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Long-Term Retention of Cardiac Resynchronization Therapy

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OBJECTIVES The purpose of this study was to determine the frequency and causes of intermittent and permanent loss of cardiac resynchronization therapy (CRT) in patients who have undergone the successful implantation of a transvenous defibrillator that delivers CRT (CRT-D).

BACKGROUND The causes of loss of CRT have not been described.

METHODS The records of 512 patients who underwent an attempt at implantation of a transvenous CRT-D device as part of the VENTAK CHF/CONTAK CD Biventricular Pacing study were analyzed.

RESULTS Device implantation was successful in 443 of 512 (87%) of patients. Among these 443 patients, CRT was interrupted in 161 (36%) patients during a mean follow-up of 2.5 ± 1.1 years. Reasons included the development of an atrial tachyarrhythmia (18%), loss of left ventricular capture (10%), diaphragmatic stimulation (2%), loss of right ventricular capture (2%), infection (1%), intentional discontinuation of CRT (1%), loss of right atrial sensing (1%), and ventricular oversensing (0.2%). Most patients underwent an intervention that permitted the reinstitution of CRT, such that only 20 of the 443 patients (5%) experienced the permanent loss of CRT. Using an intention-to-treat analysis, the long-term retention of CRT was 83% during the course of 2.5 years.

CONCLUSIONS Cardiac resynchronization therapy is interrupted in more than one-third of patients after the successful implantation of a CRT-D device. However, CRT can be reinstituted in most patients and has a high long-term retention rate. Because patients with slower heart rates were more likely to develop atrial tachyarrhythmias, a dual-chamber rate-modulated pacing mode (DDDR) may reduce interruptions of CRT. (J Am Coll Cardiol 2004;44:72–7) © 2004 by the American College of Cardiology Foundation

Cardiac resynchronization therapy (CRT) has been shown to be an effective nonpharmacological treatment option for the subset of patients with advanced congestive heart failure (HF) who have an intraventricular conduction delay and systolic dysfunction (1–3). The purpose of this study was to determine the frequency and causes of intermittent and permanent loss of CRT in patients who have undergone the successful implantation of a transvenous defibrillator that delivers CRT (CRT-D).

METHODS

Study design. The VENTAK CHF/CONTAK CD Biventricular Pacing Study and its results have been described in detail elsewhere (4). In brief, the study was a prospective, randomized, double-blind trial that compared defibrillator therapy with CRT to defibrillator therapy without CRT in patients who had an indication for defibrillator implantation, medically refractory congestive HF, a QRS duration >120 ms, and a left ventricular (LV) ejection fraction <0.35. Patients were required to have a sinus rhythm at the time of enrollment. The study required that patients were on optimal medical therapy for congestive HF, which included angiotensin-converting enzyme (ACE) inhibitors. However, patients who had a documented intolerance or contraindication to ACE inhibitors were allowed enrollment. The study was designed in 1997, before many of the major beta-blocker study results were published. For this reason, the study did not require patients to be undergoing treatment with beta-blockers. Phase I of the trial was a three-month crossover design, and phase II was a six-month parallel design. Follow-up was performed at three-month intervals after randomization.

Patients. Five hundred seventeen consecutive patients, who were enrolled between February 1999 and December 2000, underwent at least one attempt at implantation of a CRT-D device. There were 193 patients enrolled in phase I of the trial, and 324 patients enrolled in phase II. Five of the 517 patients had successful device implantation but had previously undergone epicardial LV lead placement and were therefore not included in this analysis. Implantation of a transvenous CRT-D device was successful in 443 (87%) of the remaining 512 patients. The reasons for failure of coronary sinus lead placement are summarized in Table 1. The two most common reasons were the inability to cannulate the coronary sinus (n = 29) and the inability to obtain a stable pacing site (n = 24).

