF < 35% with important caveats: if the patient requires ventricular pacing or otherwise eligible for device therapy, and atrioventricular (AV) nodal ablation or pharmacological rate control will allow near 100% ventricular pacing [12]. As clinical trials of CRT have included patients mainly in sinus rhythm, concerns exist in whether patients with permanent atrial fibrillation (AF) derive similar benefit. The presence of AF may compete with CRT pacing due to sensed events, preventing effective biventricular pacing. RAFT remains the largest randomized trial to date to include a substantial portion of patients with AF receiving a CRT device (n = 229 or 12.7%) [11]. A post hoc analysis of RAFT failed to show a benefit in patients with permanent AF who were randomized to CRT-D as compared to ICD alone [21]. However, several studies have suggested that benefit from CRT is most evident in patients when it is coupled with atrioventricular nodal ablation, thereby avoiding potentially deleterious effects of chronic RV pacing [22–26]. Although AV nodal ablation combined with CRT may be considered in those with permanent AF with persistently high ventricular rates, it is not without risk and concerns exist that AV nodal ablation renders patients pacemaker-dependent. Other strategies, particularly the use of ablation with pulmonary vein isolation in patients with HF and paroxysmal or persistent AF, should be considered first [27].

3. **Recommendations for Anticipated Significant Ventricular Pacing**

Chronic right ventricle (RV) pacing can mimic the dyssynchronous effects of LBBB, leading to progressive LV dysfunction, particularly in patients with pre-existing LV dysfunction [28]. The deleterious effects of chronic RV pacing were evaluated in the DAVID (Dual Chamber and VVI Implantable Defibrillator) trial. The trial showed that patients with LVEF $\leq$ 40% with an implantable cardiac defibrillator (ICD) programmed to dual-chamber pacing had increased HF admissions

and mortality rate compared to sinus rhythm [29]. A post hoc analysis found that patients with RV pacing cut-off of >40% was associated with worse outcomes [30]. A similar finding was observed in the MADIT II trial where those with >50% RV pacing had worse outcomes [31]. Based on the available literature at the time, the current guidelines provide a Class IIa recommendation for CRT in patients with LVEF ≤ 35% and are undergoing new or replacement device with anticipated requirement for significant (>40%) RV pacing.

Since the publication of the 2012 updated guidelines, the results of the BLOCK-HF (Biventricular Pacing for Atrioventricular Block and Systolic Dysfunction) demonstrated the benefit of CRT in a select group of patients not currently represented by the guidelines. Published in 2013, the trial demonstrated superior outcomes in patients implanted with CRT as compared to RV-only pacing in those with NYHA class I-III, LVEF ≤ 50% and atrioventricular block, in which ventricular pacing is obligatory [32]. The results of the BLOCK-HF study have already changed clinical practice and will likely liberalize the LVEF cut-off in those with high anticipated RV pacing in future guidelines.

4. **Recommendations for Upgrade to CRT**

Based on extrapolation from the 2012 updated guidelines, in patients with HFrEF who have a single or dual chamber pacemaker or ICD that subsequently develop worsening HF with high burden of RV pacing or a wide QRS that then meet criteria for CRT, an upgrade to CRT may be considered. Despite lack of evidence-based data, upgrade procedures are becoming increasingly common, particularly with heightened awareness of detrimental high RV pacing burden [33]. Importantly, upgrade procedures may be associated with worse outcomes than de novo implantations [34–36]. Thus, the benefits of CRT upgrade should be weighed against the procedural risk and complexity of adding the additional lead.

5. **Recommendations for CRT-D versus CRT-P**

The guidelines do not make specific recommendations regarding the choice between CRT-D and CRT-P. The COMPANION trial failed to show a difference in outcomes between CRT-P and CRT-D, although it lacked powered [10]. The CARE-HF trial was the first to provide evidence that CRT-P alone reduces mortality compared to medical therapy, but CRT-D was not compared [37]. It remains unclear if CRT reduces the need for an ICD by reverse remodeling and reduction in arrhythmia burden. Although a post hoc analysis from the REVERSE trial demonstrated that reverse remodeling with CRT was associated with a reduction of ventricular tachycardia (VT) [38], causal inferences cannot be made. Understandably, if a patient is scheduled for ICD implantation based on the current recommendations and is also eligible for CRT with life expectancy >1 year, then CRT-D should be considered. However, there may be a role for CRT-P in

Table 2 Indications for CRT implantation based on the 2012 ACCF/AHA/HRS focused update guidelines for device-based therapy

