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Antiarrhythmic Effect of Reverse Ventricular Remodeling Induced by Cardiac Resynchronization Therapy

The InSync ICD (Implantable Cardioverter-Defibrillator) Italian Registry

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Objectives We investigated whether the reverse remodeling after cardiac resynchronization therapy (CRT) might reduce the occurrence of ventricular arrhythmias (VAs).

Background It is currently debated whether CRT has an effect on the burden of VAs.

Methods The study included 398 patients treated with a CRT defibrillator and with a follow-up of at least 12 months. Spontaneous VAs detected by the device were reviewed and validated.

Results A significant reduction in VA episodes and shock therapies was evident during the follow-up with greater decrease after 1 month. After 6 months of CRT, 227 patients (57%) showed a reduction in end-systolic volume of ≥10% and were defined as "responders." The baseline characteristics were similar between the responders and the nonresponders. Nonetheless, the proportion of patients with recurrence of VA after 1 month of CRT was significantly lower in responders (32% vs. 43%, $p = 0.024$). Among baseline variables no parameters emerged as predictors of tachyarrhythmia recurrence. However, receiver-operating curve analysis recognized a reduction of left ventricular end-systolic volume at 6 months of 13% as the best cutoff to identify the reduction of VAs (with a sensitivity of 58% and a specificity of 54%).

Conclusions In patients treated with CRT defibrillators, a reduction in ventricular arrhythmic events occurs during the initial 12 months after implant and is correlated with the degree of ventricular remodeling induced by the therapy. Patients demonstrating reverse remodeling at midterm follow-up show a reduction in arrhythmias soon after the implant, pronounced improvements at long-term, and a better survival. (J Am Coll Cardiol 2008;52:1442–9)

Cardiac resynchronization therapy (CRT) has emerged as an effective treatment strategy for patients with advanced drug refractory heart failure (HF), left ventricular (LV) systolic dysfunction, and ventricular dyssynchrony (1,2). Several randomized trials have demonstrated that CRT improves symptoms, quality of life, and exercise capacity (3,4). In addition CRT has been shown to reduce hospital stays, morbidity, and mortality risk especially in patients implanted with cardiac resynchronization therapy defibrillators (CRT-D) (5,6). Some studies have suggested that CRT is able to reduce inducibility and spontaneous occurrence of ventricular arrhythmias (VAs) and improve the appropriateness of implantable cardioverter-defibrillator (ICD) therapy (7–12). It has been postulated that the decrease in VAs might be associated with reverse LV remodeling, thereby suggesting that reduced wall tension might result in fewer VAs (13). However, some studies have

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shown that CRT can potentially promote VAs (14–16). Nevertheless, controversy still exists as to whether CRT might affect sudden cardiac death by reducing the number of lethal VAs in addition to its efficacy in decreasing worsening HF mortality (17,18).

We hypothesized that CRT could affect the occurrence of VA as a result of the induced reverse LV remodeling. Thus, the aim of this study was to assess in a broader CRT population the recurrence of VA and appropriate shock therapies at long-term follow-up and to evaluate their association with the degree of improvement obtained with CRT.

Methods

From 1999 to 2005, the InSync ICD Italian Registry prospectively enrolled patients who underwent successful implantation of CRT-D for primary or secondary prevention of sudden death and for resynchronization therapy. The registry included patients with mild to severe symptomatic chronic HF (New York Heart Association [NYHA] functional class II to IV), a left ventricular ejection fraction (LVEF) ≤35%, and a wide QRS complex (>130 ms).

All patients were receiving stable medical therapy including beta-blocker drugs, angiotensin-converting enzyme inhibitors or angiotensin receptor blocker drugs, and diuretics. Patients with a recent myocardial infarction or coronary revascularization (<3 months) or scheduled revascularization or with decompensated HF were excluded. All patients provided written informed consent approved by each hospital's ethics committee.

Before device implantation, the following baseline demographic data were collected: medical history, clinical examination, history of ventricular tachycardias, syncope and/or cardiac arrest, 12-lead electrocardiogram, NYHA functional class, and standard echocardiographic parameters. The latter included: assessment of left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and LVEF assessed by Simpson's equation with the apical 4-chamber view (19) and evaluation of the severity of mitral regurgitation with color Doppler in the apical 4-chamber view. In addition, the interventricular mechanical delay (IVMD) was calculated as the time difference between the onset of the QRS duration and the opening of the aortic and pulmonary valves.

