

9-2007

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## Recommended Citation

Yannopoulos, Demetris; Lurie, Keith MD; Sakaguchi, Scott; and Milstein, Simon MD, "Reduced Atrial Tachyarrhythmia Susceptibility After Upgrade of Conventional Implanted Pulse Generator to Cardiac Resynchronization Therapy in Patients with Heart Failure" (2007). *Articles*. 43.

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# Reduced Atrial Tachyarrhythmia Susceptibility After Upgrade of Conventional Implanted Pulse Generator to Cardiac Resynchronization Therapy in Patients With Heart Failure

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- Objectives** We sought to identify the impact of cardiac resynchronization therapy (CRT) on atrial tachyarrhythmia (AT) susceptibility in patients with left ventricular (LV) systolic dysfunction in whom worsening heart failure (HF) resulted in upgrade from conventional dual-chamber pulse generator to cardiac resynchronization therapy-defibrillator (CRT-D).
- Background** Cardiac resynchronization therapy with a defibrillator improves survival rates and symptoms in patients with LV systolic dysfunction but little is known about its effects on AT incidence in the same patient population.
- Methods** Twenty-eight consecutive HF patients who underwent device upgrade to CRT-D were included. Patients had  $\geq 2$  device interrogations in the 1 year before upgrade and  $\geq 3$  interrogations in the 18- to 24-month follow-up after upgrade. Echocardiographic parameters were assessed before and at 3 to 6 months after CRT-D. Additional observations included number of hospital stays, HF clinical status, and concomitant pharmacological therapy. By virtue of this study design, each patient served as his/her own control. Statistical analysis was performed by 2-tailed paired *t* test and with nonparametric tests where appropriate.
- Results** Within 3 months after CRT, the number of HF patients with documented AT decreased significantly from the immediate pre-CRT value and tended to decline with time. At 1-year follow-up, 90% of patients were AT-free compared with 14% of patients 3 months before CRT ( $p < 0.001$ ). Furthermore, the number of AT episodes/year and their maximum duration decreased after CRT (mean  $\pm$  SD;  $181 \pm 50$  vs.  $50 \pm 20.2$ ,  $p < 0.05$ , and  $220.8 \pm 87$  s vs.  $28 \pm 21$  s,  $p < 0.05$ , respectively). Finally, CRT was associated with improved LV ejection fraction (mean  $\pm$  SD; from  $26 \pm 5.3\%$  to  $31 \pm 7\%$ ,  $p < 0.001$ ) and reduced number of HF or arrhythmia hospital stays ( $p < 0.05$ ).
- Conclusions** Our findings support the view that CRT might decrease AT susceptibility in HF patients with LV systolic dysfunction. (J Am Coll Cardiol 2007;50:1246–51) © 2007 by the American College of Cardiology Foundation

Cardiac resynchronization therapy (CRT) has been shown to improve both mortality and morbidity in patients with moderate to severe systolic heart failure (HF) associated with ventricular dyssynchrony (1–4). Additionally, in some but not all reports, CRT has also been associated with

diminished susceptibility to ventricular tachyarrhythmias in HF patients (5–8).

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Manuscript received February 26, 2007; revised manuscript received April 17, 2007, accepted April 24, 2007.

Improvement of left ventricular (LV) function, mitral regurgitation severity, and neurohormonal balance is thought to be the basis for CRT benefit in HF patients (3). Given these desirable CRT effects, it is reasonable to anticipate that atrial function would be similarly benefited. However, to date, the reported impact of CRT on atrial tachyarrhythmia (AT) susceptibility in HF has varied (9,10). Thus, Hoppe et al. (9) reported no apparent benefit, whereas Fung et al. (10) observed diminished AT susceptibility in CRT-treated patients.

This study re-examined the potential for CRT to diminish frequency and duration of documented AT episodes in patients with symptoms of worsening HF due to diminished LV systolic function. However, only patients undergoing “upgrade” of a conventional dual-chamber implantable pacemaker or cardioverter-defibrillator (ICD) system to a cardiac resynchronization therapy-defibrillator (CRT-D) system were included. This study design had 2 principal advantages. First, because implantable devices were present in all patients throughout the study period, characterization of AT events was as complete as possible both before and after CRT. Second, each patient served as his/her own control.