Patients in sinus rhythm with moderate to severe heart failure (NYHA III-IV)	
Class I, Level of Evidence A	• LVEF ≤ 35% despite OMT • LBBB • QRS ≥ 150 ms
Class IIa, Level of Evidence A	• LVEF ≤ 35% despite OMT • Non-LBBB • QRS ≥ 150 ms
Class IIa, Level of Evidence B	• LVEF ≤ 35% despite OMT • LBBB • QRS 120–149 ms
Class IIb, Level of Evidence B	• LVEF ≤ 35% despite OMT • Non-LBBB • QRS 120–150 ms
Class III: No Benefit	Comorbidities and/or frailty limit survival with good functional capacity < 1 year
Patients in sinus rhythm with mild heart failure (NYHA II)	
Class I, Level of Evidence B	• LVEF ≤ 35% despite OMT • LBBB • QRS ≥ 150 ms
Class IIa, Level of Evidence B	• LVEF ≤ 35% despite OMT • LBBB • QRS 120–149 ms
Class IIb, Level of Evidence B	• LVEF ≤ 35% despite OMT • Non-LBBB • QRS ≥ 150 ms
Class III: No Benefit	• LVEF ≤ 35% • Non-LBBB • QRS ≤ 150 ms
Patients in sinus rhythm and mild heart failure (NYHA I)	
Class IIb, Level of Evidence C	• LVEF ≤ 35% despite OMT • LBBB • QRS ≥ 150 ms • Ischemic cardiomyopathy
Class III: No Benefit	• QRS ≤ 150 ms • Non-LBBB
Special CRT indications	
Class IIa, Level of Evidence B	Anticipated to require frequent ventricular pacing (>40%) with LVEF ≤ 35%
Class IIa, Level of Evidence B	Atrial fibrillation, if ventricular pacing is required and rate control will result in near 100% biventricular pacing

Abbreviations: NYHA; New York Heart Association; LVEF, left ventricular ejection fraction; OMT; optimal medical therapy; LBBB, left bundle branch block

select patients for relief of symptoms without defibrillation back-up, such as elderly and frail patients with significant co-morbidities, such as severe renal insufficiency or dialysis, advanced heart failure [12, 39, 40], or controversially, those with non-ischemic cardiomyopathy [41, 42]. Until randomized data provides insight into this clinical dilemma, the choice of the device will largely be decided by the implanting physician.

6. Pre-Implantation Considerations for Predicting Response in CRT Recipients

At least one-third of patients fail to achieve benefit from CRT [43]. Although there currently does not exist a standard definition to define response, several studies have used various clinical, functional, and structural measures with various predictors of response (Table 3). In a subanalysis of the MADIT-CRT, Hsu et al. identified six baseline factors that predicted LVEF super-response in CRT-D patients, defined as the top quartile of LVEF change (mean increase $17.5 \pm 2.7\%$) [44]. The predictors included female sex, no prior myocardial infarction, left bundle branch block, QRS duration $\geq$150 ms, body mass index <30 kg/m^2, and smaller baseline left atrial volume index. As evidenced by the trials and guidelines, those with LBBB and QRS duration >150 ms have the highest likelihood of response, thus earning the highest recommendation [12]. However, women have consistently been under-represented in large-scale clinical trials of CRT and guidelines fail to differentiate gender. Gender has been shown to have differing impacts on CRT response in relation to QRS duration, as women tend to respond favorably to CRT at a markedly higher rate than men at QRS < 150 ms [45]. Furthermore, the benefits of CRT in those with RBBB, regardless of QRS duration, may have little benefit from CRT [46]. Understanding the clinical predictors that can affect the likelihood of CRT response will help with optimizing patient selection and maximizing response.

Table 3 Pre-implantation predictors of CRT response

High likelihood of response	Less likely to respond	Likely no benefit
Female	QRS duration 120–150 ms	RBBB
LBBB	High LV scar burden	End stage renal disease
QRS duration $\geq$150 ms	Atrial fibrillation	QRS $\leq$ 120 ms without pacing requirement
Nonischemic cardiomyopathy	Advanced co-morbidities	Life expectancy < 1 year
Body mass index <30 kg/m^2	Medical therapy not optimized	
Small left atrial volume index[a]	NICD	
	Right ventricular dysfunction	

[a]Per 1-U standard deviation below mean

Case Conclusion

To review, the patient is a 70-year-old man with ischemic cardiomyopathy (LVEF 20%) despite OMT, NYHA class III, normal sinus rhythm with a QRS duration of 140 ms with a non-LBBB morphology. He is expected to live >1 year. CRT recommendation for this patient is currently a Class IIb, level of evidence B. Importantly, the patient has unfavorable characteristics that suggest he is less likely to respond to CRT, such as ischemic etiology, non-LBBB, QRS <150 ms, and male gender. After a shared decision-making discussion regarding continued symptoms, potential benefits, and risks of the procedure, the patient elected to proceed with CRT implantation. Given his life expectancy and personal choice, he elected for CRT-D.

Future Directions

Improved algorithms are being developed and tested to optimize patient selection and optimization for CRT and LV lead targeting using electrocardiographic and imaging techniques to identify sites of dyssynchrony.

Key Points:

- The highest recommendation for CRT is in those with patients in sinus rhythm, LVEF <35%, QRS >150 ms with a LBBB morphology.
- As QRS duration shortens or in those with non-LBBB morphology, the guideline recommendations become weaker for CRT.
- Patients in permanent atrial fibrillation derive less benefit from CRT than patients in sinus rhythm and may benefit from AVN ablation with CRT.
- Patients with HF and anticipated or high RV pacing (>40%) benefit from CRT as opposed to dual chamber pacemaker.
- Data is limited on the CRT-D versus CRT-P and is often left to physician discretion.

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