All patients were implanted with Medtronic (Minneapolis, Minnesota) CRT-D devices. All devices were triple-chamber defibrillators capable of providing CRT and detecting and treating ventricular tachyarrhythmias. Ventricular tachycardia detection rate cutoff was requested to be at least 350 ms (171 beats/min) to avoid under-reporting of arrhythmic episodes. Right-sided pacing leads were placed with standard techniques. The LV lead was implanted transvenously via the coronary sinus tributaries and placed preferably to stimulate the lateral or posterolateral LV wall.

Echocardiography-guided atrioventricular delay programming was recommended to optimize hemodynamic function and was performed before discharge and at follow-up. Adjustments of the interventricular (V-V) interval were not required.

Patients returned for regular clinic visits at 1, 3, and 6 months and every 6 months thereafter. Besides the clinical evaluation, 12-lead electrocardiogram, NYHA functional class, and detailed device checks were performed at each follow-up visit. In addition, standard echocardiography was performed at the 6- and 12-month follow-up visits in all patients. Echocardiographic recordings were analyzed in each center by operators blinded to the arrhythmic episodes data retrieved by the ICD.

Abbreviations and Acronyms

CRT = cardiac resynchronization therapy
HF = heart failure
ICD = implantable cardioverter-defibrillator
IVMD = interventricular mechanical delay
LV = left ventricle/ventricular
LVEDD = left ventricular end-diastolic diameter
LVEDV = left ventricular end-diastolic volume
LVEF = left ventricular ejection fraction
LVESD = left ventricular end-systolic diameter
LVESV = left ventricular end-systolic volume
NYHA = New York Heart Association
VA = ventricular arrhythmia

The impact of CRT on clinical and echocardiography outcome was evaluated, comparing the baseline with 6- and 12-month follow-up data.

Spontaneous arrhythmic episodes detected by the device were validated by 2 independent electrophysiologists blinded to the patient outcome. If a consensus could not be reached, a third electrophysiologist was involved in episode review.

To assess the recurrence of VA at long-term follow-up, we included in the analysis all patients with complete clinical and device data at the 12-month follow-up and we counted the total number of ventricular tachyarrhythmia episodes that occurred during the study and the number of patients experiencing arrhythmias. The episodes considered in the analysis were all spontaneous ventricular tachyarrhythmias detected by the implanted device and subsequently validated.

We assumed that CRT would result in progressive reverse remodeling during follow-up. Thus, we counted ventricular tachycardias during the first month after implant as a measure of the baseline patient arrhythmic status, and we assessed the recurrence of ventricular tachyarrhythmias in the period from the second to the twelfth month to test the hypothesis of the antiarrhythmic effect of CRT secondary to the clinical and echocardiographic improvement.

Moreover, we divided patients with and without evidence of relevant LV remodeling after CRT (LVESV reduction ≥10%) (20), and we estimated the incidence of arrhythmias in these groups.

Statistical analysis. Continuous data were expressed as means ± SD. Categorical data were expressed by percentages. Differences between mean data were compared by a *t* test for

Gaussian variables and by the Mann-Whitney-Wilcoxon or Wilcoxon signed-rank nonparametric test for non-Gaussian variables, respectively, for independent or paired samples. Normality of distributions was tested by the 1-sample Kolmogorov-Smirnov test. Differences in proportions were compared by a chi-square analysis. Mortality rate was summarized by construction of Kaplan-Meier curves, and the distributions of the groups were compared by a log-rank test.

Univariable Cox regression analysis was used for the analysis of predictors of tachyarrhythmia recurrence. All variables associated with a p value <0.1 at univariable analysis were entered into the multivariable Cox regression analysis.

Receiver-operating characteristic (ROC) curve analysis was applied to assess the optimal cutoff value of the variables. In our analysis, we optimized sensitivity and specificity simultaneously; that is, we considered as an optimal cut-off the value resulting in the maximum product of sensitivity and specificity on the ROC curve.

A p value <0.05 was considered significant for all tests. All statistical analyses were performed with SPSS software (version 12.0, SPSS Inc., Chicago, Illinois).