## Methods

**Patient population.** The study population comprised a consecutive series of 28 patients  $\geq 18$  years of age who underwent successful upgrade from a conventional dual-chamber pacemaker or ICD to a biventricular ICD (CRT-D) at either the University of Minnesota Medical Center, Minneapolis, or Central Minnesota Heart Center, St. Cloud, Minnesota. All patients had moderate to severe congestive HF associated with diminished LV systolic function and had a dual-chamber pacemaker or dual-chamber ICD implanted for  $>1$  year before upgrade to a CRT-D.

**Implantation technique.** Pulse generator and pacing electrode placement used standard transvenous implantation techniques. In the case of CRT-D implantation, details have been previously published (8). Devices were programmed to assure biventricular pacing for as much time as possible. Initial programming was DDDR mode with a base-rate of 70 beats/min.

Devices from 3 major U.S. manufacturers were used (St. Jude Medical Inc., Guidant Corp., and Medtronic Inc.). The same manufacturer was used before and after upgrade in all cases to maintain consistency of AT detection criteria. **Indications for upgrade, inclusion/exclusion criteria.** The decision for upgrade to CRT-D was based on clinical judgment when there was a need, despite aggressive medical therapy, to address worsening HF as indicated by 1 or more of:

- Increasing frequency of HF hospital stays
- Deteriorating exertional tolerance or development of HF symptoms at rest
- Clinical signs of increasing pulmonary congestion and/or peripheral edema

In addition to the clinical indications for CRT upgrade just described, study inclusion criteria included:

- QRS duration  $>120$  ms. No echocardiographic criteria of mechanical dyssynchrony were used.
- The presence, before CRT “upgrade,” of a full-featured conventional dual-chamber pulse generator (pacemaker or ICD) capable of recording and storing occurrence, duration, and cycle length of high-rate atrial events.

- Successful placement of a complete CRT-D system by transvenous technique.
- At least 2 pulse generator interrogations each year before upgrade and every-3-month interrogations within the 18 to 24 months after upgrade.
- A minimum follow-up of  $>2$  years, including  $>1$  year before and 18 to 24 months after CRT upgrade.

Study exclusion criteria were the presence of any of the following:

- Inability of implanted device to provide atrial data as defined earlier
- Permanent atrial fibrillation
- Incomplete follow-up

The AT episodes were defined as all high-rate atrial events documented by the implanted pulse generator. After CRT, high-rate atrial episodes were assessed prospectively for up to 2 years. All patients were alive at last follow-up. No patient was lost to follow-up. All patients underwent echocardiographic assessment of LV systolic function within 3 months before and 3 to 6 months after CRT-D implantation.

Before initiation of CRT therapy, no patient was exposed to prolonged periods of right ventricular apex pacing. The percent ventricular paced cardiac cycles obtained at the most recent device interrogation before CRT “upgrade” was  $<15\%$ . Device follow-up confirmed biventricular pacing  $>85\%$  (range 85% to 100%) of the time, subsequent to initiation of CRT.

**Follow-up procedures.** Study patients underwent pulse generator interrogation at a minimum every 3 months but were also seen and device interrogation was undertaken at intervening times as circumstances dictated. Clinical data collected at each visit included:

