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Impact of Upgrade to Cardiac Resynchronization Therapy on Ventricular Arrhythmia Frequency in Patients With Implantable Cardioverter-Defibrillators

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OBJECTIVES This study compared cardiac resynchronization therapy's (CRT) impact on ventricular tachyarrhythmia susceptibility in patients who, due to worsening heart failure (HF) symptoms, underwent a replacement of a conventional implantable cardioverter-defibrillator (ICD) with a CRT-ICD.

BACKGROUND Cardiac resynchronization therapy is an effective addition to conventional treatment of HF in many patients with left ventricular systolic dysfunction. However, whether CRT-induced improvements in HF status also reduce susceptibility to life-threatening arrhythmias is less certain.

METHODS Clinical and ICD electrogram data were evaluated in 18 consecutive ICD patients who underwent an upgrade to CRT-ICD. Pharmacologic HF therapy was not altered during follow-up. The definition of ventricular tachycardia (VT) and ventricular fibrillation (VF) for each patient was as determined by device programming. Statistical comparisons used paired *t* tests.

RESULTS Findings were recorded during two time periods: 47 ± 21 months (range 24 to 70 months) before and 14 ± 2 months (range 9 to 18 months) after CRT upgrade. At time of upgrade, patient age was 69 ± 11 years and ejection fraction was 21 ± 8%. Before CRT the frequency of VT, VF, and appropriate ICD shocks was 0.31 ± 1.23, 0.047 ± 0.083, and 0.048 ± 0.085 episodes/month/patient, respectively. After CRT-ICD, VT and VF arrhythmia burdens and frequency of shocks were respectively 0.13 ± 0.56, 0.001 ± 0.004, and 0.003 ± 0.016 episodes/month/patient ($p = 0.59$, 0.03, and 0.05 vs. pre-CRT).

CONCLUSIONS Arrhythmia frequency and number of appropriate ICD treatments were reduced after upgrade to CRT-ICD for HF treatment. Thus, apart from hemodynamic benefits, CRT may also ameliorate ventricular tachyarrhythmia susceptibility in HF patients. (J Am Coll Cardiol 2005;46:2258–63) © 2005 by the American College of Cardiology Foundation

Biventricular stimulation (i.e., cardiac resynchronization therapy [CRT]) has been shown to improve cardiac function, diminish heart failure (HF) hospitalization frequency, and enhance quality of life for many patients with severe left ventricular systolic dysfunction and intraventricular conduction disease who are already being administered maximally tolerated pharmacological treatment for HF (1–11). However, whether CRT benefits extend to diminished susceptibility to potentially life-threatening arrhythmias remains controversial (8–15). This study was designed to further address the potential for CRT to provide an antiarrhythmia benefit. To this end, we compared the impact of biventricular stimulation on the frequency and characteristics of documented ventricular tachyarrhythmias in patients who, for purposes of ameliorating HF symptoms, underwent an "upgrade" of a conventional implantable cardioverter-defibrillator (ICD) system to a CRT-ICD system. Thus, each patient included in this study served as his/her own control.

METHODS

Patient population. The study population comprised a consecutive series of 18 patients who underwent successful upgrade from conventional ICD therapy to a biventricular ICD (CRT-ICD) at either the University of Minnesota, Minneapolis, Minnesota, or Central Minnesota Heart Center, St. Cloud, Minnesota. Upgrade to CRT was based solely on conventionally accepted HF indications at the time (i.e., increased pulmonary and/or peripheral edema, increasing exertional intolerance), with enrollment concluding in

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Abbreviations and Acronyms

ATP	= antitachycardia pacing
CARE-HF	= Cardiac Resynchronization Heart Failure trial
COMPANION	= Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure trial
CRT	= cardiac resynchronization therapy
HF	= heart failure
ICD	= implantable cardioverter-defibrillator
LVEF	= left ventricular ejection fraction
MIRACLE	= Multicenter InSync Randomized Clinical Evaluation trial
NYHA	= New York Heart Association
VF	= ventricular fibrillation
VT	= ventricular tachycardia

December 2003. In order to evaluate the impact of CRT on the frequency and nature of documented ventricular arrhythmias, only those individuals with a minimum eight months after CRT follow-up were included. Arrhythmia frequency and characteristics before upgrade were determined by retrospective assessment of ICD follow-up records. After CRT, all arrhythmia features were assessed prospectively. In regard to hemodynamic effects of CRT upgrade, left ventricular ejection fraction (LVEF) was reassessed at approximately three to six months. Improvement of 5% to 10% was observed in 13 patients, and no detectable change occurred in the remainder. Two deaths occurred at >8 months after CRT-ICD; otherwise none of the patients was lost to follow-up. Data review procedures were approved in accordance with institutional guidelines.

