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Patient Selection for Cardiac Resynchronization Therapy

From the Council on Clinical Cardiology Subcommittee on Electrocardiography and Arrhythmias and the Quality of Care and Outcomes Research Interdisciplinary Working Group, in Collaboration With the Heart Rhythm Society

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*Endorsed by the American College of Cardiology Foundation
and the Heart Failure Society of America*

Abstract—Cardiac resynchronization therapy (CRT) is a relatively new therapy for patients with symptomatic heart failure resulting from systolic dysfunction. CRT is achieved by simultaneously pacing both the left and right ventricles. Biventricular pacing resynchronizes the timing of global left ventricular depolarization and improves mechanical contractility and mitral regurgitation. Published clinical trials have demonstrated that CRT results in improved clinical status and lower mortality rate when selected patients with systolic ventricular dysfunction and heart failure are treated with CRT. This advisory identifies appropriate candidates for CRT on the basis of the inclusion criteria and results from the published clinical trials. (*Circulation*. 2005;111:2146-2150.)

Key Words: AHA Science Advisories ■ heart failure ■ pacing ■ arrhythmias ■ therapy

Cardiac resynchronization therapy (CRT) is a relatively new therapy for patients with symptomatic heart failure resulting from systolic dysfunction. CRT is only one aspect of the treatment of patients with heart failure. A comprehensive discussion of the recommendations for treatment of heart failure soon will be available in the 2005 update of the “American College of Cardiology/American Heart Association Guidelines for the Diagnosis and Management of Chronic Heart Failure in the Adult” (www.americanheart.org and www.acc.org). Briefly, CRT is achieved by simultaneously pacing both the left and right ventricles. Theoretically, biventricular pacing resynchronizes the timing of global left ventricular depolarization and as a result improves mechanical contractility and mitral regurgitation. Several recently published clinical trials demonstrated clinical improvement when selected patients with systolic ventricular dysfunction and heart failure were treated with CRT.¹⁻⁶ The designs and results of these studies, although not identical, have been concordant. The goal of the present advisory is to

characterize appropriate candidates for CRT on the basis of the inclusion criteria and results from these clinical trials.

Mechanism of Action for CRT

Conduction delay, as manifested by a prolonged QRS complex duration, is common among patients with systolic dysfunction and heart failure and is associated with an increased prevalence of mechanical dyssynchrony, as opposed to patients with a narrow QRS complex. Cardiac dyssynchrony results in a decrease in stroke volume, facilitation of mitral regurgitation, increased wall stress, and delayed relaxation. The primary objective of CRT is restoration of a more normal ventricular activation pattern. Secondly, CRT allows optimization of the atrioventricular interval for patients in sinus rhythm.

Compared with the delayed activation that occurs in the setting of an interventricular conduction delay, CRT depolarizes the left ventricle earlier. CRT is believed to reverse the deleterious effects of dyssynchronous ventricular activation

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TABLE 1. Functional Benefits of CRT

↑ 6-Minute walking distance
↑ Health-related quality-of-life score
↑ Peak oxygen consumption
↓ Hospitalizations for decompensated heart failure
↓ NYHA functional classification

↑ indicates increased; ↓, decreased.

by decreasing the electromechanical delay associated with an interventricular conduction delay and providing near-simultaneous contraction of the ventricular septum and the left ventricular free wall. Numerous clinical investigations have demonstrated that in selected patients CRT significantly improves cardiac output, systolic pressure, maximal rate of pressure rise, the magnitude of wall contraction, mitral regurgitation, and left atrial pressure. Furthermore, these acute hemodynamic benefits are achieved while reducing myocardial energy consumption.^{7,8}

To a much lesser degree than biventricular pacing, optimization of the atrioventricular interval for patients in sinus rhythm may improve cardiac hemodynamics by coordinating the timing of atrial systole relative to ventricular filling.

Benefits of CRT

CRT has been shown to improve functional status as demonstrated by the 6-minute walk test, peak oxygen uptake, the New York Heart Association (NYHA) classification system, and health-related quality of life as assessed by the Minnesota Living with Heart Failure questionnaire (Tables 1 and 2). As with most therapeutic interventions, not all patients improve with CRT. Although improvements in survival have not been demonstrated with CRT alone, a recent meta-analysis suggested a trend toward improvement.⁹ The largest and most recent randomized trial of CRT demonstrated a significant reduction in the combined end point of all-cause mortality and hospitalization.⁶ In addition, when CRT is combined with

a device that has defibrillation capabilities, total mortality is reduced.⁶

Patient Selection for CRT

The inclusion criteria for the published trials that have randomized patients to CRT are summarized in Table 3.¹⁻⁶ The inclusion criteria were similar but not identical in each of the studies. In general, the CRT trials included patients with sinus rhythm, a QRS complex duration >120 to 130 ms, heart failure resulting from systolic dysfunction with NYHA class III or IV symptoms, and optimal medical treatment for heart failure, including β -blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and diuretics.

