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# The Utility of 12-Lead Holter Monitoring in Patients With Permanent Atrial Fibrillation for the Identification of Nonresponders After Cardiac Resynchronization Therapy

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**Objectives** This study sought to determine the incidence of ineffective capture using 12-lead Holter monitoring and to assess whether this affects response to cardiac resynchronization therapy (CRT).

**Background** Cardiac resynchronization therapy is used in patients with atrial fibrillation (AF), prolonged QRS duration, and heart failure in the setting of ventricular dysfunction. The percentage of ventricular pacing is used as an indicator of adequate biventricular (BiV) pacing. Although device counters show a high pacing percentage, there may be ineffective capture because of underlying fusion and pseudo-fusion beats.

**Methods** We identified 19 patients (age 72 ± 8 years, ejection fraction 18 ± 5%), with permanent AF who underwent CRT. All patients received digoxin, beta-blockers, and amiodarone for rate control; device interrogation showed >90% BiV pacing. Patients had a 12-lead Holter monitor to assess the presence of effective (>90% fully paced beats/24 h) pacing. At 12 months post-CRT, the New York Heart Association functional class was reassessed and an echocardiogram was obtained and compared with pre-CRT.

**Results** Only 9 (47%) patients had effective pacing. The other 10 (53%) patients had 16.4 ± 4.6% fusion and 23.5 ± 8.7% pseudo-fusion beats. Long-term responders (≥1 New York Heart Association functional class improvement) to CRT had a significantly higher percentage of fully paced beats (86.4 ± 17.1% vs. 66.8 ± 19.1%; p = 0.03) than nonresponders.

**Conclusions** Pacing counters overestimate the degree of effective BiV pacing in patients with permanent AF undergoing CRT therapy. Only patients with complete capture responded clinically to CRT. These findings have important implications for the application of CRT to patients with permanent AF and heart failure. (J Am Coll Cardiol 2009;53:1050–5) © 2009 by the American College of Cardiology Foundation

Atrial fibrillation (AF) frequently coexists with heart failure (HF), and its prevalence is closely related to the New York Heart Association (NYHA) functional class, with up to 25% for class III and 50% for class IV HF (1). The permanent form of AF (2) is present in 10% to 30% of patients with HF (3) and is associated with increased morbidity and mortality (4,5).

Cardiac resynchronization therapy (CRT) has been increasingly used to treat patients who have ejection fraction ≤35%, ventricular dyssynchrony (currently defined by a QRS duration ≥120 ms) and NYHA functional class III to IV HF. However, there are only limited clinical data on the efficacy of CRT in patients with permanent AF, and the available data to date have been inconsistent (6–9).

There is no possibility of response to CRT if ventricular capture does not occur during biventricular (BiV) pacing. In patients with HF and AF, there is no atrioventricular (AV) synchrony and BiV capture is difficult to ensure. The

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percentage of BiV pacing alone as recorded by the CRT device may be an ineffective surrogate of complete and consistent BiV capture. Fusion and pseudo-fusion beats resulting from an interaction between intrinsically conducted and paced beats may be responsible for ineffective pacing, despite apparent delivery of CRT as assessed by a high percentage of BiV pacing (10). The objectives of this study were: 1) to determine the incidence of effective and ineffective pacing, the latter defined by the presence of fusion and pseudo-fusion beats using a novel 12-lead Holter analysis, in patients with permanent AF who underwent CRT; and 2) to assess the effect of ineffective capture on clinical response in these patients.

## Methods

**Patient selection.** During an enrollment period of 18 months, consecutive patients who underwent CRT were screened for participation in the study. Informed written consent was obtained from all patients in the study, and the protocol was approved by our institutional review board. Inclusion criteria for the study included: age ≥18 years; presence of permanent AF, defined as AF present for >1 year in which no effort was made to restore sinus rhythm or in which such efforts had previously failed; NYHA functional class III/IV HF; left ventricular ejection fraction (LVEF) ≤35%; and QRS duration ≥120 ms. All patients were on optimal drug therapy for HF, which included beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, diuretics, and spironolactone. In addition, all patients were treated for rate control of AF with a beta-blocker, digoxin, and amiodarone. Amiodarone was also used for suppression of ventricular arrhythmia, which could also interfere with pacing capture. Patients were excluded if they had undergone atrioventricular junction (AVJ) ablation for uncontrolled ventricular rates. The study cohort consisted of patients who were documented to have a high degree (>90%) of BiV pacing as documented by the device counters at follow-up post-CRT.