Results

Characteristics and outcome of the study population. Three hundred ninety-eight patients were enrolled in the InSync ICD Italian Registry and had complete clinical and device data at the 12-month follow-up. Of these, 175 received CRT-D for primary prevention and 223 for secondary prevention of sudden cardiac death. For the secondary prevention patients, 60 (27%) were cardiac arrest survivors, 94 (42%) had a history of spontaneous sustained ventricular tachycardia, and 69 (31%) had a history of syncope associated with spontaneous ventricular tachycardia or syncope of unknown origin with inducible ventricular tachyarrhythmia. The primary cause of HF was coronary artery disease (67% of patients) with, frequently, a past history of myocardial infarction and of prior coronary revascularization. Baseline clinical and echocardiographic characteristics of the study population are given in Table 1. The pharmacological treatment was optimized at post-implant discharge visit (Table 1) and remained stable during follow-up.

Improvements in NYHA functional class and echocardiographic parameters after 6 and 12 months of CRT are summarized in Table 2. At the 6-month follow-up, a significant improvement in the clinical and echocardiographic parameters was observed in the overall population. The NYHA functional class improved ($p < 0.001$) together with a decrease in QRS duration ($p < 0.001$). A significant increase in LVEF ($p < 0.001$) and significant reduction of both LVEDD ($p = 0.039$) and LVESD ($p = 0.048$) occurred.

The LVEDV and LVESV were reduced at the 6-month follow-up ($p = 0.046$ and $p = 0.004$, respectively). Baseline ventricular dyssynchrony, assessed by IVMD, also decreased ($p = 0.010$). The severity of mitral regurgitation was also significantly decreased ($p = 0.006$). All of these changes remained stable at the 12-month follow-up visit.

With a reduction in LVESV of ≥10% as cutoff value to define patients with clinically relevant LV reverse remodeling after CRT, we identified 227 "responders" (57%) and 171 "nonresponders" (43%).

The baseline characteristics including medical history and echocardiographic data were similar between groups, except for a higher percentage of ischemic patients among nonresponders (Table 1).

The implantation site of the LV lead was the lateral or posterolateral wall in 191 responders (84%) and 147 nonresponders (86%, $p = 0.615$). The atrioventricular delay optimization was performed before discharge in 166 responders (73%) and 130 nonresponders (76%, $p = 0.512$).

At baseline, 27 patients (12%) among responders and 16 among nonresponders (9%, $p = 0.420$) had history of documented paroxysmal or persistent forms of atrial fibrillation. During follow-up, episodes of device-detected atrial fibrillation were reported in 73 patients (32%) in the responder group and 41 patients (24%) in the nonresponder group ($p = 0.074$). The overall percentage of biventricular pacing during follow-up was similar between groups (96 ± 5% vs. 95 ± 4%, $p = 0.362$) as well as the number of patients with a percentage of biventricular pacing higher than 85% (216 [95%] vs. 164 [96%], $p = 0.721$).

During follow-up, both groups demonstrated a significant reduction in QRS duration and NYHA functional class at 6 months (all $p < 0.001$), which was sustained at 12 months (Table 2). For nonresponder patients, echocardiographic parameters did not change significantly either at 6 or 12 months, whereas responder patients demonstrated a significant reduction in LV dimensions and volumes at 6 months (all $p < 0.02$), together with a decrease of IVMD ($p = 0.006$) and mitral regurgitation ($p = 0.003$) that were maintained at 12 months.

We extended the patient follow-up beyond 12 months and collected the survival status for all patients. The total mean follow-up duration was 23 ± 10 months and was comparable in the 2 groups (24 ± 11 months for responders and 23 ± 9 months for nonresponders, $p = 0.207$). A total of 12 deaths occurred in the overall population: 4 in the responder group (2 nonsudden cardiac, 2 noncardiac) and 8 in the nonresponder group (6 nonsudden cardiac, 2 noncardiac).

Kaplan-Meier event-free survival analysis demonstrated that the responder group had a significantly lower rate of all-cause mortality ($p = 0.042$) (Fig. 1).

Ventricular tachyarrhythmias during follow-up. For the entire cohort, the programmed mean cycle length cutoff for the detection of ventricular tachycardia was 395 ± 29 ms, which needed to be sustained for 16 consequence beats. A ventricular fibrillation episode was detected if the cycle length was shorter than a mean of 313 ± 14 ms and sustained for 12 of 16 beats.

