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Biventricular Pacing Reduces Ventricular Arrhythmic Burden and Defibrillator Therapies in Patients with Heart Failure

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Summary

Background: Cardiac resynchronization therapy (CRT) has recently emerged as a new modality for the treatment of patients with advanced heart failure (HF).

Hypothesis: Cardiac resynchronization therapy reduces atrial and ventricular arrhythmia burdens.

Methods: We analyzed the clinical data of patients who underwent an upgrade from a dual-chamber to a biventricular implantable cardioverter-defibrillator (ICD) at a tertiary care center.

Results: Nineteen patients (age 67 ± 10 years, 18 men, left ventricular [LV] ejection fraction 0.24 ± 0.07) underwent an upgrade to CRT-ICD. The LV lead was placed in a lateral position in 11, posterolateral in 4, and anterolateral in 3 patients. Baseline New York Heart Association class of HF improved in 11 (58%) patients who were considered "responders." After adjusting for the duration of follow-up before and after the upgrade, the number of patients receiving any ICD therapy decreased significantly from 13 to 4 ($p = 0.004$) and the total number of therapies decreased from 72 to 17 ($p = 0.067$). Also, the number of detections of sustained ventricular arrhythmias decreased from 40 to 11 episodes ($p = 0.05$), but the decrease in the number of detected supraventricular arrhythmias and mode switch episodes was not significant. The reduction in the ventricular arrhythmia load was independent of whether or not the patient responded to CRT.

Conclusion: Our data suggest that CRT reduces ventricular but not atrial arrhythmia burden in patients with HF irrespective of their clinical response. This suggests that the reduction in arrhythmia is primarily an electrical phenomenon. Further studies are needed to confirm these findings and to uncover their underlying mechanisms.

Key words: biventricular pacing, ventricular tachycardia, supraventricular tachycardia

Introduction

Cardiac resynchronization therapy (CRT) has recently emerged as a treatment option for selected patients with moderate to severe heart failure (HF). Landmark biventricular pacing trials have demonstrated improvements in exercise capacity, functional class, quality of life, and HF hospitalization rates.[1–3] Data regarding the effects of CRT on arrhythmia occurrence are sparse. The Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE-ICD) trial[4] showed no significant difference in ventricular arrhythmia frequency or appropriate implantable cardioverter-defibrillator (ICD) therapies between patients receiving biventricular pacing and controls. However, more recent data suggest that CRT may decrease the frequency of ventricular arrhythmias, possibly through reverse remodeling.[5]

Biventricular pacing results in structural, hemodynamic, and neurohormonal changes, which may alter arrhythmia burden. We sought to test the hypothesis that, in patients with a dual-chamber ICD, upgrade to biventricular pacing decreases the frequency of both atrial and ventricular rhythm disturbances and ICD therapies.

Methods

Study Population

We identified 19 consecutive patients undergoing successful upgrade of dual-chamber ICD to CRT-ICD at the University of Pittsburgh Medical Center between October 2002 and

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October 2003. Baseline clinical information was ascertained from a review of the medical records. Arrhythmic events and device therapies were recorded from ICD-stored electrograms and device clinic notes before and after upgrade to biventricular pacing. Clinical response to CRT was defined as any improvement in New York Heart Association (NYHA) functional class, as determined by the responsible cardiologist at follow-up.

Statistical Analysis

Continuous variables are presented as a mean ± standard deviation and categorical variables as percentages. Continuous variables were compared using the Student's *t*-test and categorical variables using the chi-square test. The number of device therapies and arrhythmia detections was adjusted in each patient for the duration of follow-up before compared with after CRT therapy. Comparisons of the number of arrhythmias or device therapies before and after CRT were performed using the paired-samples *t*-test. A p value ≤ 0.05 was considered statistically significant.

Results

Nineteen patients (18 men) with a mean age of 67 ± 10 years and a left ventricular (LV) ejection fraction of 0.25 ± 0.07 underwent a successful upgrade of a dual-chamber to a CRT-ICD. Device programming as it relates to arrhythmia detection and therapy remained unaltered after the upgrade procedure. Baseline characteristics of the patients are shown in Table I. All but 3 patients had coronary artery disease, 15 patients had hypertension, and 7 had diabetes mellitus.

Of the 19 patients, 16 also had a diagnosis of atrial fibrillation (AF) or atrial tachycardia (10 with paroxysmal AF, 5 with persistent or chronic AF, and 1 with atrial tachycardia). As shown in Table I, patients were on optimal medical therapy for their HF, including the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta blockers, spironolactone with or without other diuretics, and digoxin. None of the patients was on chronic inotropic therapy.