On the basis of the inclusion criteria and the results of these studies, a high level of evidence supports CRT in patients with systolic dysfunction and heart failure resulting from either ischemic or nonischemic cardiomyopathy who have a left ventricular ejection fraction (LVEF) ≤ 0.35 , are in NYHA functional class III or IV, are on maximal medical therapy, have a QRS complex duration >120 ms, and are in sinus rhythm (Table 4).

Uncertainties of CRT

The bulk of clinical evidence strongly endorses the use of CRT in patients with either ischemic or nonischemic cardiomyopathy, heart failure with NYHA functional class III or IV despite maximal medical therapy, an LVEF ≤ 0.35 , a QRS complex duration >120 ms, or sinus rhythm.¹⁻⁶ Some trials suggest that CRT may be of benefit for other clinical scenarios in addition to this patient profile.

Recently, 2 randomized multicenter trials assessed the benefit of CRT in patients with NYHA functional class II symptoms despite medical therapy, a depressed LVEF, a wide QRS duration, and an indication for implantable defibrillator therapy.^{5,10} In these studies, CRT demonstrated functional improvement as well as left ventricular remodeling. At present, however, the use of CRT in patients with

TABLE 2. Effect of Cardiac Resynchronization on Health Status Measures

	MUSTIC-SR ¹ (n=58, F/U 12 wk)		PATH-CHF ² (n=40, F/U 4 wk)		MIRACLE ³ (n=453, F/U 6 mo)		MIRACLE-ICD ⁴ (n=369, F/U 6 mo)		CONTAK CD ⁵ (n=490, F/U 3-6 mo)		COMPANION ⁶ (n=1520, F/U 6 mo)	
	Control	CRT*	Control	CRT*	Control	CRT	Control	CRT	Control	CRT	Control	CRT
6-Min walk test, m	...	74	...	74	10	39†	55	53	15	35†	1	40†
Peak oxygen uptake, mL · min ⁻¹ · kg ⁻¹	...	1.2	...	1.2	0.2	1.1†	0.1	1.1†	0	0.8†
NYHA, % I/II/III/IV	Before: 0/0/100/0	...	Before: 0/0/85/15	After: 15/34/44/7	38% of patients ↓	68% of patients ↓	Mean: ↔	Mean: -1 NYHA class†	36% of patients ↓	32% of patients ↓	38% of patients ↓	61% of patients ↓
Minnesota Living With Heart Failure questionnaire‡	...	-14	...	-14	-9	-18†	-11	-17.5†	+5	-7†	-12	-25†

MUSTIC-SR indicates Multisite Stimulation in Cardiomyopathies; PATH-CHF, Pacing Therapies in Congestive Heart Failure; MIRACLE, Multicenter InSync Randomized Clinical Evaluation; MIRACLE-ICD, MIRACLE-implantable cardioverter defibrillator; CONTAK CD, combined heart failure/bradycardia/tachycardia ICD device; COMPANION, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure. ↓ indicates decreased; ↔, no change; mean, mean change in NYHA class; and F/U, follow-up.

*Comparison is with baseline.

† $P < 0.05$ for comparison with control.

‡Lower score indicates improved quality of life.

TABLE 3. Inclusion Criteria and Patient Characteristics for CRT Trials

	MUSTIC ¹ (n=67)	PATH-CHF ² (n=36)	MIRACLE ³ (n=453)	MIRACLE-ICD ⁴ (n=369)	CONTAK ⁵ (n=490)	COMPANION ⁶ (n=1520)
CRT-D or CRT-P	CRT-P	CRT-P	CRT-P	CRT-D	CRT-D	Both
Cardiac rhythm	SR	SR	SR	SR	SR	SR
Optimal HF Rx	Yes	Yes	Yes	Yes	Yes	Yes
NYHA class	III	III, IV	III, IV	III, IV	II, III, IV	III, IV
Distribution, %	100	86/14	91/9	89/9	33/59/8	85/15
ICM/NICM	Both	Both	Both	Both	Both	Both
Distribution, %	37/63	29/71	54/46	70/30	69/31	55/45
QRS, ms	≥150	≥120	≥130	≥130	≥120	≥120
Mean±SD, ms	176±19	175±32	166±20*	164±22*	158±26*	160†
LVEF	≤0.35	N/A	≤0.35	≤0.35	≤0.35	≤0.35
Mean±SD	0.23±7	0.21±7	0.22±6.3*	0.24±0.06*	0.21±7*	0.22†
LVEDD, mm	≥60	N/A	≥55	≥55	N/A	N/A
Mean±SD, mm	73±10	73±11	69±10*	76±10*	71±10*	67†
6-Min walk, m	N/A	N/A	≤450	≤450	N/A	N/A
Mean±SD, m	320±97	357±20	298±93*	243±123*	318±120*	262†

CRT-D indicates device with cardiac resynchronization therapy and defibrillation; CRT-P, device with cardiac resynchronization therapy only; HF Rx, optimal pharmacological heart failure therapy; ICM/NICM, ischemic cardiomyopathy/nonischemic cardiomyopathy; LVEDD, left ventricular end-diastolic dimension; and N/A, not applicable.