**Holter monitoring.** At a median of 12 months after device implantation, patients were instructed to wear an ambulatory 12-lead Holter (ScottCare Corporation, Cleveland, Ohio; formerly Rozinn Electronics) for 24 h. This 12-lead Holter monitor consisted of 6 chest wall leads, which were placed in the standard manner, and limb electrodes, which were placed on the trunk close to arms and legs, corresponding to a modified Mason-Likar lead configuration (11). Data were stored on a digital flash card, with a capacity for 24-h recording. The system provided 20-bit resolution with a digital sampling rate of 180/s/lead for standard evaluation. The data were transferred from the flash card to a computer for analysis. Two electrophysiologists blinded to the identity of the patient performed standard Holter analysis (heart rate, RR interval, detection of supraventricular and ventricular arrhythmia) using the Windows S+ version 10.01 (ScottCare Corporation). In addition, a complete 12-lead electrocardiogram (ECG) was obtained and analyzed for the whole period of 24 h.

**Abbreviations and Acronyms**

AF = atrial fibrillation
AV = atrioventricular
AVJ = atrioventricular junction
BiV = biventricular
CRT = cardiac resynchronization therapy
ECG = electrocardiogram
HF = heart failure
HR = hazard ratio
LVEF = left ventricular ejection fraction
MR = mitral valve regurgitation
NYHA = New York Heart Association

Additional data that were collected from the Holter monitor included percentage of fusion, pseudo-fusion, and complete capture beats (using template-matched analysis software). The heartbeat waveforms were evaluated within a fixed-length window around the fiducial points (100 ms before, 100 ms after). The operator was required only to initially select 3 normal heartbeats (ventricular or paced complexes) for each of the 12 leads selected. These were named original QRS templates, and their copies were substituted continuously throughout the ECG analysis to capture slight variations in the heartbeat waveforms of the patient's sustained rhythm. The method is based on matching of the evaluated heartbeat with the QRS templates by a complex set of ECG descriptors, including maximal cross-correlation, area difference, and frequency spectrum difference. The achieved unbiased accuracy is represented by sensitivity of 98.4% and specificity of 98.8% (12).

A fusion beat was defined by the presence of a pacemaker spike in the setting of a QRS complex with intermediate morphology compared with a fully paced and native QRS complex. A pseudo-fusion beat was defined as a beat in which the pacemaker spike fell on top of an intrinsic beat. The spike occurred, but played no part in depolarization, therefore, no capture occurred and the QRS complex reflected the morphology of the native QRS morphology. Effective pacing was defined by the presence of more than 90% fully paced beats with complete capture of the heart as confirmed in all 12 leads.

**Device implantation and programming.** The right ventricular lead was positioned in the right ventricular apex in all patients' systems. Left ventricular lead placement was guided by the intraoperative coronary sinus venogram; in all cases, either a lateral or a posterolateral vein was selected for lead implantation. All patients were programmed to ventricular pacing mode. The lower pacing rate at implantation was set at 70 beats/min. However, this could be altered at follow-up based on physician discretion. Seven patients had Guidant/Boston Scientific devices (Natick, Massachusetts), 11 had Medtronic devices (Minneapolis, Minnesota), and 1 had a St. Jude Medical device (St. Paul, Minnesota) implanted. All Guidant devices had ventricular rate regularization activated. In all Medtronic devices, ventricular sense response and conducted AF response features were activated. These algorithms are designed to maximize ventricular pacing during potentially disruptive events such as

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**Table 1** Baseline Characteristics of Study Population (n = 19)

| | |
|---|---|
| Clinical data | |
| Age (yrs) | 72 ± 8 |
| Male sex | 12 (63%) |
| QRS duration (ms) | 158 ± 40 |
| Heart rate (beats/min) | 70 ± 7 |
| NYHA functional class III/IV | 15/4 |
| Etiology of cardiomyopathy | |
| Ischemic | 11 (58%) |
| Nonischemic | 8 (42%) |
| Ejection fraction (%) | 18 ± 5 |
| CRT device data | |
| Biventricular capture (%) | 95.4 ± 3.2 |
| Programmed lower pacing rate (ppm) | 67.1 ± 6.9 |
| Programmed upper pacing rate (ppm) | 116.8 ± 8.8 |

CRT = cardiac resynchronization therapy; NYHA = New York Heart Association; ppm = pacing per minute.

premature ventricular complexes or rapidly conducted atrial arrhythmias.

**Measures of clinical outcome.** Assessment of patient status was performed at 1, 3, 6, and 12 months after CRT. A baseline echocardiographic examination had been performed according to American Society of Echocardiography guidelines within 3 months preceding device implantation per our routine laboratory protocol. The following parameters were collected in all patients: left ventricular end-systolic diameter, left ventricular end-diastolic diameter, LVEF, and degree of mitral valve regurgitation (MR). In addition, left ventricular end-systolic volume and left ventricular end-diastolic volume were obtained in 15 patients; in 4 patients the echocardiographic examination was performed on a machine that was not capable of rendering accurate volumetric data. The CRT device was interrogated at all follow-up visits. The left ventricular pacing output was adjusted as needed to maintain adequate left ventricular capture. Care was taken to evaluate for the presence of ventricular ectopy that could preclude 100% BiV pacing.