Demographic features, LVEF, pharmacological treatment, and HF functional class (New York Heart Association [NYHA]) are summarized in Table 1. The primary end point during follow-up was ventricular tachyarrhythmia burden (see definitions in the following text).

Implantation technique. Left ventricular stimulation was achieved in most cases by placement of a permanent pacing lead in the coronary sinus using a pre-formed introducer technique (16–18), and advancing it to a venous tributary serving the mid-left ventricular free wall. In a minority of instances, conventional over-the-wire introduction systems were utilized. In all cases, devices were programmed with ≥2-fold voltage safety factor in each chamber and a sufficiently rapid base rate to assure biventricular pacing for as much time as possible.

Follow-up procedures. At a minimum, all ICD patients included in this study were seen in the clinic and examined at every three months after implantation. Individual patients were also seen and ICD interrogation undertaken at intervening times as circumstances dictated. At each visit, clinical status was documented, pharmacological therapy was recorded, and the ICD was interrogated. All ICD generators permitted full disclosure of arrhythmia recurrence date, duration, and cycle length, as well as the nature and effectiveness of delivered therapies. As appropriate, intracardiac electrograms were reviewed, and to the extent possible, the appropriateness of ICD shocks and/or antitachycardia pacing (ATP) applications were determined.

Table 1. Clinical and Demographic Features

Number of patients	18
Follow-up duration (months)	
Prior (range)	47 ± 21 (24–70)
Post (range)	14 ± 12 (9–18)
Age (yrs)	69 ± 11
Gender	
Male	15 (83%)
Female	3 (17%)
Presenting arrhythmia	
NSVT	17%
VT	55%
VF	28%
LVEF at upgrade (%)	21 ± 8
NYHA functional class at upgrade	
II	1
III	13
IV	4
NYHA functional class at last follow-up	
II	6
III	11
IV	1
Underlying disease	
Ischemic (%)	11 (61%)
Nonischemic (%)	7 (39%)
Medications	
Amiodarone (typical long-term dosing: 200 mg once daily)	7 (39%)
Beta-blockers (typical dosing: metoprolol 50 mg twice daily, or 100 mg long-acting once daily)	8 (44%)
ACE inhibitors	14 (77%)

ACE = angiotensin-converting enzyme; LVEF = left ventricular ejection fraction; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; VF = ventricular fibrillation; VT = ventricular tachycardia.

None of the patients included in this study were deemed "pacemaker-dependent." Thus, before initiation of CRT therapy, none of the patients were exposed to prolonged periods of right ventricular apex pacing. The percent of cardiac cycles that were ventricular paced based on findings obtained at the most recent device interrogation before "upgrade" ranged from 0% to 15%. Subsequent to initiation of CRT, device follow-up confirmed biventricular pacing >85% (range 85% to 100%) of the time in all cases. However, technological limitations preclude being able to confirm that biventricular capture was consistently achieved at all points in time.

Definitions. ARRHYTHMIA BURDEN. The total number of episodes and total duration of an arrhythmia in a given time frame, presented on a per month basis.

VENTRICULAR TACHYCARDIA (VT). Ventricular tachyarrhythmia with cycle length <400 ms but ≥320 ms leading to ICD therapy.

VENTRICULAR FIBRILLATION (VF). Ventricular tachyarrhythmia with cycle length ≤320 ms leading to ICD therapy.

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Table 2. Individual Event Rates (Event/Month) and Therapy Episodes (Episode/Month) of Patients Pre- and Post-CRT Implantation