During 12 months of follow-up, spontaneous tachyarrhythmia episodes detected by the device as ventricular tachycardia or fibrillation and confirmed by subsequent validation occurred in 163 of 398 patients (41%) of the

Table 1 Demographic Data, Baseline Clinical Parameters, and Pharmacological Treatment of the Overall Population and the 2 Subgroups

Parameter	Total (n = 398)	Responders (n = 227)	Nonresponders (n = 171)	p Value
Male gender	349 (88)	193 (85)	156 (91)	0.062*
Age, yrs	66 ± 9	66 ± 9	66 ± 9	0.978
Ischemic etiology	266 (67)	142 (63)	124 (73)	0.037*
Myocardial infarction	211 (53)	114 (50)	97 (57)	0.198*
Previous CABG or angiography	144 (36)	75 (33)	69 (40)	0.133*
Valvular disease	50 (13)	27 (12)	23 (13)	0.643*
Secondary prevention	223 (56)	121 (53)	102 (60)	0.207*
Hospital stays for HF (prior 12 months), n/yr	1.4 ± 1.4	1.5 ± 1.5	1.2 ± 1.1	0.166
QRS duration, ms	166 ± 31	167 ± 31	165 ± 31	0.493
Left bundle branch block	273 (69)	154 (68)	119 (70)	0.710*
NYHA functional class	2.9 ± 0.6	3.0 ± 0.6	2.8 ± 0.6	0.123
LVEF, %	26 ± 7	26 ± 6	27 ± 8	0.095
LVEDD, mm	70 ± 9	70 ± 8	71 ± 10	0.471
LVESD, mm	59 ± 10	59 ± 8	59 ± 12	0.816
LVEDV, ml	247 ± 91	249 ± 92	242 ± 90	0.737
LVESV, ml	178 ± 79	189 ± 75	164 ± 83	0.200
IVMD, ms	39 ± 25	44 ± 23	32 ± 29	0.248†
Mitral regurgitation, degree	2.2 ± 0.9	2.1 ± 1.0	2.2 ± 0.9	0.828
Spironolactone use				
At enrollment	203 (51)	109 (48)	94 (55)	0.170*
At post-implant discharge	213 (54)	115 (51)	98 (57)	0.188*
Diuretic use	357 (90)	204 (90)	153 (89)	0.898*
At enrollment				
At post-implant discharge	368 (92)	210 (93)	158 (92)	0.966*
ACE inhibitors or ARB use				
At enrollment	303 (76)	177 (78)	126 (74)	0.320*
At post-implant discharge	320 (80)	187 (82)	133 (78)	0.252*
Beta-blocker use				
At enrollment	221 (56)	129 (57)	92 (54)	0.547*
At post-implant discharge	240 (60)	141 (62)	99 (58)	0.394*
Digoxin use				
At enrollment	159 (40)	94 (41)	65 (38)	0.493*
At post-implant discharge	161 (40)	94 (41)	67 (39)	0.654*
Class III antiarrhythmics use				
At enrollment	154 (39)	83 (37)	71 (42)	0.315*
At post-implant discharge	158 (40)	85 (37)	73 (43)	0.290*
Nitrates use				
At enrollment	78 (20)	47 (21)	31 (18)	0.522*
At post-implant discharge	78 (20)	47 (21)	31 (18)	0.522*

Values are presented as n (%) or mean ± SD. The p values were determined on the basis of unpaired *t* test except for: *chi-square analysis and †Mann-Whitney nonparametric test.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; HF = heart failure; IVMD = interventricular mechanical delay; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association.

whole population. Overall, 986 arrhythmic episodes occurred during the first 12 months; 354 of these were treated with shock therapy and the remaining with anti-tachycardia pacing, according to the device programming. The distribution of tachyarrhythmias and shock therapies in the first 12 months is shown in Figure 2. In general, a significant reduction in detected ventricular tachyarrhythmia episodes and shock therapies was evident during the follow-up with greater decrease after 1 month.

We observed a similar incidence of ventricular tachyarrhythmias in the 2 groups of primary (70 of 175 patients [40%]) and secondary prevention patients (93 of 223 patients [42%], p = 0.732) and comparable trends of reduced tachyarrhythmias (Fig. 3).

