Cardiac Resynchronization Therapy in Older Adults with Heart Failure

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KEYWORDS

• Heart failure • Cardiac resynchronization therapy • Older adults • Mortality

KEY POINTS

- Heart failure is a disease of poor prognosis marked by frequent hospitalizations, premature death, and impaired quality of life.
- Cardiac resynchronization therapy (CRT), or biventricular pacing, has led to significant improvement in both survival and symptoms in patients with heart failure and reduced ejection fraction (HFrEF) and evidence of a left bundle branch pattern on electrocardiogram.
- The beneficial effects of CRT, especially in combination with ICD, are not as well documented for the older population as they are for younger individuals with HFrEF, but do not reveal dramatic effects of age on outcomes.
- Placement of CRT, like other pacemakers, is well-tolerated in older patients and complications are infrequent.

CASE PRESENTATION

An 84-year-old man with a past medical history of coronary artery disease and ischemic cardiomyopathy with a recent left ventricular ejection fraction (LVEF) of 20% to 25% as demonstrated by echocardiogram, presents to the cardiology clinic with progressive dyspnea on exertion. Despite being on a medical regimen of lisinopril, carvedilol, spironolactone, and furosemide at stable doses over the past 3 months, the patient is not able to ambulate for more than 2 blocks without having to rest owing to his shortness of breath. An electrocardiogram in clinic reveals a normal sinus rhythm with a left bundle branch block (LBBB) and a QRS interval of 165 msec. He wants to know if there are any additional therapies available to treat his heart failure (HF) and symptoms.

INTRODUCTION

HF is a common chronic disease that carries a poor prognosis. It is a disease marked by frequent hospitalizations and premature death

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despite optimal medical therapy. It is also associated with a dramatic impairment in quality of life, especially in older patients, when associated with other comorbidities.[1] Despite advances in medical therapy for patients with HF and reduced ejection fraction (HFrEF), defined as an LVEF of 40% or less, mortality and hospitalizations with advanced disease are still increased, and the quality of life continues to be poor in this population.

The advent of cardiac resynchronization therapy (CRT), also known as biventricular pacing, has led to a significant improvement in both survival and symptom management in select patients with HFrEF. This improvement is achieved through a standard atrial and ventricular pacing lead placed in the right atrium and right ventricle with a third lead that is advanced into a lateral or posterolateral branch of the coronary sinus to allow synchronized pacing of both the right and left ventricles (**Fig. 1**). Beneficial changes as seen in randomized clinical trials include not only an increase in survival, but also improved contractile function and ventricular remodeling and a significant improvement in quality of life.[2–7] Despite all of its benefits, data on the role of CRT in older patients has been scarce, because this population is not well-represented in most of the large-scale clinical trials. In this article, we review the role of CRT in the treatment of older patients, defined as patients over the age of 65 years, with HFrEF.

EVOLUTION OF CARDIAC RESYNCHRONIZATION THERAPY

Conduction defects leading to a delay in the onset of right and left ventricular systole occur in about 30% of patients with HFrEF.[8,9] This dyssynchrony can be seen on an electrocardiogram as a QRS interval of greater than or equal to 120 msec with a LBBB morphology. The delay in conduction leads to an impaired ability of the weak heart to eject blood, worsening flow through the mitral valve and leading to progression of HF, and a subsequent impaired quality of life and increased risk of death. The development of atrial-synchronized biventricular pacing that helps to coordinate contraction between these 2 chambers has improved not only cardiac contractility and enhanced quality of life, but also survival as demonstrated by several major randomized clinical trials (**Table 1**).

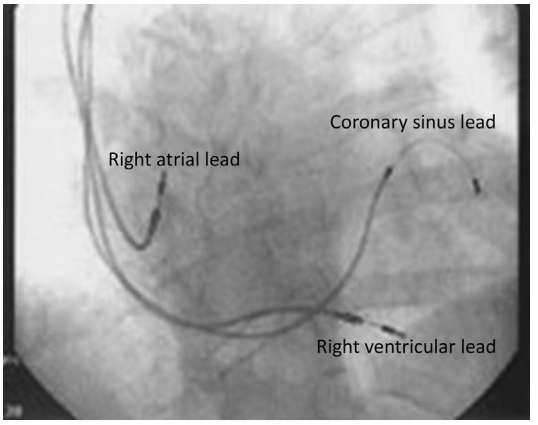

Fig. 1. An anterior-posterior fluoroscopic projection showing all 3 leads involved in cardiac resynchronization therapy.