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
AT = atrial tachyarrhythmia
AV = atrioventricular
CI = confidence interval
CRT = cardiac resynchronization therapy
CRT-D = cardiac resynchronization and defibrillation therapy
DDI = dual-chamber nonatrial tracking
DDDR = dual-chamber rate-modulated
HR = hazard ratio
LV = left ventricular
RV = right ventricular
VDD = atrial synchronous ventricular
VVI = ventricular demand
VVIR = ventricular rate-modulated

The characteristics of the 443 patients who underwent successful implantation of a transvenous CRT-D device are summarized in Table 2. One hundred twenty-three patients (28%) had a history of atrial fibrillation or other supraventricular tachyarrhythmias. Among these patients, amiodarone had been prescribed in 49%, a sodium channel blocker in 5%, sotalol in 2%, and a calcium channel blocker in 1%. The mean follow-up was 2.5 ± 1.1 years (range, 0 to 4 years).

Implantable device characteristics. Patients received an implantable defibrillator system that delivers defibrillator therapy and CRT pacing. The system has been described in detail elsewhere (4). The coronary sinus lead is a unipolar lead that is designed to advance into a branch of the coronary sinus over a standard 0.014-inch coronary angioplasty wire. Tripolar pacing was used for biventricular capture, and tripolar sensing was used for both ventricular pacing and defibrillation therapy. When CRT was programmed "on," the pacing mode was atrial-synchronous ventricular pacing (VDD) with a lower rate of 40 beats/min. The automatic mode-switch feature (atrial tachycardia response) was programmed to "on" in all patients. This feature switches the pacing mode to a nonatrial tracking mode (ventricular demand pacing, VVI) during atrial tachyarrhythmias (ATs). Therefore, CRT was not delivered during ATs when mode switching occurred unless the ventricular response rate was <40 beats/min.

Table 1. Causes and Frequencies of Coronary Venous Lead Implantation Failure

Cause	n (%)
Inability to cannulate the coronary sinus	29 (6%)
Inability to obtain a stable pacing site	24 (5%)
Inability to obtain adequate pacing thresholds	6 (1%)
Coronary sinus dissection/perforation	5 (1%)
Diaphragmatic stimulation that could not be corrected	1 (0.2%)
Inability to place a right atrial pacing lead	1 (0.2%)
Transient atrioventricular block caused by guide catheter	1 (0.2%)
Vascular trauma during attempt at venous access	1 (0.2%)
No reason reported	1 (0.2%)
Total	69/512 (13%)

Table 2. Patient Characteristics

Age (yrs)	66 ± 11
Gender (male)	83%
LVEF	0.21 ± 0.07
NYHA class	
II	33%
III	58%
IV	9%
QRS width (ms)	158 ± 22
CAD	69%
BBB	
Left BBB	57%
IVCD	30%
Right BBB	13%
Medications	
ACEI/ARB	87%
Beta-blockers	49%
MR grade	
None	5%
I	57%
II	19%
III	7%
Not reported	12%
History of atrial tachyarrhythmias	
None	73%
Atrial fibrillation	22%
PSVT	3%
Atrial flutter	3%

ACEI = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; BBB = bundle branch block; CAD = coronary artery disease; IVCD = intraventricular conduction delay; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; NYHA = New York Heart Association; PSVT = paroxysmal supraventricular tachyarrhythmia.

Identification of loss of CRT. To identify patients who had interruption of CRT, the study data base was searched for the following adverse events: pacing mode reprogrammed to VVI or dual-chamber nonatrial tracking mode (DDI), pacing output increased, lead dislodgement, infection, or AT. The management of each patient who experienced one of these adverse events was analyzed to determine whether CRT was interrupted, the specific reason for the interruption of therapy, what interventions were performed to permit the reinstitution of CRT, and whether CRT was permanently lost. For each patient who experienced an AT as an adverse event, CRT was considered interrupted if the device automatically switched to a nonatrial tracking mode and if the ventricular rate exceeded the lower pacing rate of the pacemaker.