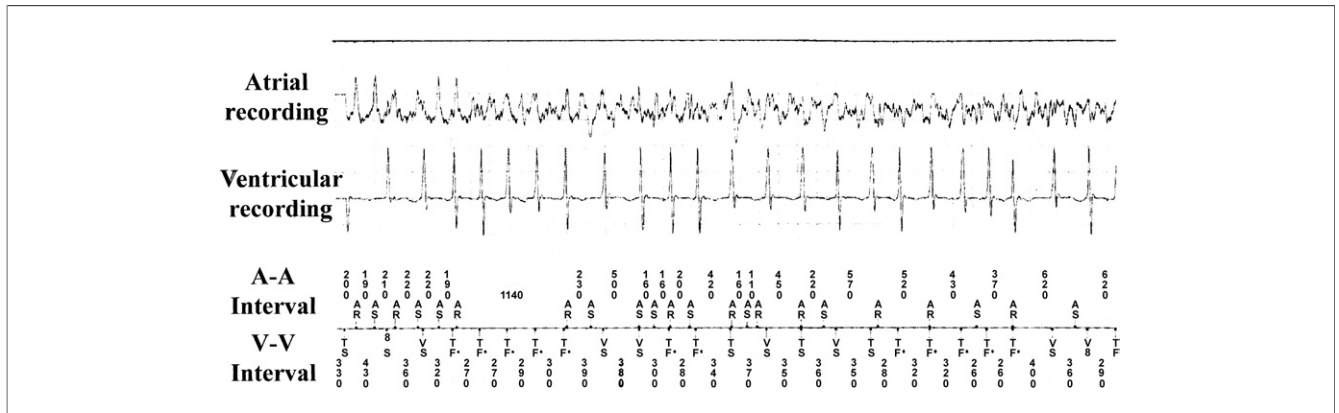
- Number and nature of intervening hospital stays or illness, if any
- HF clinical status
- Current pharmacological therapy

All pulse generators permitted full disclosure of AT events with date, duration, and cycle length. However, owing to memory limitations, intracardiac electrograms were not available for all events. Those that were available were examined to assess the regularity of atrial cycle lengths (Fig. 1). Arrhythmia data recorded at each clinic visit included:

- Number of AT episodes
- Longest and shortest duration of recorded episodes
- Highest atrial rates recorded by the devices

## Abbreviations and Acronyms

<b>AT</b> = atrial tachyarrhythmia
<b>CRT</b> = cardiac resynchronization therapy
<b>CRT-D</b> = cardiac resynchronization therapy-defibrillator
<b>HF</b> = heart failure
<b>LV</b> = left ventricular
<b>LVEF</b> = left ventricular ejection fraction



**Figure 1. Intracardiac Electrogram of Atrial Fibrillation**

Intracardiac atrial and ventricular electrograms during atrial tachyarrhythmia episodes from one patient before cardiac resynchronization therapy. Atrio-atrial (A-A) and ventriculo-ventricular (V-V) intervals are indicated.

**Definitions.** Atrial tachyarrhythmias were defined as extended episodes (>5 beats) of atrial rates  $\geq 180$  beats/min. When intra-atrial electrograms showed an irregularly irregular atrial rate >180/min, atrial fibrillation was diagnosed. However, because electrograms were available in only a minority (approximately 40%) of episodes, the more general term “AT” was used. The AT burden was determined from the total number and duration of documented high-rate atrial events and is presented on a per-month basis.

**Statistical analysis.** Nonparametric tests (Wilcoxon matched-pairs signed ranks, exact McNemar’s and Friedman’s tests) were used to analyze differences in medications, percent of patients with ATs, number of episodes/month and hospital stays before and after CRT upgrade due to absence of normal distributions. A paired *t* test was used for the analysis of QRS duration and echocardiographic parameters due to normal distribution. A *p* value of <0.05 was considered statistically significant.

**Results**

**Clinical findings.** The initial implanted device was a dual-chamber pacemaker in 3 (10%) patients, whereas the remaining 25 (90%) patients had had an implanted dual-chamber ICD. Baseline clinical and demographic data are provided in Table 1. During 2-year follow-up there were no changes in the comorbid conditions associated with HF and no significant change in pharmacological therapy (Table 2).

Baseline and post-CRT echocardiographic findings and QRS duration are summarized in Table 1, and medications are summarized in Table 2. Upgrade to CRT resulted in a significant improvement of LV ejection fraction (LVEF) from  $26 \pm 5.3\%$  to  $31 \pm 7.0\%$ , *p* < 0.05. Left atrial size and estimated severity of mitral regurgitation were not significantly altered.

**Arrhythmia observations.** At 1 year before CRT upgrade, 45% of patients exhibited AT episodes documented by device interrogation (Fig. 2). At 3 months before upgrade,

device interrogation revealed AT events in approximately 86% of patients (Fig. 2). After initiation of CRT, the frequency and duration of AT episodes significantly decreased (*p* < 0.05) (Fig. 3). The average number of AT episodes/year was significantly higher and their durations were significantly longer before CRT compared with findings after upgrade (number/year: pre-CRT,  $181 \pm 50$  vs. post-CRT,  $50 \pm 20$ , *p* < 0.05; and duration: pre-CRT,  $221 \pm 87$  s vs. post-CRT,  $28 \pm 21$  s, *p* < 0.05). Figure 4 summarizes findings with respect to AT frequency on a per-month basis during follow-up.