The MIRACLE (Multicenter Insync Randomized Clinical Evaluation) study was the first double-blind randomized control trial to achieve its primary outcome of improved 6 minute walk test (P = .005), quality of life (P = .001), and New York Heart Association (NYHA) functional class (P<.001) in patients with HFrEF who received CRT plus medical therapy compared with medical therapy alone.[2] In the trial, patients with HF associated with an LVEF of 35% or less and a QRS interval of 130 msec or more were randomized to either receive CRT and medical therapy or medical therapy alone.

The addition of CRT to an implantable cardioverter defibrillator (ICD) was explored in the MIRACLE-ICD (Multicenter Insync ICD Randomized Clinical Evaluation) study, which once again achieved a primary outcome of improved quality of life (P = .02) and NYHA functional class (P = .007) in patients with systolic HF who received CRT in addition to an ICD for life-threatening arrhythmias.[3]

The COMPANION trial (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) was the first study to compare CRT-pacing (CRT-P) and CRT-defibrillator (CRT-D) plus medical therapy to optimal pharmacologic therapy alone and included mortality as one of its outcomes. Patients in both the CRT-D and CRT-P groups had a 20% decrease in death or hospitalization compared with the medical therapy group (**Table 2**).[4] Compared with medical therapy alone, the reduction in mortality was noted to be greater in patients receiving CRT-D than those receiving CRT-P at 36% (P = .003) and 24% (P = .059), respectively.[4]

The CARE-HF trial (Cardiac Resynchronization in Heart Failure) randomized patients with NYHA functional class III or IV HF owing to HFrEF and evidence of cardiac dyssynchronization, defined as a QRS duration of 120 msec or greater, to either receive CRT-P and medical therapy or optimal pharmacologic therapy alone.[5] Patients in the CRT-P had a significant reduction in death from any cause or hospitalization for major cardiovascular events compared with those receiving only

Table 1
Major randomized controlled trials and outcomes in patients with heart failure and reduced ejection fraction receiving CRT

Study	Year	Mean Age of Intervention Group	Number of Patients	Results
MIRACLE	2002	63.9 ± 10.7	453	Improved NYHA functional class, 6-min walk test, and quality of life
MIRACLE-ICD	2003	66.6 ± 11.3	369	Improved NYHA functional class, 6-min walk test, and quality of life
COMPANION	2004	65.0 ± 11.0	1520	Decreased all-cause mortality or all-cause hospitalization
CARE-HF	2005	67 (60–73)	813	Decreased all-cause mortality or cardiovascular hospitalization
MADIT-CRT	2009	65.0 ± 11.0	1820	Decrease all-cause mortality of heart failure hospitalization
RAFT	2010	66.6 ± 9.4	1798	Decreased death from any cause or hospitalization for heart failure

Abbreviations: CRT, cardiac resynchronization therapy; NYHA, New York Heart Association.

medical therapy (P = .001; **Table 3**).[5] Secondary outcomes revealed a reduction in death from any cause (P<.002) and HF hospitalization (P<.001), along with an improvement in quality of life (P<.001), and left ventricular ejection function (P<.001) in patients who received CRT-P plus optimal medical therapy compared with medical therapy alone.[5] Both the COMPANION and CARE-HF trials helped to established CRT as treatment for patients with HFrEF (NYHA functional class III or IV) and a wide QRS complex. In all these studies, patients like the one in our case presentation were underrepresented.

Although the body of evidence for CRT and its benefits in patients with HFrEF is vast for patients with NYHA functional class III or IV, little was known about its efficacy in patients with mild to moderate HF (NYHA functional class I or II).

Table 2
Percentage free of death or hospitalization in patients enrolled in the COMPANION trial

	0.5 y	1 y	1.5 y	2 y	2.5 y
Pacemaker	58.5	43.7	32.1	23.3	18.5
Pacemaker + defibrillator	58.5	43.7	32.1	23.3	18.5
Medications alone	55	31.4	22	17.9	11.6
Difference favoring devices	3.5	12.3	10.1	5.4	6.9

Data from Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350(21):2140–50.