Both with univariate and multivariate Cox regression analysis, no parameters emerged as predictors of tachyarrhythmia recurrence among baseline clinical, echocardiographic, and medication status variables.

LV reverse remodeling and recurrence of ventricular tachyarrhythmias. During the 12 months of follow-up, 85 of 227 (37%) responders experienced tachyarrhythmias, compared with 78 of 171 (46%) nonresponders (p = 0.101). In particular, arrhythmic episodes were detected in 31 (14%) responders and 30 (18%) nonresponders (p = 0.287) during

Table 2 Clinical and Echocardiographic Parameters at Baseline and 6- and 12-Month Follow-Up

Parameter	Baseline			6-Month Follow-Up			12-Month Follow-Up		
	Total (n = 398)	Responders (n = 227)	Nonresponders (n = 171)	Total (n = 398)	Responders (n = 227)	Nonresponders (n = 171)	Total (n = 398)	Responders (n = 227)	Nonresponders (n = 171)
QRS duration, ms	166 ± 31	167 ± 31	165 ± 31	138 ± 45*	136 ± 46*	141 ± 44*	146 ± 29*	144 ± 30*	148 ± 28*
NYHA functional class	2.9 ± 0.6	3.0 ± 0.6	2.8 ± 0.6	2.1 ± 0.7*	1.9 ± 0.6*	2.3 ± 0.7*†	2.1 ± 0.6*	1.9 ± 0.6*	2.3 ± 0.7*†
LVEF, %	26 ± 7	26 ± 6	27 ± 8	32 ± 10*	35 ± 10*	27 ± 9†	33 ± 11*	36 ± 11*	29 ± 10†
LVEDD, mm	70 ± 9	70 ± 8	71 ± 10	67 ± 10*	65 ± 10*	70 ± 9†	67 ± 10*	65 ± 10*	69 ± 9†
LVESD, mm	59 ± 10	59 ± 8	59 ± 12	55 ± 12*	53 ± 12*	59 ± 11†	56 ± 12*	53 ± 12*	59 ± 11†
LVEDV, ml	247 ± 91	249 ± 92	242 ± 90	203 ± 81*	195 ± 78*	216 ± 85†	200 ± 79*	194 ± 80*	211 ± 77†
LVESV, ml	178 ± 79	189 ± 75	164 ± 83	137 ± 65*	126 ± 61*	153 ± 67†	134 ± 64*	126 ± 65*	146 ± 62†
IVMD, ms	39 ± 25	44 ± 23	32 ± 29	17 ± 20‡	14 ± 19‡	19 ± 21	17 ± 18‡	16 ± 20‡	17 ± 16
Mitral regurgitation, degree	2.2 ± 0.9	2.1 ± 1.0	2.2 ± 0.9	1.8 ± 0.8*	1.6 ± 0.7*	2.1 ± 0.9†	1.8 ± 0.8*	1.6 ± 0.7*	2.1 ± 0.9†

*$p < 0.05$ versus baseline on the basis of paired *t* test; †$p < 0.05$ versus responders; ‡$p < 0.05$ versus baseline on the basis of Wilcoxon nonparametric test.
Abbreviations as in Table 1.

the first month and in 72 (32%) responders and 73 (43%) nonresponders ($p = 0.024$) in the period from the second to the twelfth month of follow-up.

The distribution of tachyarrhythmias in the first 12 months for the 2 groups is shown in Figure 4. A significant reduction in detected ventricular tachyarrhythmia episodes was evident from the second month only for responder patients.

On the basis of the ROC curve analysis of the total population, a reduction of LVESV at 6 months of 13% was recognized as the best cutoff to identify the reduction of tachyarrhythmias (area under the curve 0.59; 95% confidence interval: 0.53 to 0.65). There were 200 patients with a reduction of LVESV ≥13%, and with this cutoff, we obtained a sensitivity of 58% and a specificity of 54%. With the a priori defined cutoff of 10% for LVESV reduction, both the sensitivity and the specificity were 54%.

Discussion

Our results show that in patients treated with CRT, a reduction of the number of ventricular tachyarrhythmia episodes and appropriate shock therapies occurred during follow-up both in terms of total number of events and number of patients with episodes. Moreover, the reduction of tachycardias is associated with the reverse remodeling induced by the therapy. We observed an association between the remission of arrhythmic episodes during follow-up and the improvement of echocardiography parameters after CRT.