Given the high prevalence of AF, a significant fraction of patients received warfarin (74%) and class III Vaughan Williams antiarrhythmic drugs (79%), including amiodarone (n = 11), sotalol (n = 1), and dofetilide (n = 3). Amiodarone doses were 200–400 mg/day. No blood levels of medications were recorded.

No complications were documented during the upgrade of the ICD to a CRT device capable of pacing the left and right ventricles simultaneously. The LV lead was placed in a lateral position in 12, posterolateral in 4, and anterolateral in 3 patients. Clinical, electrocardiographic, and echocardiographic data before and after the upgrade of the ICD to a CRT device are shown in Table II. Note that there was a significant improvement in the NYHA classification of HF after the upgrade to a CRT device (2.44 ± 0.62 after CRT compared with 2.89 ± 0.43 at baseline, p = 0.005) with 21% of patients before CRT versus 63% after CRT belonging to NYHA HF class < 3 (p = 0.051). There was also a significant improvement in LV function after CRT (31 ± 9% after CRT compared with 25 ± 7% at baseline, p = 0.044) and a trend toward decrease in the amount of mitral regurgitation (1.3 ± 1.2 after CRT compared with 1.9 ± 1.1 at baseline, p = 0.06). All other parameters were unchanged with CRT. The duration of follow-up was significantly longer before compared with after the upgrade to CRT (13.3 ± 3.1 compared with 5.4 ± 1.2 months, p < 0.001). This difference in duration was adjusted for in all comparisons of arrhythmic events before and after CRT.

Baseline NYHA class of HF improved in 11 (58%) patients who were considered "responders." After adjusting for the du-

TABLE I Patients' baseline characteristics

Number of patients	19
Age (years)	67±11
Gender (men : women)	18 : 1
Left ventricular ejection fraction	24±7 %
NYHA class of HF	2.89±0.43
Coronary artery disease	84 %
Hypertension	79 %
Diabetes mellitus	37 %
Atrial fibrillation	84 %
Heart rate (beats/min)	77 ± 14
PR interval (ms)	203 ± 50
QRS interval (ms)	171 ± 49
QTc interval (ms)	515 ± 78
ACE inhibitors or angiotensin receptor blockers	95 %
Beta blockers	79 %
Spironolactone	16 %
Other diuretics	79 %
Digoxin	58 %
Coumadin	74 %
Class 3 antiarrhythmic medications	79 %

Abbreviations: NYHA = New York Heart Association, HF = heart failure, ACE = angiotensin-converting enzyme.

TABLE II Comparisons of clinical and echocardiographic parameters before and after cardiac resynchronization therapy (CRT)

	Pre CRT	Post CRT	p Value
Follow-up time (months)	13.3 ± 3.1	5.4 ± 1.2	< 0.001
NYHA class of heart failure	2.89 ± 0.43	2.44 ± 0.62	0.005
NYHA class <3 (%)	21	63	0.051
LA diameter (cm)	5.4 ± 1.1	5.4 ± 0.9	NS
LVEDD (cm)	6.3 ± 0.9	6.4 ± 1.0	NS
LVEF	0.25 ± 0.07	0.31 ± 0.09	0.044
Mitral regurgitation	1.9 ± 1.1	1.3 ± 1.2	0.06

Abbreviations: NYHA = New York Heart Association, LA = left atrium, LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction.

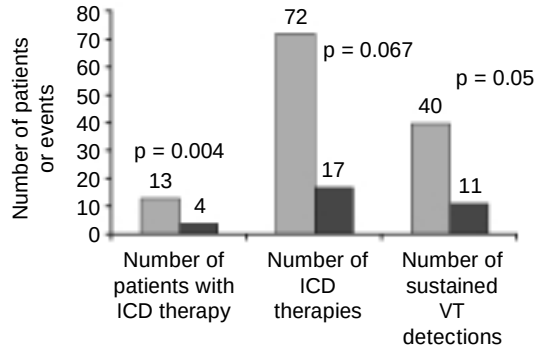

FIG. 1 Bar graph representing the number of patients receiving any implantable cardioverter-defibrillator (ICD) therapy, the number of ICD therapies, and the number of sustained ventricular arrhythmias detected by the ICD before and after cardiac resynchronization therapy (CRT). Note that for the number of events, the p values were adjusted to account for the difference in follow-up duration before and after the ICD upgrade. VT = ventricular tachycardia. □ = Before CRT, ■ = after CRT.