The MADIT-CRT trial (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy), one of the largest randomized CRT trials with a sample size of 1820 patients, randomized patients with HFrEF, NYHA functional class I or II, and QRS duration of 130 msec or greater to receive either CRT-D or ICD alone.[6] Although it achieved its primary outcome of total mortality or HF hospitalizations reduction at 34% in the CRT-D group compared with the ICD group (P = .001), it was largely driven by the reduction in HF hospitalizations[6] (**Table 4**).

The RAFT trial (Resynchronization–Defibrillation for Ambulatory Heart Failure) randomized patients with NYHA class II or III HF, LVEF of 30% or less, and a QRS duration of greater than or equal to 120 msec to receive either an ICD alone or ICD plus CRT. The study revealed a significant reduction in death from any cause or hospitalization for HF in the group who received both an ICD and CRT compared with ICD alone (P<.001; **Table 5**).[7] Other outcomes, including all-cause mortality, were also lower in the group that received both ICD and CRT (P = .003).[7] Taken together, both the MADIT-CRT and RAFT trials provide evidence of the clinical efficacy of CRT in patients with mild-to-moderate HF in addition to patients with moderate-to-severe HF.

The evolution of CRT over the last 15 years has led to the establishment of a national consensus for the placement of CRT in patients with evidence of left ventricular dysfunction and cardiac dyssynchrony. Given the significant improvement in not only survival, but also other parameters such as quality of life in patients with HFrEF, it is currently

Table 3
Percentage free of death or cardiovascular hospitalization in patients enrolled in the CARE-HF trial

	0.5 y	1 y	1.5 y	2 y	2.5 y	3 y	3.5 y
Cardiac resynchronization	83	72	67	62	59	57	54
Medical therapy	79	65	56	49	43	33	30
Difference favoring cardiac resynchronization therapy	4	7	11	13	16	24	24

Data from Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352(15):1539–49.

a class I indication for the placement of CRT in patients with LVEF of 35% or less, sinus rhythm, left bundle branch block with a QRS duration of 150 msec or greater, and NYHA functional class II, III, or ambulatory IV who are already on goal directed medical therapy as stated in the recent 2012 American College of Cardiology/American Heart Association guidelines.[10] It is also reasonable to consider CRT in patients who have QRS duration of 120 to 149 msec, a class IIa indication.[10]

CLINICAL EFFICACY OF CARDIAC RESYNCHRONIZATION THERAPY IN OLDER PATIENTS

Despite the emergence of CRT for the HFrEF population, to date it remains unclear whether the favorable results from the trials are generalizable to older patients. Few older adults were included during the randomization period. Furthermore, none of the trials have specifically addressed the benefit of CRT in this population. In both the COMPANION and CARE-HF trials, the mean age was about 65 years and the benefit of CRT was seen in patients above the mean age. A subgroup analysis in the COMPANION trial revealed both a reduction in all-cause mortality or all-cause hospitalization and all-cause mortality in patients over the age of 65 years who received CRT-D compared with patients who only received pharmacologic therapy, with an estimated relative risk reduction of 20% to 25% within each group.[4] Subsequent analyses of both the MIRACLE and MIRACLE-ICD trials also revealed a comparable benefit of CRT in older patients to those who were younger.[11] Patients in both studies who were 65 years of age and older had a similar significant improvement in NYHA functional class ($P = .002$) and LVEF ($P = .03$) when compared with patients under the age of 65.[11] The benefits of CRT in the older population extend beyond those with moderate to severe HF. In the MADIT trial, which looked at a population with mild to moderate HF, patients in the age of 60 to 74 years old age group and the greater than 74 years old age group had a similar reduction in combined all-cause mortality or HF readmission when compared with those who were less than the age of 60 ($P<.001$, $P<.001$, and $P = .043$ in each group, respectively).[12]