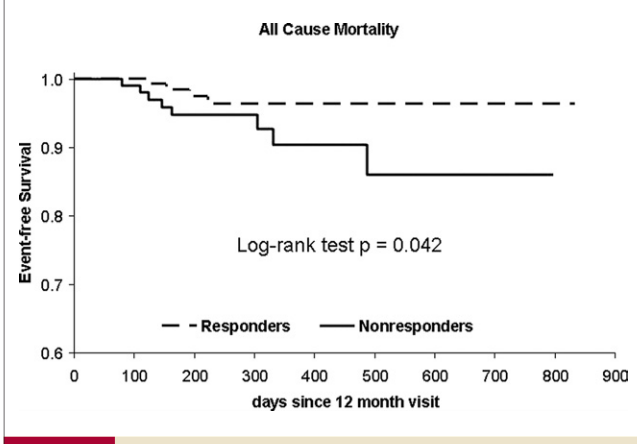

Figure 1 Survival Analysis

Kaplan-Meier estimates of time to death from any cause in the responder and the nonresponder groups.

Patient subgroups. Previous studies demonstrated that CRT results in progressive reverse remodeling during the first months after implant. In our study, at the 6-month follow-up the overall population seemed to have both clinical and echocardiography improvements. The significant reduction in LVEDV and LVESV that were evident after 6 months persisted to 12-month follow-up, as already reported in published reports (21), and were associated with a better survival after the 12-month visit, confirming the findings of Yu et al. (20).

Our hypothesis was that the reverse remodeling induced by CRT could affect the occurrence of VAs. Thus, we sorted patients into 2 groups: patients with and without evidence of relevant LV remodeling after CRT, as measured by a decrease of LVESV ≥10% at 6-month follow-up (20).

No baseline variable distinguished the groups, with the exception of a higher incidence of ischemic etiology among the nonresponders. This finding supports previous results showing larger improvements after CRT in patients with nonischemic etiology (21) and, at the same time, confirms the lack of strong baseline predictors of response to CRT among the baseline clinical and echocardiographic variables (22).

The arrhythmic status at the time of CRT implant was similar: the prevalence of secondary prevention indications as well as the incidence of arrhythmic episodes in the first month of follow-up was comparable between groups. Nonetheless, the proportion of patients with recurrence of VA after 1 month of CRT was significantly lower among those with evidence of relevant LV remodeling. In particular, in this group the significant reduction in detected ventricular tachyarrhythmia episodes was evident starting from the second month of follow-up.