ration of follow-up before and after the upgrade to CRT, the number of patients receiving any ICD therapy, including all shocks and antitachycardia pacing episodes, decreased significantly from 13 to 4 patients (p = 0.004). The number of patients receiving appropriate shocks for ventricular arrhythmias decreased from 9 to 4, those receiving inappropriate shocks for any reason excluding ventricular arrhythmias decreased from 3 to 0, and the number of those receiving antitachycardia pacing decreased from 6 to 2 patients (Fig. 1). Also, the total number of ICD therapies decreased from 72 prior to CRT to 17 after CRT (adjusted p value 0.067). This included a decrease in the number of appropriate shocks from 45 to 15, a decrease in the number of inappropriate shocks from 12 to 0, and a decrease in the number of antitachycardia pacing events from 15 to 2. For all these comparisons, the adjusted p value was < 0.1 but did not reach statistical significance.

The number of detected ventricular arrhythmic events decreased significantly following the addition of CRT. The number of detections of sustained ventricular arrhythmias decreased from 40 to 11 episodes (adjusted p = 0.05). Seven patients had a decrease in their number of episodes of ventricular tachycardia (VT), while 2 had increased episodes of VT, and 10 had no change in their VT burden after CRT. The decrease in the number of detected supraventricular tachycardias (116 to 3, p = NS) and of mode switch episodes (6,098 to 1,869, p = NS) was not statistically significant. Of note, the reduction in the ventricular arrhythmia loads was documented despite a significant reduction in the number of patients treated with antiarrhythmic medications (79% before CRT vs. 47% after CRT, p = 0.014). No changes in the dosage of the medications were noted in those patients who continued to take antiarrhythmic medications after CRT (n = 9). In all six patients in whom antiarrhythmic drugs were discontinued, the medication was stopped at the time of upgrade. In these patients, the antiarrhythmic drug was used to suppress AF and was discontinued because it was ineffective (n = 5 patients, one of whom had atrioventricular nodal ablation) or secondary to lung toxicity (n = 1). To ensure near-continuous biventricular pacing, ventricular pacing in AF was programmed at rates faster than the ventricular response rate during the arrhythmia. No changes in the usage of any HF medication were noted after the upgrade to a CRT device.

It is important to note that the reduction in ventricular arrhythmia burdens after the initiation of biventricular pacing was independent of whether or not the patient was classified as a "responder" or "nonresponder" to CRT therapy. During follow-up, one patient died and two patients underwent successful orthotopic heart transplantation; all three of these were "nonresponders" to CRT.

Discussion

Our data suggest that CRT significantly reduces the frequency of ICD therapy in patients with HF and decreases the number of sustained ventricular arrhythmic events, which is consistent with previously published data.[5] These effects were independent of whether or not the patients had experienced NYHA functional class improvement after upgrade to biventricular pacing.

There are several plausible mechanisms by which CRT could reduce arrhythmic burden. First, biventricular pacing reduces the severity of mitral regurgitation[6] and has been associated with reverse remodeling, with a reduction in LV end-diastolic diameter (even though not documented in our dataset), improvement in ejection fraction, and increase in diastolic filling time.[7] Second, CRT is associated with beneficial neurohormonal effects, such as a decrease in brain natriuretic peptide levels.[8]

Biventricular pacing has been shown to improve heart rate variability, a marker of increased mortality and arrhythmia susceptibility in patients with HF.[9] Finally, CRT appears to exert a beneficial effect on electrical remodeling in the failing heart.

Following institution of CRT, suppression of VT storm,[10] spontaneous conversion of chronic AF to sinus rhythm,[11] and loss of native left bundle-branch block[12] have also been reported in the literature.

Limitations

This retrospective study has several important limitations. Assessment of response to CRT was based on review of notes by physicians in follow-up. Our small study has limited statistical power that has probably prevented some trends toward decrease in atrial arrhythmic loads from reaching statistical significance and precluded correlation of markers of LV reverse remodeling such as ventricular size and mitral regurgitation severity with arrhythmia frequency or clinical response as measured by the improvement in class of HF. Also, this study is observational and lacks a control group.

Conclusion

In summary, CRT appears to decrease the number of patients receiving ICD therapy and the frequency of device therapy in patients with HF who previously had received ICDs. In addition, CRT significantly reduces the number of detected episodes of ventricular but not of atrial arrhythmias despite a significant decrease in the use of antiarrhythmic drugs. These effects are independent of clinical response, suggesting a role for electrical remodeling. The underlying mechanisms for these findings deserve further study.

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