Equivalent benefits of CRT in older adults were also noted in several observational studies when comparing this population with younger patients. Several studies have noted improvement in both echocardiographic findings of improved LV function and comparable survival benefits when comparing older patients to those who were younger.[13,14] In one study, patients with HFrEF over the age of 70 who received CRT had similar improvement in functional class ($P<.05$), quality of life ($P<.05$), and ejection fraction ($P<.05$) when compared with their less than 70 years old age group counterparts.[13] Older adults receiving CRT not only demonstrated comparable clinical benefits compared with those who were younger, but also displayed similar survival outcomes, with

Table 4
Percentage free of heart failure hospitalization in patients enrolled in the MADIT-HF trial

	0.5 y	1 y	1.5 y	2 y	2.5 y	3 y	3.5 y
CRT + ICD	95.6	92.1	88.4	85.1	82.4	79.9	78.5
ICD only	92.7	88.4	81.7	77.7	74.5	70.7	67.5
Difference favoring ICD + CRT	2.9	3.7	6.7	7.4	7.9	9.2	11

Abbreviations: CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator.

Data from Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361(14):1329–38.

Table 5
Percentage free of death or heart failure hospitalization in patients enrolled in the RAFT trial

	0.5 y	1 y	1.5 y	2 y	2.5 y	3 y	3.5 y	4 y	4.5 y	5 y
CRT + ICD	93.7	88.6	84.4	81.3	77.5	73.7	69.5	66	60.6	57.8
ICD only	90.8	85.4	80.3	75.6	70.8	66	60.3	55.9	52.4	47.6
Difference favoring ICD + CRT	2.9	3.2	4.1	5.7	6.7	7.7	9.2	10.1	8.2	10.2

Abbreviations: CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator.
Data from Tang AS, Wells GA, Talajic M, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med 2010;363(25):2385–95.

one study revealing similar survival at 2-year follow-up when comparing patients over the age of 75 with patients under 75 years of age (P = .961).[14,15]

IMPACT OF COMORBIDITIES ON THE EFFICACY OF CARDIAC RESYNCHRONIZATION THERAPY

Geriatricians have concerns that typical multimorbid geriatric patients may be excluded from getting devices such as CRT and ICD. Although the burden of comorbidities such as atrial fibrillation, diabetes mellitus, and chronic kidney disease may preclude some patients from receiving CRT given the concern for the cost of the device placement over its potential benefits, there have been several studies that have shown a clinical benefit of CRT in patients with these comorbidities.[16–18] In one meta-analysis of prospective cohort studies comparing the impact of CRT for patients in atrial fibrillation and sinus rhythm, mortality is similar in both groups at 1-year follow-up (P = .13).[16] In a study from Fantoni and colleagues,[17] diabetic HF patients treated with CRT had outcomes not different from their nondiabetic counterparts for death from any cause (P = .710), cardiovascular death (P = .679), HF death (P = .806), and sudden death (P = .972). In HF patients with renal dysfunction, a prominent comorbidity in this population, CRT has not only demonstrated an improvement in renal function recovery, but it was shown to also improve patients with severe renal dysfunction. A study of 73 consecutive patients with an average age of greater than 70 receiving either CRT or ICD revealed an improvement in both estimated glomerular filtration rate and functional status in patients who received CRT compared with those who received ICD (P = .04 and P<.001, respectively).[18] Although age was not studied specifically as a marker of response to CRT in the landmark randomized trials, it is reasonable to apply these findings to an older population based on these subsequent analyses. Therefore, in patients with a good life expectancy, regardless of age, CRT should be considered in patients with HFrEF and existing comorbidities.

COMPLICATIONS OF IMPLANTATION

The complications of CRT are similar to the placement of any standard pacemaker device. These include pneumothorax, bleeding from perforation of vessels or the myocardium, infection, and arrhythmias. Overall, the implantation of any pacemaker device, including CRT, is safe and well-tolerated. The low rate of perioperative complications can also be applied to geriatric patients. Subgroup analyses of both the MIRACLE and MIRACLE-ICD did not reveal an increase of adverse events after CRT implantation in this population.[11] Another study also revealed a similar rate of device-related complication such as the dislodgement of LV leads and pocket erosions in patients younger than and older than 80 years of age.[15] However, these studies are either post hoc analyses or observational studies, which are limitations. To date, there have been no prospective, randomized trials addressing the safety of CRT in the geriatric population.