At the 1- and 2-year follow-ups, CRT device interrogation failed to reveal AT episodes in 90% and 86% of patients, respectively (Fig. 2). There were no differences in

Table 1	Baseline Clinical, Demographic, Electrocardiographic, and Echocardiographic Characteristics	
	Before CRT	After CRT
Age (yrs)		69 ± 9
Male		90%
Female		10%
NICM		24%
ICM		76%
HTN		71%
Hyperlipidemia		81%
DMII		29%
QRS duration (ms)	167 ± 22*	148 ± 13
Echocardiographic parameters		
EF %	25.8 ± 5.3*	31.3 ± 7
MR	1.1 ± 0.6	1.2 ± 0.7
LA size (cm)	4.64 ± 0.9	4.98 ± 1

Percentages of comorbid conditions, QRS duration, and echocardiographic data are shown before and after cardiac resynchronization therapy (CRT). \*Statistically significant difference with *p* < 0.05.

DMII = diabetes mellitus type 2; EF = ejection fraction; HTN = hypertension; ICM = ischemic cardiomyopathy; LA = left atrium; MR = mitral regurgitation; NICM = nonischemic cardiomyopathy.

**Table 2 Medications Before and After CRT**

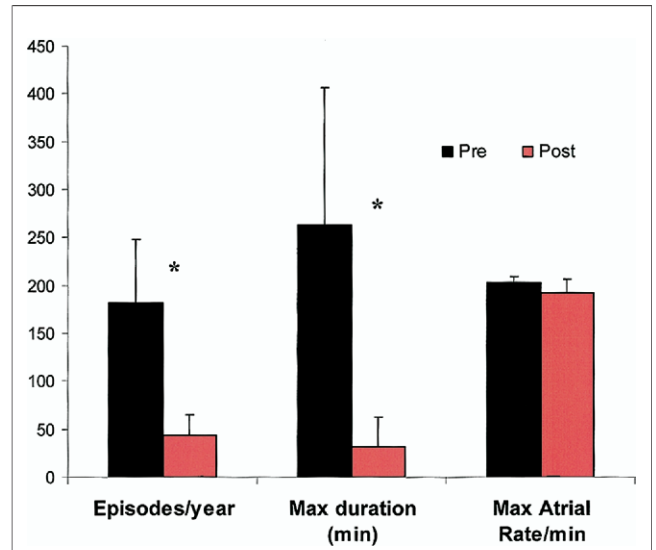
Medications	Before CRT (Mean Dose in mg/day)	After CRT (Mean Dose in mg/day)
Metoprolol	86% (120 ± 22)	92% (120 ± 22)
Amiodarone	44% (246 ± 83)	43% (230 ± 67)
Sotalol	11% (240)	14% (240)
Digoxin	43% (0.14 ± 0.06)	38% (0.16 ± 0.08)
ACEI/ARB	76%	81%
Diuretics	71%	71%
Spironolactone	10%	20%
ASA/clopidogrel	95%	95%
Statin	61%	67%
Nitrates	20%	20%
Coumadin	67%	71%
CCB	11%	11%

Medications before and after cardiac resynchronization therapy (CRT) "upgrade." There were no significant differences in prescription frequency or dosing of the main antiarrhythmic medications. The mean doses/day are shown in parentheses.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ASA = acetylsalicylic acid; CCB = calcium channel blocker.

the mean doses of antiarrhythmic drugs before and after CRT upgrade (Table 2).