*SD is estimated from data provided in citation.

†Median value is shown.

minimal heart failure symptoms is not universally recommended and is the focus of ongoing clinical trials.

The majority of patients enrolled in CRT trials had a wide QRS complex on the basis of a left bundle-branch block¹⁻⁶; however, the relative therapeutic benefit among patients with a left versus a right bundle-branch block is unclear. Nonetheless, the current recommendation for CRT is based on QRS duration, not on QRS morphology.

The role of CRT in other groups of patients with heart failure resulting from systolic dysfunction, including patients with atrial fibrillation or a wide QRS morphology on the basis of right ventricular pacing, is unclear. Preliminary data from a large study and results from a few small studies suggest that in patients with atrial fibrillation and complete atrioventricular block, CRT may provide functional improvement when compared with right ventricular pacing.¹¹⁻¹⁴ Among patients with a cardiomyopathy, sinus rhythm, and an indication for an implantable defibrillator but not permanent pacing, right ventricular pacing precipitates and has a negative impact on heart failure.¹⁵ The results of this study¹⁵ suggest that right ventricular pacing is not optimal in this group of patients and

that biventricular pacing may be better; however, there are no prospective data to support this approach.

The published randomized CRT studies have used QRS complex duration as a surrogate marker for dyssynchrony.¹⁻⁶ In the future, we may be able to identify patients with ventricular dyssynchrony and who will respond to CRT with the use of tissue Doppler or other echocardiographic or visualization techniques.¹⁶

Three other unresolved issues with regard to CRT are (1) the risks and benefits of left ventricular pacing without a right ventricular lead, (2) the risks and benefits of a surgically placed left ventricular pacing lead versus a nonthoracotomy approach, and (3) the use of CRT in patients with NYHA class IV symptoms who are nonambulatory and dependent on intravenous inotropes for hemodynamic support.

Risks and Complications of CRT

The risks associated with the implantation of a CRT device are relatively small and are similar to the risks and complications associated with the transvenous implantation of a conventional permanent pacemaker or implantable defibrillator.¹⁻⁶ These risks include bleeding (≈1%); infection (≈1%); hematoma (≈1%); pneumothorax (≈1%); pericardial effusion with or without tamponade (≈1%); and myocardial infarction, stroke, and death (≈1/500). Transvenous implantation of a left ventricular lead for CRT is accomplished via the coronary sinus and its tributaries. The specific risks associated with implantation of a left ventricular lead for CRT include coronary sinus dissection and perforation (≈1%), lead dislodgment (≈5%), extracardiac stimulation (≈5%), and the risks associated with intravenous contrast, including acute renal fail-

TABLE 4. Characteristics of Patients in Whom CRT Is Strongly Supported by Randomized Trials

Sinus rhythm
LVEF ≤0.35
Ischemic or nonischemic cardiomyopathy
QRS complex duration ≥120 ms
NYHA functional class III or IV
Maximal pharmacological therapy for heart failure

ure (<1%).^{1–6} Limited data suggest that ventricular proarrhythmia may be a rare but potential risk of CRT.¹⁷

Conclusions

The results of numerous randomized clinical trials provide the necessary data to identify appropriate patients for CRT. Optimal candidates for CRT have a dilated cardiomyopathy on an ischemic or nonischemic basis, an LVEF ≤ 0.35 , a QRS

complex >120 ms, and sinus rhythm, and are NYHA functional class III or IV despite maximal medical therapy for heart failure. In general, these patients are treated with a CRT device that also has defibrillation capabilities. A variety of unresolved issues include the role of CRT for patients with NYHA functional class II symptoms or with atrial fibrillation, prospective identification of responders to CRT, and the role of CRT in other categories of patients.

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Edward Havranek	Denver Health and Hospital Authority	Abbott Pharmaceuticals; Pfizer; Sanofi-Syntholab	None	None	None	None
Mandeep R. Mehra	Ochsner Clinic Foundation	None	AstraZeneca; Bristol-Myers Squibb; Fujisawa Healthcare; GlaxoSmithKline; Guidant; Scios; Medtronic; Merck; Novartis; Pfizer; Roche	None	AstraZeneca; Bristol-Myers Squibb; Fujisawa Healthcare; GlaxoSmithKline; Guidant; Scios; Medtronic; Merck; Novartis; Pfizer; Roche	None
Ileana L. Piña	Temple University	Centers for Medicare and Medicaid Services	AstraZeneca; GlaxoSmithKline; Novartis; Pfizer	None	Food and Drug Administration	None
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