	VT		VF		Total		ATP		Shocks	
Patient #	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	0	0	0.27	0	0.27	0	0.27	0	0	0
2	0.08	0	0.07	0	0.15	0	0.08	0	0.08	0
3	0	0	0.14	0	0.14	0	0	0	0.14	0
4	0.54	0	0	0	0.54	0	0.22	0	0	0
5	0.06	0	0.2	0	0.26	0	5	0	0.37	0
6	0	0	0.02	0	0.02	0	0.08	0	0	0
7	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0
9	33	0	0.4	0.5	33.4	0.5	32.8	0	0.18	0.35
10	0	0	0	0	0	0	0	0	0	0
11	0.05	0	0	0	0.05	0	0.05	0	0	0
12	0.06	0	0	0	0.06	0	0.06	0	0	0
13	0	0	0	0	0	0	0	0	0	0
14	0.01	0	0.07	0	0.08	0	0.04	0	0.04	0
15	0.14	0	0.03	0	0.17	0	0.11	0	0.06	0
16	6.27	0	0	0	6.27	0	0.08	0	0.02	0
17	0.02	0	0	0	0.02	0	0.02	0	0	0
18	0	0.19	0	0.09	0	0.28	0	0.21	0	0.05

ATP = antitachycardia pacing; CRT = cardiac resynchronization therapy; VF = ventricular fibrillation; VT = ventricular tachycardia.

Statistical analysis. Comparison of arrhythmia frequency and characteristics before and after initiation of CRT therapy utilized the two-tail paired *t* test. A p value of <0.05 was considered statistically significant.

RESULTS

Eighteen patients (15 men, 3 women, mean age was 69 ± 11 years) received an upgrade to CRT-ICD from a pre-existing conventional ICD system. In each case, the indication for upgrade was to facilitate HF therapy in individuals thought to have been already administered maximum tolerable pharmacological treatment. The mean ejection fraction at time of upgrade was 21 ± 8%. Clinical and demographic features including mean age, male-to-female ratios, underlying heart disease, LVEF, presenting arrhythmia and symptom, NYHA functional class, and medications are provided in Table 1. Ischemic heart disease comprised 61% of the population. Medications and dosing remained unchanged after CRT upgrade, except for one patient in whom amiodarone therapy was terminated due to cutaneous side effects.

Patients had been followed for 47 ± 21 months (range 24 to 70 months) before CRT upgrade, and were thereafter followed prospectively for an additional 14 ± 2 months (range 9 to 18 months). Presenting arrhythmias were VT in 55%, VF in 28%, and nonsustained VT in 17%. During the baseline period, 13 of 18 (72%) patients had at least one VT and/or VF event. After CRT-ICD placement, only 2 of 18 (11%) had tachyarrhythmic events. The total number of events before upgrade was 32 ± 80.5 compared with 0.7 ± 2.2 after the upgrade ($p = 0.01$). Findings were essentially unchanged when re-examined using comparable durations of pre- and post-CRT-ICD follow-up in each patient. No statistically significant correlation between event rate and change in LVEF was detected.

Before CRT the frequency of VT and VF was 0.31 ± 1.23 and 0.047 ± 0.083 episodes per patient per month, respectively (Table 2). After CRT the frequency of VT and VF was 0.13 ± 0.56 and 0.001 ± 0.004 per patient per month, respectively ($p = 0.01$) (Table 2). The decrease in event rates after CRT for VT and VF was 0.18 ($p = 0.59$) and 0.046 ($p = 0.03$) episodes per patient per month, respectively.

The frequency of both appropriate ATP applications and ICD shocks was also reduced after CRT upgrade (Table 2). During conventional ICD treatment, ATP was applied in 10 of 18 (56%) patients compared with 1 of 18 (3%) after CRT-ICD placement. Similarly, the number of patients receiving ICD shocks diminished after CRT. The frequency of shocks was 0.048 ± 0.085 episodes/month/patient with the conventional ICD versus 0.003 ± 0.016 episodes/month/patient after CRT-ICD ($p = 0.05$). Among the study patients, only one individual exhibited aggravation of arrhythmia status after CRT initiation.

There were two deaths recorded during follow-up. One in-hospital death occurred at 18 months after upgrade to CRT-ICD and was due to progressive intractable HF. This patient had VT episodes after CRT-ICD, but at a decreased frequency than previously. The second death was unwitnessed, but occurred in an otherwise apparently stable patient at approximately 16 months after CRT-ICD upgrade. The ICD was not interrogated. This death was deemed to be a sudden death, and occurred in a patient who had not exhibited any arrhythmias during the CRT-ICD phase of follow-up.