At 12 months, the NYHA functional class was reassessed and an echocardiogram was obtained; both were compared with the pre-CRT evaluation. An increase of ≥1 NYHA functional class was considered evidence of response to CRT. The echocardiograms before and after CRT were analyzed by an echocardiographer who was blinded to device programming parameters, Holter results, and information regarding clinical response to CRT.

**Statistical analysis.** All continuous variables are expressed as mean ± SD. Categorical variables are summarized as absolute number and relative frequencies (%). Changes in the before and after measurements were compared using the nonparametric Wilcoxon matched-pairs signed rank test. The Mann-Whitney *U* test was used to compare the change between the 2 groups. The SPSS version 15.0 software package (SPSS Inc., Chicago, Illinois) was used for the statistical analysis. Logistic regression analyses were used to identify univariate correlates of clinical response. Results with $p < 0.05$ were considered statistically significant.

## Results

A total of 19 patients were enrolled in the study. The clinical characteristics of the patients and device settings are summarized in Table 1. The group was characterized by severe left ventricular dysfunction, advanced HF, and long-standing AF.

**Holter findings.** Overall, in this cohort, only 76% of the beats were fully paced with complete capture, whereas the remaining beats were ineffective. Further review of the Holter monitor results showed that only 9 (47%) patients met criteria for effective pacing. The remaining 10 (53%) patients met criteria for ineffective pacing; in these patients, nearly 40% of pacing was accounted for fusion and pseudo-fusion (Table 2). Of the study group, 78% (7 of 9) of the patients with effective pacing were responders, whereas 80% (8 of 10) of patients with noneffective pacing were nonresponders (odds ratio: 3.9, 95% confidence interval [CI]: 1.1 to 14.1, p = 0.023).

**Clinical outcome and echocardiographic findings.** There were no significant differences among responders and nonresponders at baseline with respect to age, heart rate, NYHA functional class HF, or baseline echocardiographic data (Table 3).

During a median follow-up of 12 months, 47% of patients showed evidence of clinical response. In addition to an improvement in end-systolic dimension (0.75 ± 0.9 cm vs. 0.2 ± 0.5 cm; p = 0.11) as compared with nonresponders, responders had a significant improvement in ejection fraction (15.6% vs. 2.1%; p = 0.02) and end-diastolic diameter (0.9 ± 0.8 cm vs. 0.2 ± 0.2 cm; p = 0.02). Responders had a greater reduction in the end-systolic volume (−29.8 ± 25.3% vs. −6.2 ± 14.8%; p = 0.07) and end-diastolic volume (−16.8 ± 13.8% vs. −8.1 ± 7.2%; p = 0.27) as compared with nonresponders (Table 3).

Review of the Holter data showed significant differences between responders and nonresponders (Table 3). Responders had a higher percentage of fully paced beats than nonresponders (86.4 ± 17.1% vs. 66.8 ± 19.1%; p = 0.03). In contrast, nonresponders had a significantly higher per-

**Table 2** Data From 24-h 12-Lead Holter Recordings

| | Entire Group (n = 19) | Effective Paced Group (n = 9) | Noneffective Paced Group (n = 10) |
|---|---|---|---|
| Fully paced beats (%/24 h) | 76.1 ± 20.3 | 93.9 ± 3.2 | 60.1 ± 14.8 |
| Fusion beats (%/24 h) | 9.8 ± 7.9 | 2.4 ± 1.6 | 16.4 ± 4.6 |
| Pseudo-fusion beats (%/24 h) | 14.1 ± 12.0 | 3.7 ± 2.3 | 23.5 ± 8.7 |