Statistical analysis. Kaplan-Meier survival curves were constructed to represent the rate of permanent loss of CRT over time. When CRT was permanently lost, the time of loss was considered to be the time when CRT was first discontinued. Patients were censored from the analysis at the time of death or cardiac transplantation. Cox regression analysis was used to identify predictors of permanent loss of CRT. New York Heart Association functional class was treated as an ordered categorical variable. All continuous variables were treated as such except for heart rate, which

Table 3. Causes and Frequencies of Temporary and Permanent Loss of CRT During Follow-Up in 443 Patients Who Underwent Successful Implantation of a Defibrillator With CRT

Cause	CRT Interrupted n (%)	CRT Restored n (%)	CRT Permanently Lost n (%)
Atrial tachyarrhythmia	81 (18)	79 (18)	2 (0.5)
Loss of left ventricular capture	44 (10)	39 (9)	5 (1)
Extracardiac stimulation	11 (2)	6 (1)	5 (1)
Loss of right ventricular capture	9 (2)	9 (2)	0
Infection/pericarditis	5 (1)	2 (0.5)	3 (1)
Patient intolerance	5 (1)	1 (0.2)	4 (1)
Loss of right atrial sensing	5 (1)	5 (1)	0
Ventricular oversensing	1 (0.2)	0	1 (0.2)
Total	161 (36)	141 (32)	20 (5)

CRT = cardiac resynchronization therapy.

was treated as an ordered categorical variable in 10-beats/min increments. Hazard ratios (HRs) are presented with 95% confidence intervals (CIs). Data are presented as mean ± standard deviation. A value $p \leq 0.05$ was considered statistically significant.

RESULTS

Interruption of CRT. Among the 443 patients who underwent a successful CRT-D implant, CRT was interrupted in 161 (36%) patients at some time during follow-up (Table 3). The reasons for interruption of CRT included the development of atrial fibrillation, atrial flutter, or atrial tachycardia (n = 81); loss of LV capture (n = 44); diaphragmatic or phrenic nerve stimulation (n = 11); loss of right ventricular (RV) capture (n = 9); infection requiring device explantation (n = 5); loss of atrial sensing (n = 5); intentional discontinuation of CRT as the result of intolerance or worsening symptoms associated with CRT (n = 5); and ventricular oversensing (n = 1).

Variables that independently predicted interruption of CRT as the result of ATs included a previous history of supraventricular tachyarrhythmia (HR 5.21; 95% CI 3.09 to 8.77; $p < 0.001$), a low resting heart rate (HR 1.28 for every 10-beat/min decrease in heart rate; 95% CI 1.04 to 1.59; $p = 0.006$), and the absence of treatment with both a beta-blocker and an ACE inhibitor (HR 1.92; 95% CI 1.05 to 3.57; $p = 0.032$).

Management of CRT interruption. Atrial tachyarrhythmias interrupted the delivery of CRT in 81 of 443 (18%) patients during follow-up. In addition, 26 of these patients received an inappropriate defibrillator shock for an AT. In 18 of the 26 patients, a shock was delivered because the ventricular response rate exceeded the tachycardia detection cut-off rate of the device, and in eight patients a shock was delivered because of double counting of the ventricular electrogram during ventricular sensing.

The ATs, which were predominantly atrial fibrillation, were managed by reprogramming of the device, cardioversion if necessary, and occasionally amiodarone. Of the 81 patients with ATs, 31 successfully returned to normal sinus rhythm and had no further recurrences. Forty-one patients had recurrent AT but continued to receive CRT at least 90% of the time on the basis of the results of the device histograms that were retrieved between the initial event and the last follow-up visit. The remaining nine patients exhibited recurrent AT that continued to significantly inhibit the delivery of CRT. Five of these nine patients underwent catheter ablation of the atrioventricular junction, and CRT was restored using a ventricular rate-modulated (VVIR) pacing mode. Two of these patients underwent successful catheter ablation for atrial flutter and had CRT reinitiated. Cardiac resynchronization therapy could not be restored because of refractory AT in the remaining two patients. Therefore, permanent loss of CRT because of ATs occurred in 2 of 443 patients and occurred 149 ± 194 days after implantation.