DISCUSSION

This study examined the impact of CRT on ventricular tachyarrhythmia susceptibility in patients with pre-existing conventional ICDs. In each case, an "upgrade" to CRT-ICD was initiated as part of the HF treatment strategy in that individual. Pharmacological therapy of HF was already deemed to be as effective as possible in each patient, and was not substantially altered during follow-up. The principal findings were that CRT-ICD was associated with reduction of both ventricular tachyarrhythmia burden and number of appropriate ICD therapies, particularly shocks. Further, after CRT-ICD placement, the nature of ventricular tachyarrhythmia recurrences was altered. Specifically, the frequency of those tachycardias having the shortest cycle lengths (i.e., those falling within the "VF zone" as defined by ICD programming) was the most markedly diminished.

Impact of CRT therapy on ventricular arrhythmias. Recent clinical trials have provided ample evidence supporting the effectiveness of CRT therapy in the treatment of HF patients with poor left ventricular systolic function (1–11). The most important positive findings have been diminished frequency of hospitalization, enhanced exercise capacity, and improved quality of life. However, the impact of CRT on arrhythmia susceptibility and mortality has been less clear, with multiple studies providing differing outcomes (9,11–15,19,20).

The CONTAK-CD (9) and Multicenter InSync Randomized Clinical Evaluation-ICD (MIRACLE-ICD) (10) trials directly addressed the question of whether CRT-ICD therapy offers additional antiarrhythmic benefit not available with conventional ICDs. CONTAK-CD (9) compared CRT-ICD therapy to conventional ICD treatment. A parallel two-arm design (i.e., CRT-ICD vs. conventional ICD) was employed. Ultimately, 490 HF patients (NYHA functional class II to IV) were enrolled. Apart from HF, these individuals exhibited intraventricular conduction delays and sufficiently severe ventricular arrhythmias to warrant ICD therapy. All patients received a CRT-capable device; in 245 patients the CRT feature was disabled, whereas in the remaining patients (n = 245) both features were enabled. After six months, the frequency of observed arrhythmias did not differ in the two treatment groups; 15% of CRT patients received appropriate ICD shocks compared with 16% of no-CRT patients. Further, the distribution of arrhythmias was not substantially different for CRT-ICD versus no-CRT-ICD (VT: 10% vs. 11%, VF: 3% vs. 2%, both VT and VF: 2% vs. 2%). Thus, an antiarrhythmic benefit for CRT was not demonstrable. Similarly, MIRACLE-ICD (10) enrolled 369 patients (182 randomized to CRT off, and 187 to ICD-CRT on) with LVEF ≤35% and abnormally prolonged QRS duration (≥130 ms). All enrollees were considered to be NYHA functional class III (n = 328) or class IV (n = 41) despite best available pharmacological treatment. The primary end points were changes between baseline and six months in quality of life, functional class, and 6-min walk distance. However, survival, incidence of ventricular arrhythmias, and rates of hospitalization were also compared. At six months, there was no evident antiarrhythmic impact of CRT. In terms of "intention-to-treat" numbers, 26% of control patients had appropriate ICD shocks versus 24% in CRT-ICD patients ($p = 0.76$). Similarly, the frequency of ATP did not differ between the two groups (31% of controls vs. 33% of CRT-ICD patients, $p = 0.89$).

The absence of CRT-associated antiarrhythmic benefit in CONTAK-CD and MIRACLE-ICD trials is in contrast to our findings. In part, this difference may be due to the fact that the CONTAK-CD and MIRACLE-ICD studies examined treatment effect in parallel patient populations rather than within the same individuals. In this regard, important findings previously reported by Higgins et al. (13) from the Ventak-CD trial tend to support this view. The latter report restricted its observations to two periods of three months each in patients subjected to biventricular ICD therapy versus ICD treatment without pacing. Among 32 patients enrolled in the Ventak CHF study, ventricular tachyarrhythmias were recorded in 16% of patients during the CRT phase versus 34% in the no-CRT portion of the follow-up ($p = 0.035$).

With regard to mortality, both the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial (11) and the Cardiac Resynchronization Heart Failure (CARE-HF) trial (20) were sufficiently powered to address this end point. These studies differed in that COMPANION combined both CRT and ICD, whereas CARE-HF examined CRT effect alone. Nevertheless, both tended to support a mortality benefit; COMPANION reported a mortality reduction that approached conventionally accepted statistical significance (11) and CARE-HF (20) reported a clear-cut statistically significant reduction of both the primary combined end point (i.e., mortality and major cardiovascular events) as well as mortality alone (a secondary end point). Over an approximate 29 months of average follow-up, CRT was associated with a 20% mortality, compared to 30% mortality in controls (95% confidence interval 0.48 to 0.85, $p < 0.002$).