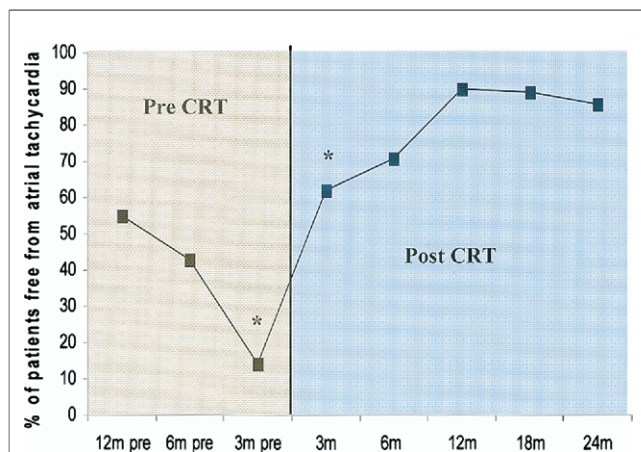
**Hospital stays.** Compared with the year before CRT, follow-up at 18 to 24 months after CRT revealed a significant reduction in number of total hospital stays as well as hospital stays deemed to be primarily due to HF or arrhythmia (Fig. 5A). The number of patients with more than 1 hospital stay/year (AT-related and total) significantly decreased after CRT upgrade, as can be seen in Figures 5B and 5C, respectively. Before CRT upgrade there were 9 hospital stays due primarily to atrial fibrillation, 5 hospital stays associated with atrial flutter or other AT, and 9 hospital stays related to ventricular tachycardia. During the follow-up period after CRT upgrade there was 1 atrial fibrillation-related hospital stay and 4 hospital stays due to



**Figure 3 Atrial Tachycardia Characteristics**

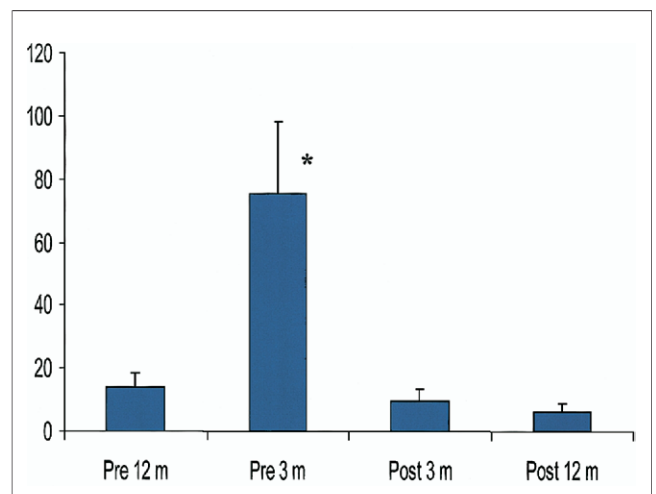
Bar graphs depicting mean ± SD of frequency (atrial tachycardia episodes/year), maximum atrial tachycardia duration in minutes, and maximum atrial rate recorded by the implanted device (in most cases equal to the mode switch rate) before and after the upgrade to cardiac resynchronization therapy. \*Statistically significant difference,  $p < 0.05$ .

ventricular tachycardia/fibrillation shocks. The difference in the number of hospital stays associated with AT before and after CRT (14 vs. 1) was statistically significant ( $p < 0.001$ ). Ventricular tachycardia/fibrillation-related hospital stays did not change significantly. The total number of hospital stays (excluding the hospital stays for the "upgrade") significantly decreased after CRT upgrade ( $p = 0.001$ ).