Cardiac resynchronization therapy was interrupted in 44 of 443 (10%) patients as a result of the loss of LV capture 74 ± 119 days (median, 13 days) after implantation. The causes of loss of capture included coronary sinus lead dislodgement in 33 patients, an elevated pacing threshold in 10 patients, and conductor failure in 1 patient. Thirty-two of these 44 patients underwent an attempted revision of the coronary sinus lead that was successful in 29 patients. Cardiac resynchronization therapy was restored in each of the 10 patients with an elevated pacing threshold after the pacing output was increased. Permanent loss of CRT as a result of the loss of LV capture occurred in 5 of 443 patients 258 ± 159 days after implantation.

Cardiac resynchronization therapy was interrupted in 11 of 443 (2%) patients 138 ± 158 days after implantation because of diaphragmatic or phrenic nerve stimulation that could not be corrected with device reprogramming. In 2 of the 11 patients, the RV lead was the cause of diaphragmatic stimulation, and the problem resolved after the RV lead was repositioned. In the remaining nine patients, diaphragmatic stimulation was due to LV pacing. The coronary sinus lead had been implanted in a posterior branch vein in a majority of these nine patients. Six of the nine patients underwent repositioning of the coronary sinus lead to a more basal position or into a more lateral vein, which was successful in four patients. Permanent loss of CRT because of diaphrag-

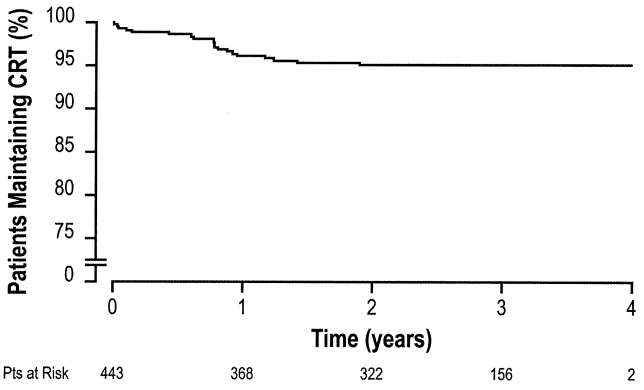

Figure 1. The rate of long-term retention of cardiac resynchronization therapy (CRT) among the 443 patients who underwent successful implantation of a device that delivers CRT is depicted as a survival curve.

matic or phrenic nerve stimulation occurred in 5 of 443 patients 162 ± 143 days after implantation.

Cardiac resynchronization therapy was interrupted in 9 of 443 (2%) patients because of loss of RV capture (elevated RV pacing threshold in 6 patients and lead dislodgment in 3 patients) and in 5 of 443 (1%) patients because of atrial lead dislodgment. Cardiac resynchronization therapy was restored successfully in all patients after lead revision or device reprogramming.

A device infection occurred in 5 of 443 patients 329 ± 180 days after implantation. Each patient underwent extraction of the device. Two of the five patients underwent reimplantation of a CRT-D device. Permanent loss of CRT because of infection occurred in 3 of 443 patients 429 ± 93 days after implantation.

There were five patients who did not tolerate CRT. Symptoms that were reported included palpitations, shortness of breath, and weakness, which resolved immediately upon disabling CRT. Three of these patients were felt to have left-sided pacemaker syndrome. One patient was managed by reprogramming the atrioventricular delay, and CRT was restored. All four of the remaining patients had CRT disabled by programming the pacing mode to VVI. Permanent loss of CRT occurred in 4 of 443 patients 218 ± 129 days after implantation because of the inability to tolerate CRT. Ventricular oversensing of atrial activity occurred in one patient 23 months after implantation. In this patient, lead revision was unsuccessful, and the lead was capped.