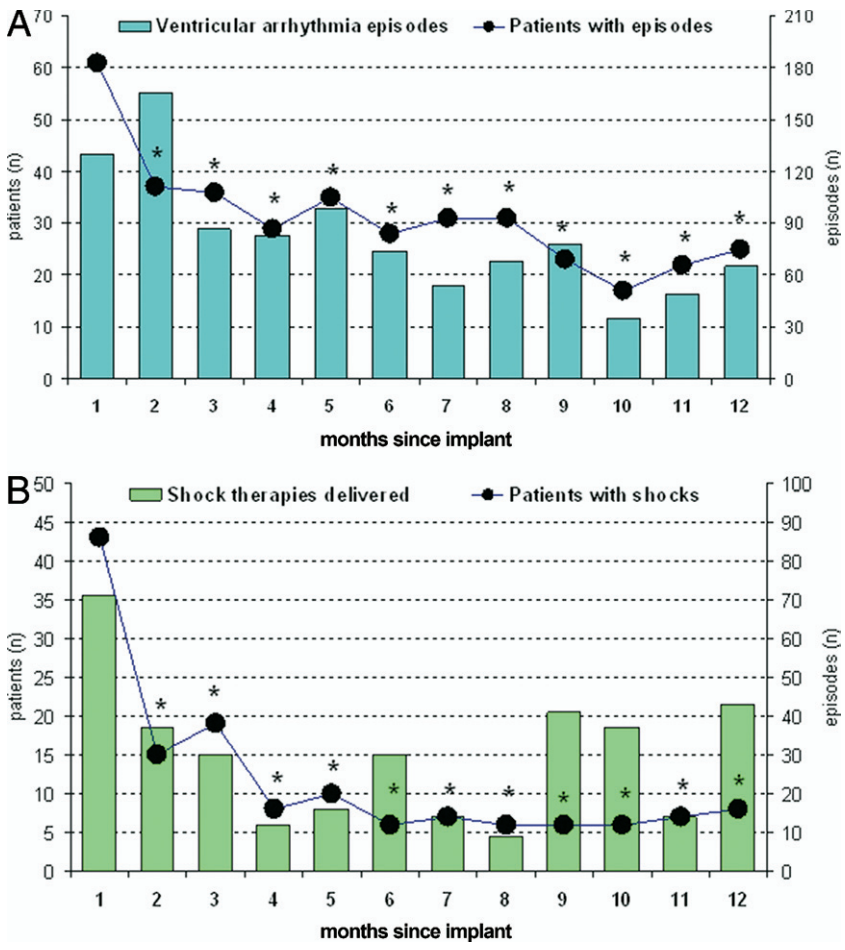

Figure 2 **Distribution of Tachyarrhythmias and Shock Therapies**

(A) Number of patients with episodes, and distribution of ventricular tachyarrhythmia episodes occurring during the 12 months after implant. **(B)** Trend of shock therapies delivered and patients with shock during the observation period. *$p < 0.05$ versus month 1, on the basis of chi-square analysis.

Yu et al. (20) demonstrated that the change in LV volume, specifically the reduction of LVESV, is a strong predictor of response and survival after CRT implant. In the present study, for the first time we showed that LVESV improvement is also associated with a reduction in VAs.

This study demonstrates that CRT reduces the burden of VAs and consequently the incidence of defibrillator discharges. The expected reduction of VA burden could influence the decision to implant a CRT system alone or a CRT system associated with ICD. However, the data from this study do not solve the issue of whether CRT pacing alone without ICD therapy is sufficient in this patient population for several reasons.

In our analysis no parameters emerged as predictors of tachyarrhythmia recurrence among baseline clinical, echocardiographic, and medication status variables. Therefore, subsequent reduction of VAs seems to be not predictable at the time of the implant.

Similarly, as shown by our data and by several contradictory investigations on the refinement of selection criteria for CRT (22), reverse remodeling itself cannot be identified before device implantation.

Moreover, we observed that the sensitivity value for prediction of tachyarrhythmia recurrence was <60% at ROC curve analysis and that the response to CRT seemed to reduce but not to eliminate the recurrence of VA. Thus, the occurrence of a single life-threatening arrhythmic episode, possibly treatable by an ICD discharge, cannot be excluded.

Previous studies. Several reports describe the potential proarrhythmic or antiarrhythmic effect of CRT (7–17). Inversion of depolarization and repolarization occurring during LV and biventricular pacing and the dispersion of refractoriness has been evaluated (23). Under normal physiologic conditions, depolarization proceeds from the endocardium across the ventricular wall to the epicardium with repolarization occurring in the opposite direction. During epicardial pacing the sequence is altered, potentially contributing to either the development or suppression of VA. It is unknown whether restoring synchrony leads to normalization of these changes and whether mechanical remodeling is a prerequisite.

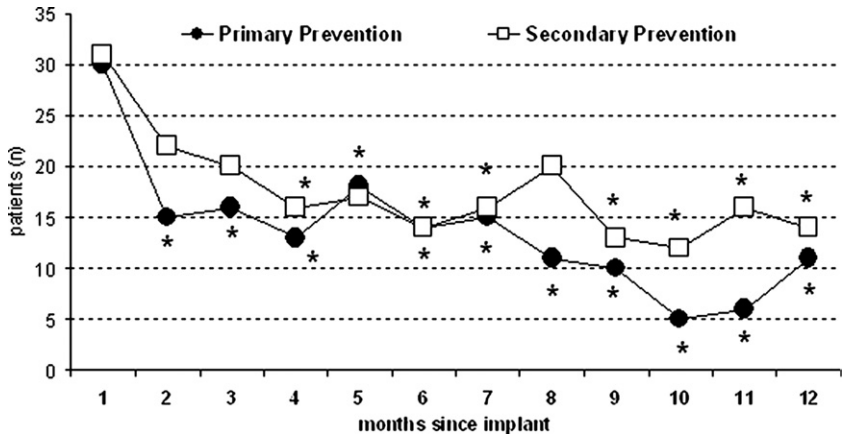

Figure 3 Primary and Secondary Prevention Patients

Number of patients with episodes of ventricular arrhythmia during the 12 months after implant in primary and secondary prevention groups. *$p < 0.05$ versus month 1, on the basis of chi-square analysis.