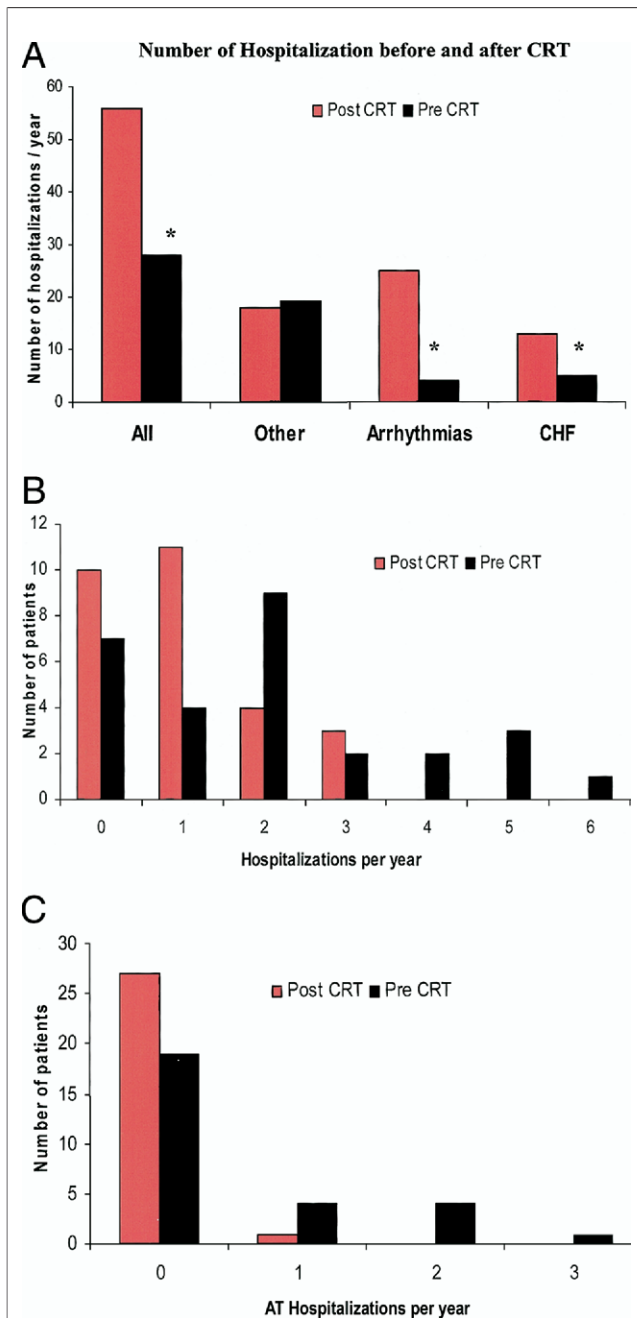
**Figure 2 Percentage of Patients Free From Atrial Tachycardia Over the Course of the Study**

Graph illustrating the percentage of patients without atrial tachyarrhythmia over the course of the study (1 year before and 2 years after cardiac resynchronization therapy [CRT]). \*Statistically significant difference,  $p < 0.01$ .



**Figure 4 Frequency of AT Episodes/Month**

Bar graphs illustrating mean ± SD of the number of atrial tachycardia (AT) episodes in 1 month recorded at 12 months before cardiac resynchronization therapy (CRT), 3 months before CRT, and 3 and 12 months after upgrade to CRT. \*Statistically significant difference,  $p < 0.05$ .



**Figure 5** Effect of CRT Upgrade on Hospital Stays

(A) Bar graphs summarizing the number of hospital stays in 1 year before and after the upgrade to cardiac resynchronization therapy (CRT). Findings show diminished number of atrial tachyarrhythmia (AT) and heart failure (HF) hospital stays after CRT, whereas other hospital stays (see text) were unaffected. \*Statistically significant difference in the number of hospital stays before and after CRT ( $p < 0.05$ ). (B and C) Distribution (number of patients) of the number of hospital stays/year/patient (total and AT-related) before and after CRT upgrade.  $p$  values = 0.001 and  $<0.001$ , respectively.

## Discussion

This study examined the impact of CRT on AT susceptibility in patients in whom the presence of pre-existing conventional pulse generators permitted relatively precise

assessment of baseline AT burden. There were 3 principal observations. First, in most patients, an upgrade to CRT significantly decreased the number of device-documented AT episodes within the first 3-month observation period after the upgrade. Second, the post-CRT decrease in AT seemed to be progressive over the 2-year prospective observation period. This finding suggests that the arrhythmia benefit was not simply due to short-term CRT reversal of the deteriorating hemodynamic state that had triggered the “CRT upgrade” decision. Finally, CRT upgrade was associated with a significant decrease in HF and arrhythmia hospital stays. This observation suggests an important interaction between CRT-induced improvement of LV function and generation of arrhythmia-related symptoms leading to hospital admissions. In contrast, and not surprisingly, the frequency of noncardiac hospital stays (e.g., orthopedic and noncardiac procedures, general medical conditions) was unchanged by CRT; this observation tends to support the validity of the clinical characterization of hospital admissions used in this study.