Antiarrhythmic and proarrhythmic balance in CRT. The potential for CRT to offer a beneficial antiarrhythmic effect was anticipated by virtue of a theoretically diminished risk of myocardial ischemia due to improved cardiac output with reduced wall stress, and a more advantageous neurohumoral impact on diseased myocardium (19–22). On the other hand, the potential for an epicardial pacing-induced proarrhythmic effect to occur during CRT by altering the direction and duration of left ventricular repolarization has raised concern (23). Thus, the possibility exists that the beneficial and adverse effects of CRT on arrhythmia susceptibility may tend to counteract each other making it difficult to discern a true arrhythmia or mortality benefit. Large study populations may overcome this difficulty, as suggested by the

demonstration of CRT mortality benefit in a recent meta-analysis combining multiple CRT studies (24).

In terms of a possible CRT-triggered proarrhythmic effect, early concern arose in the Multisite Stimulation in Cardiomyopathy (MUSTIC) trial (4) as a result of deaths that occurred shortly after cross-over from conventional pacing to biventricular stimulation. Ultimately, it was concluded that the deaths were attributable to specific clinical circumstances in each case. More recently, despite improved hemodynamic state in CARE-HF, the investigators did observe a 7% sudden death rate in their CRT patients. A similar trend was noted in COMPANION. However, rather than a proarrhythmic effect, it is more likely that CRT, by reducing HF deaths, may seem to tip the balance toward sudden deaths. In any case, such an outcome further favors the need for CRT-ICD combinations.

Study limitations. The analysis in this study is subject to important limitations. First, by virtue of the fact that our patient cohort included only individuals in whom upgrade to CRT was based on hemodynamic indications, we may have selected a relatively sick patient population. Such a population may have had a higher ambient level of cardiac arrhythmia than would be observed in a more typical group of CRT candidates. If true, one could argue that any CRT-ICD benefit was magnified by the study design, thereby allowing benefit to be detectable in a relatively small cohort. On the other hand, even if the benefit were small and only discernable in this manner, one would not expect the direction of this treatment effect to have been altered by virtue of being studied in a very sick population. A demonstrable benefit or, at worst, a neutral effect, would be a reasonable expectation in less sick patients. Second, we have inferred from the findings that the CRT feature was the principal factor reducing arrhythmia susceptibility. However, CRT therapy is inherently accompanied by "overdrive" pacing in order to maintain control over the ventricular activation sequence. Although unlikely, it is possible that pacing alone could have been primarily responsible for diminishing arrhythmia susceptibility in our cohort. Third, the patient population, although consecutive, was not randomized and the pre-upgrade arrhythmia status was determined retrospectively. While a prospective approach is generally conceded to be superior, this aspect of the study design eliminated inclusion of patients in whom upgrade to CRT was motivated principally by a desire to try to reduce arrhythmia burden. Fourth, the study population was small, and the two deaths during follow-up might be considered to represent a mortality concern. On the other hand, the crude mortality rate in this study was only approximately 7.4% per year, which is reasonable given the nature of the HF population. Fifth, we were unable to demonstrate a correlation between reduction of arrhythmia event rates and positive change in LVEF. Conceivably, more sensitive measures of altered hemodynamic status, such as changes in circulating catecholamines or brain natriuretic peptide levels, might be more effective in evaluating such a relationship. Finally, the small study population leaves open concern that the detected apparent CRT benefit was overestimated by chance. Consequently, given this last concern, as well as the previously stated limitations, the findings reported here must be interpreted with caution, and perhaps are best used as the basis for designing a prospective randomized trial.

Conclusions. This study examined ventricular arrhythmia burden and ICD treatment frequency in patients in whom HF treatment dictated the need for replacing a pre-existing conventional ICD system with a CRT-ICD. The availability in each of these individuals of a full-featured ICD, both before and after introduction of CRT, along with absence of substantial alterations of drug therapy, permitted detailed assessment of the impact of CRT on arrhythmia susceptibility in these patients. The findings suggest that, in the setting of diminished left ventricular systolic function and HF, CRT does diminish both tachyarrhythmia susceptibility and the frequency of either ICD shock or ATP. Thus, while potential mortality benefits cannot be addressed in this study, CRT appears to reduce tachyarrhythmia risk and also the need for ICD treatment intervention in these high-risk patients.

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