Permanent loss of CRT. Overall, 20 of 443 patients (5%) experienced permanent loss of CRT during follow-up. These data are depicted as a survival curve in Figure 1. The only independent predictor of permanent loss of therapy was LV ejection fraction (HR 1.09 for every percentage point decrease; 95% CI 1.01 to 1.16; $p = 0.03$). When patients who underwent an unsuccessful attempt at CRT-D device implantation are included in the analysis, the long-term retention of CRT is 83% during the time period of 2.5 years.

DISCUSSION

Main findings. The main findings of this study are that CRT is interrupted in over one-third (36%) of patients after successful implantation of a CRT-D device, and the most common reasons for interruption of CRT are the development of ATs (18%) and loss of LV capture (10%). However, CRT can be reinstituted in a high proportion of patients so that only 5% of patients who successfully undergo implantation of a CRT device permanently lose CRT. In an intention-to-treat analysis, the long-term retention of CRT is 83% during the course of 2.5 years.

Loss of CRT as the result of ATs. In this study, almost one fifth of patients who underwent successful implantation of a defibrillator capable of delivering CRT experienced an AT with a rapid ventricular response, which at least temporarily resulted in the inability to deliver CRT. The high prevalence of atrial fibrillation in this population is not surprising given the association between atrial fibrillation and congestive HF (5), but the finding that atrial fibrillation was the most common reason for interruption of CRT in this study emphasizes the importance of maintaining sinus rhythm in patients treated with CRT devices. It is not clear whether CRT reduces the incidence of atrial fibrillation in patients with HF. In the present study, only 15 of the 81 patients who experienced an AT that interrupted CRT had their AT during the six-month randomization period. Eight of these 15 patients were among the 222 patients (3.6%) randomized to CRT, and 7 of these 15 patients were among the 221 patients (3.2%) randomized to no CRT ($p = 0.80$).

Predictors of interruption of CRT as the result of the development of ATs in this patient population include a previous history of AT, a relatively slow resting heart rate, and the absence of therapy with both beta-blockers and ACE inhibitors. These findings are consistent with a recent analysis of the Studies Of Left Ventricular Dysfunction (SOLVD) study that found that treatment with enalapril markedly reduces the risk of development of atrial fibrillation in patients with LV dysfunction (6). Therefore, although it is not clear whether the use of both beta-blockers and ACE inhibitors directly influence the effectiveness of CRT, their use appears to improve the ability to deliver CRT.

Although a history of ATs appears to predict recurrent AT, it was not associated with the development of ventricular arrhythmias in the present study. The incidence of an appropriate defibrillator therapy among the patients with a history of ATs was similar to the incidence of an appropriate defibrillator therapy among patients without a history of ATs (12.3% vs. 14.9%, respectively; $p = 0.55$).

LV pacing lead problems. The second most common cause of transient loss of CRT in this study was the loss of LV capture, and the most common causes of permanent loss of CRT were loss of LV capture and extracardiac stimulation. The coronary sinus lead that was used in the study was the first transvenous LV lead that was commercially avail-

able from Guidant Inc. (St. Paul, Minnesota). The adverse event rates observed with this pacing lead are similar to that of other commercially available coronary venous leads. Overall, the proportion of patients who required a surgical intervention to restore LV capture in this study was 34 of 443 (8%), which is similar to proportions reported in the Summaries of Safety and Effectiveness published by the U.S. Food and Drug Administration for coronary venous leads implanted in the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial (37 of 532 patients; 7%) and in the MIRACLE ICD trial (37 of 351 patients; 11%) (7,8). In addition, the proportion of patients who required a surgical intervention in this study to correct extracardiac stimulation was 11 of 443 (3%), which is comparable with the proportions in the MIRACLE trial (4 of 532 patients; 1%) and in the MIRACLE ICD trial (12 of 351 patients; 3%). Newer lead designs that include different fixation methods and bipolar electrodes may improve the long-term ability to deliver CRT by improving pacing thresholds, reducing dislodgements, and avoiding extracardiac stimulation.