Some studies have demonstrated that chronic biventricular pacing might reduce ICD therapy and the inducibility of ventricular tachycardia (7–10). However, all of these studies included a small number of patients.

Recently, McSwain et al. (17) retrospectively analyzed data from MIRACLE (Multicenter InSync Randomized Clinical Evaluation) ICD and Contak-CD (Guidant Corporation, Indianapolis, Indiana) trials. In this combined population, CRT was not associated with a measurable change in the incidence of VAs. As reported by Ermis et al. (8), the absence of CRT-associated antiarrhythmic benefit in these trials might be due to the fact that the treatment effect was examined in parallel patient populations rather than within the same individuals. Moreover, the follow-up duration of these trials was 6 months, whereas, as in our study, the reduction of ventricular tachyarrhythmia can take place during the first 12 months after implantation.

Additional indirect evidence of the effect of CRT on arrhythmic status comes from the extension phase of the CARE-HF (Cardiac Resynchronization-Heart Failure) trial (24). Cleland et al. (24) observed a reduction of sudden death in the CRT arm that became evident late in the study and hypothesized that it could be potentially dependent on improvements in cardiac function and beneficial ventricular remodeling.

Study limitations. The main limitation of the study is the lack of a randomization. However, it is difficult to address this issue in a randomized study. Programming of ICD therapy did

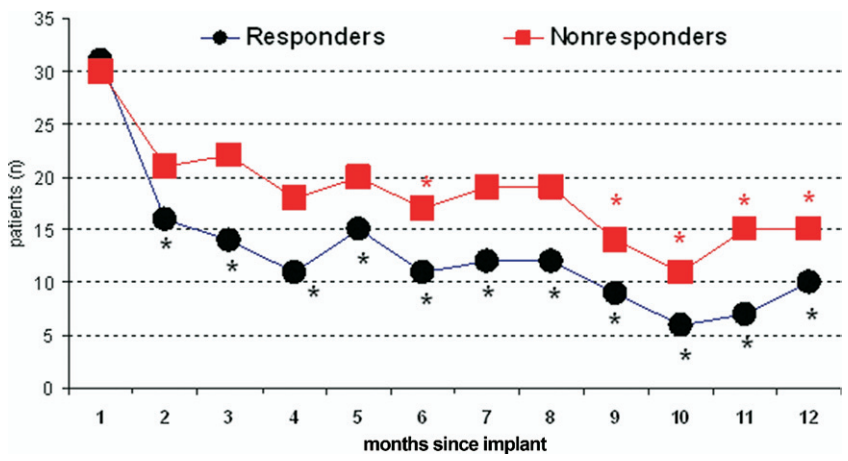

Figure 4 Responder and Nonresponder Patients

Number of patients with episodes of ventricular arrhythmia during the 12 months after implant in responder and nonresponder groups. *$p < 0.05$ versus month 1, on the basis of chi-square analysis.

not follow a pre-defined protocol. However, it is unlikely that device programming influenced arrhythmic events.

Antiarrhythmic drugs can be considered a potential bias in the arrhythmic recurrence. However, antiarrhythmic drugs were given to a similar proportion of patients in both groups.

Finally, the collection of echocardiographic parameters by local operators and the lack of a central validation might represent a bias.

Conclusions

To our knowledge, this is the first large prospective study describing VA recurrence at long-term follow-up in CRT-D patients, with objective data resulting from ICD interrogations. In patients treated with CRT, a reduction in ventricular arrhythmic events occurs during the initial 12 months after implant and correlates with the degree of ventricular remodeling induced by the therapy, as measured by decrease in LV volumes. Patients demonstrating significant reverse remodeling at midterm follow-up might show a reduction in VAs soon after the implant, pronounced improvements at long-term, and a better survival.

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Key Words: cardiac resynchronization therapy ■ defibrillators ■ reverse remodelling ■ ventricular arrhythmias.

APPENDIX

For a complete list of investigators, please see the online version of this article.