COST EFFECTIVENESS OF CARDIAC RESYNCHRONIZATION THERAPY

HF is the leading cause for hospital admission and readmission in the United States in patients over the age of 65, which creates a significant health care and financial burden.[19] It has been shown that a readmission for HF not only increases cost and cumulative duration of stay in older patients with HF, it also has clinical implications for patient survival.[20] This has created a significant push from the government to reduce this number, leading to the creation of the Affordable Care Act, which penalizes hospitals with a high rate of hospital readmissions in patients with HF.

CRT has been shown to not only improve survival, but reduce cost and hospitalizations. In the CARE-HF trial, the rate of hospitalization for

worsening HF was significantly lower in patients who received CRT compared with those who received only pharmacologic therapy.[5] This observation was also seen in patients with mild to moderate HFrEF as demonstrated in the RAFT trial.[7] A cost analysis of the COMPANION trial was performed over a 2-year period, follow-up hospitalizations were reduced by 29% and 37% in the CRT-P group and CRT-D group, respectively.[21] This translated to a saving of $43,000 per quality-adjusted life-year for CRT-P and $19,600 per quality-adjusted life-year for those who received CRT-D at 7 years.[21] Although this analysis did not make calculations based on patient age, the mean age of the COMPANION trial was 67 years, suggesting that CRT may be a cost-effective method in the prevention of hospitalization in this particular population.

BIVENTRICULAR PACING ALONE IN OLDER ADULTS

As demonstrated in the CARE-HF trial, biventricular pacing alone without an ICD improves survival compared to optimal medical therapy.[4] In addition to the hemodynamic and functional benefits, biventricular pacing may also reduce the number of ventricular arrhythmias, decreasing the need for ICD shocks.[22,23] ICDs have been shown to have a significant impact on a patient's quality of life. The conversion of a malignant arrhythmia can lead to various psychological complications, including anxiety and depression.[24,25] Such findings lead to the debate of whether CRT alone is preferred to CRT plus ICD in patients with HFrEF, and in particular in an older population. The significant reduction in mortality and hospitalizations when CRT is added to ICD compared with ICD alone as demonstrated in the MADIT-HF trial also raises the question of whether ICD alone is beneficial in patient outcomes, particularly in the older adults.[6] Further complicating the decision to implant the type of device, the recent DANISH trial (Danish Study to Assess the Efficacy of ICDs in Patients with Nonischemic Systolic Heart Failure on Mortality),[26] which randomized patients with nonischemic cardiomyopathy and NYHA functional class II through IV symptoms to receive either and ICD plus optimal therapy or optimal medical therapy alone, revealed no survival benefit in the group who received an ICD compared with medical therapy alone ($P = .28$; **Table 6**). In both groups, about 58% of the patients had CRT. Subgroup analyses of the trial revealed a lack of benefit of ICD in patients over the age of 59 years.[26]

Taking into consideration the data that have been presented and discussed, it is reasonable to consider implantation of only CRT in symptomatic older patients with HFrEF and evidence of dyssynchrony on optimal medical therapy without the addition of ICD. However, current guidelines state that an ICD is still indicated in patients with HFrEF, regardless of age, who have a reasonable expectation of survival with an acceptable functional status for at least 1 year.[27] Perhaps a prospective, randomized trial will definitively answer the question of the benefit of CRT in older adults.

Table 6
All-cause mortality rate (%) in patients enrolled in the DANISH trial

	1 y	2 y	3 y	4 y	5 y	6 y
ICD	3.5	5.4	9.9	14.3	18.8	23.4
Control	3.5	8	12.6	18.2	24.5	27.7

Abbreviation: ICD, implantable cardioverter defibrillator.
Data from Kober L, Thune JJ, Nielsen JC, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. N Engl J Med 2016;375(13):1221–30.

SUMMARY: CLINICAL DECISION

Our patient meets the criteria for both an ICD and CRT implantation. His ejection fraction is less than 35% and he has a left bundle branch block with a QRS duration of greater than 150 msec. Because he maintains an active lifestyle, which includes mowing the lawn and spending time outdoors with his family, and he wishes to continue to be able to perform these activities, the decision was made to pursue with a CRT and ICD combination placement.

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