The likelihood that a significant number of patients had unrecognized intermittent loss of biventricular capture is low. The potential for unrecognized loss of LV capture has been examined previously by a comparison of the LV pacing thresholds and the programmed device pacing outputs (9). The results revealed that investigators programmed devices conservatively by using a 200% safety margin instead of the customary 100% safety margin that is used with conventional implantable pacemakers and defibrillators. In addition, biventricular capture was verified during daily activities using periodic Holter monitoring and during exercise using cardiopulmonary exercise testing.

Intolerance to CRT. Cardiac resynchronization therapy was discontinued permanently in 4 of 443 patients who were thought by their physicians to be intolerant of CRT. It is interesting that in the Multisite Stimulation in Cardiomyopathy trial, approximately 4% of patients who were asked whether they preferred CRT or no CRT actually preferred no CRT (10). Potential explanations for intolerance to atrial-biventricular pacing include left-sided pacemaker syndrome and aggravation of ventricular dyssynchrony. Although intolerance to CRT is uncommon, its occurrence emphasizes the need for careful follow-up for patients who are treated with CRT.

Comparison with pharmacologic therapy. The standard pharmacological therapy for congestive HF includes beta-blockers, ACE inhibitors, and spironolactone. The discontinuation rate for beta-blockers is at least 6% per year. In the U.S. Carvedilol Heart Failure Study, 6% of patients failed to complete the open-label run-in period with carvedilol because of adverse events, and carvedilol was discontinued in an additional 6% of patients during the double-blind treatment phase over a median follow-up period of 6.5 months (11). In the Carvedilol Or Metoprolol European Trial (COMET), a randomized trial that compared carvedilol with metoprolol in patients with chronic HF, the study drug was permanently stopped in 32% of patients in the carvedilol group and 32% in the metoprolol group during a mean follow-up of 58 months (12). Assuming that study drug discontinuation occurred steadily over time, the average discontinuation rate was approximately 6% per year. In the Assessment of Treatment with Lisinopril And Survival (ATLAS) trial, lisinopril was discontinued in 17% of patients because of side effects in the high-dose group and in 18% of patients in the low-dose group during a follow-up that ranged from 39 to 58 months (13). The high discontinuation rate in the ATLAS trial occurred despite nearly 90% of patients having previously tolerated some dose of an ACE inhibitor before entering the study. For captopril, the discontinuation rate was 15% during a median follow-up period of 555 days in the Evaluation of Losartan In The Elderly (ELITE) trial (14). Spironolactone appears to be fairly well tolerated and was discontinued in approximately 8% of patients in the Randomized Aldactone Evaluation Study (RALES) trial (15). The long-term retention of CRT in patients who underwent an attempt at implantation of a CRT-D device was 83% over 2.5 years is comparable with the long-term retention of pharmacological therapy for HF.

Compliance is another factor that is associated with the long-term successful delivery of HF therapy. Although CRT has the advantage over pharmacologic HF therapy of being less dependent on daily patient compliance, this study highlights the importance of compliance with device follow-up for the successful delivery of CRT.

Study limitations. The primary limitation of the present study is that loss of CRT was evaluated in patients who received CRT that was delivered by a specific device and specific coronary venous lead. Although some of the causes of loss of CRT that were identified, such as phrenic nerve stimulation, may be specific to the device that was implanted, most of the results of this study are likely to apply to any device that delivers CRT.

Clinical implications. The results of this study suggest that prevention of atrial fibrillation would significantly improve the ability to deliver CRT in patients with HF. The protocol for the present study required that the pacing mode be programmed to VDD so that the effect of CRT could be determined without the confounding effect of an increase in heart rate. Because patients with slower heart rates were more likely to develop ATs in this study, a CRT trial that compares a dual-chamber rate-modulated (DDDR) pacing mode that increases the atrial rate to the conventional VDD pacing mode seems logical. An evaluation of pacing algorithms that may prevent atrial fibrillation in this HF population is also needed.

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