**Impact of CRT on ATs.** Among previously published studies assessing the potential impact of CRT on AT susceptibility in HF patients, excluding case reports (11,12), the results have been disparate (9,10).

The CARE-HF (Cardiac Resynchronization-Heart Failure) trial provides to date the largest data set in which an effort was made to compare the impact of CRT in conjunction with conventional HF drug therapy versus conventional pharmacological HF treatment alone on frequency of atrial fibrillation events (9). The study included more than 800 patients followed for an average of 29 months. Atrial fibrillation was detected in 66 CRT-treated patients versus 58 conventional-treatment patients ( $p = \text{NS}$ ), suggesting no apparent CRT benefit. However, because the conventional-treatment group did not have implanted devices, end point detection was restricted to adverse event reporting or electrocardiograms recorded during regular follow-up. In essence, it is likely that many AT events were overlooked.

Fung et al. (10) used a case control method to assess atrial fibrillation frequency during follow-up in 36 patients receiving CRT for conventional HF indications. Control subjects were matched for age, gender, and LVEF. In this report, CRT patients had a significantly lower atrial fibrillation recurrence rate than did control subjects. By 36 months' follow-up,  $>90\%$  of CRT patients were free of atrial fibrillation recurrences compared with approximately 70% in the control group.

The LVEF improvement associated with CRT in our patient population ( $26 \pm 5.3\%$  to  $31 \pm 7.0\%$ ) was more closely aligned with observations in the CARE-HF study (9) than with those of Fung et al. (10). Nevertheless, our AT outcomes tend to be more in concordance with Fung et al. (10). Possibly, the use of each patient as his/her own control in our study permitted identification of differences not detectable by other study designs.

During the year before CRT upgrade, most of our study patients had an increasing number of episodes of symptomatic and/or asymptomatic (these cannot be distinguished by our method) AT episodes as documented by their implanted pulse generator; 25 of 28 patients had multiple AT episodes at the last interrogation of the ICD before CRT. In this regard, it is probable but cannot be determined with certainty that the increased arrhythmia frequency was a byproduct of the hemodynamic deterioration that led to CRT upgrade. A less likely possibility is that more frequent AT episodes led to clinical deterioration. In any case, 3 months after CRT upgrade, 60% of patients had no recorded high-rate atrial episodes. Furthermore, at the 1-year post-CRT mark, fully 90% of patients were free from recorded AT episodes (a percentage similar to that reported by Fung *et al.* [10]).

Possible explanations for a beneficial association between CRT and decrease of atrial fibrillation remain speculative. It has been argued that many HF-induced structural changes are often irreversible (13). It seems likely then that structural change is only part of the story. A combination of decreased ischemic burden by improvement in cardiac output and reduction of both atrial and ventricular myocardial wall stress, in conjunction with a favorable change in neurohumoral milieu, could theoretically account for antiarrhythmic benefit.

**Study limitations.** Our study has important limitations. First, we identified device-documented high-rate atrial episodes. This approach has diagnostic limitations, because electrocardiographic evidence is not always available and far-field R- or T-wave over-sensing might result in “detection” of an atrial high rate. Second, our findings are observational. We cannot comment on causality in terms of the apparent beneficial association that has been described. Finally, although this study used a paired analysis with each patient acting as his/her own control—a design that enhances statistical power in small sample populations—it cannot quantify the magnitude of a possible placebo effect accompanying an invasive CRT implantation procedure. A true randomized control group undergoing a CRT implant with the LV stimulation deactivated for a test period would provide a stronger study design. However, inasmuch as indications for CRT-D upgrade were already well established at the start of this study, it was not considered ethical to insert an inactive device. Ultimately, a multicenter randomized and controlled clinical trial might be needed to evaluate the true impact of CRT on AT susceptibility, and the latter study design issue will then need to be re-examined.

## Conclusions

Atrial tachyarrhythmias are a common occurrence in HF patients in whom CRT is being contemplated. Furthermore, the frequency of AT episodes seems to increase in the months before CRT implantation. Introduction of CRT might lead to both an immediate as well as long-term decrease in the number of AT events in a substantial proportion of HF patients. The mechanism of this association needs further investigation.

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