**Table 3** Comparison of Responders and Nonresponders

| | Responders (n = 9) | Nonresponders (n = 10) | p Value |
|---|---|---|---|
| Age (yrs) | 72 ± 8 | 71 ± 9 | 0.70 |
| Heart rate (beats/min) | 68 ± 7 | 72 ± 7 | 0.26 |
| Pre-CRT NYHA functional class | 3.3 ± 0.5 | 3.1 ± 0.3 | 0.24 |
| Post-CRT NYHA functional class | 1.7 ± 0.5 | 3.2 ± 0.4 | <0.005 |
| Echocardiographic results | | | |
| Baseline ejection fraction (%) | 18.3 ± 6.1 | 18.3 ± 4.8 | 0.99 |
| Baseline end-systolic diameter (cm) | 4.9 ± 0.4 | 5.3 ± 1.0 | 0.46 |
| Baseline end-systolic volume (ml) | 119.4 ± 31.6 | 102.4 ± 38.6 | 0.19 |
| Baseline end-diastolic diameter (cm) | 6.3 ± 0.7 | 6.5 ± 0.5 | 0.41 |
| Baseline end-diastolic volume (ml) | 142.3 ± 28.1 | 139.1 ± 43.6 | 0.64 |
| Baseline MR grade | 2.7 ± 0.8 | 2.6 ± 1.1 | 0.77 |
| Change in MR grade | −1.0 ± 1.1 | −0.6 ± 0.7 | 0.42 |
| Change in ejection fraction (%) | 15.6 ± 12.6 | 2.1 ± 9.9 | 0.02 |
| Change in end-systolic diameter (cm) | −0.75 ± 0.9 | −0.2 ± 0.5 | 0.11 |
| Change in end-systolic volume (%)* | −29.8 ± 25.3 | −6.2 ± 14.8 | 0.07 |
| Change in end-diastolic diameter (cm) | −0.9 ± 0.8 | −0.21 ± 0.2 | 0.02 |
| Change in end-diastolic volume (%)* | −16.8 ± 13.8 | −8.1 ± 7.2 | 0.27 |
| Holter data (%/24 h) | | | |
| Fully paced beats | 86.4 ± 17.1 | 66.8 ± 19.1 | 0.03 |
| Fusion beats | 5.9 ± 7.6 | 13.3 ± 6.7 | 0.04 |
| Pseudo-fusion beats | 7.7 ± 9.7 | 19.9 ± 11.2 | 0.02 |

*Data available in 15 patients: 6 responders, 9 nonresponders.
CRT = cardiac resynchronization therapy; MR = mitral regurgitation; NYHA = New York Heart Association.

centage of ineffective pacing than responders because of a combination of fusion (13.3 ± 6.7% vs. 5.9 ± 7.6%; p = 0.04) and pseudo-fusion (19.9 ± 11.2% vs. 7.7 ± 9.7%; p = 0.02) (Fig. 1). Ventricular ectopy was similar between responders and nonresponders and low because of chronic amiodarone therapy (ventricular premature beats/24 h = 17.3 ± 25.1 vs. 20.0 ± 26.7; p = 0.8, nonsustained ventricular tachycardia runs/24 h = 1.13 ± 1.2 vs. 1.0 ± 1.3, p = 0.8).

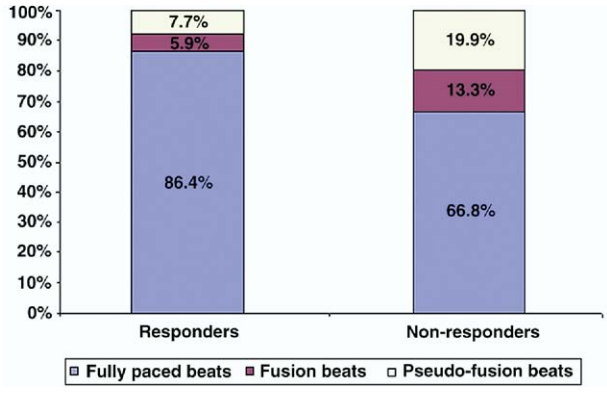


**Figure 1** 24-h Holter Data for Responders and Nonresponders

Responders had a higher percentage of fully paced beats than nonresponders (p = 0.03). Nonresponders had a significantly higher percentage of ineffective pacing because of a combination of fusion (p = 0.04) and pseudo-fusion (p = 0.02) beats.

**Correlates of clinical response.** There was no significant correlation of age (hazard ratio [HR]: 1.0; 95% CI: 0.91 to 1.14, p = 0.8), sex (HR: 2.3; 95% CI: 0.34 to 16.2, p = 0.4), baseline heart rate (HR: 0.92; 95% CI: 0.79 to 1.06, p = 0.23), baseline LVEF (HR: 1.0; 95% CI: 0.85 to 1.2, p = 0.9), or NYHA functional class (HR: 5.4; 95% CI: 0.44 to 66.6, p = 0.2) with clinical response. The presence of >90% fully paced beats was the only significant correlate of clinical response (HR: 12.0; 95% CI: 1.3 to 111.3, p = 0.03).

## Discussion

Our study shows that the absolute percentage of BiV pacing alone, as obtained from CRT device interrogation in patients with permanent AF, is an unreliable surrogate of effective pacing. Although CRT devices documented >90% pacing, in actuality fusion and pseudo-fusion beats constituted as much as 40% of the overall paced beats as determined by the use of a 12-lead Holter monitor. Thus, in patients with permanent AF and HF, using data from CRT counters alone to estimate percentage of BiV stimulation time may be misleading, because counters likely overestimate the degree of BiV pacing.

This study also confirms the importance of effective BiV capture to ensure clinical response from CRT. Only effectively paced patients showed a favorable clinical response and evidence of reverse remodeling after CRT. Previous studies have aimed for high percentages on CRT device counters to obtain adequate BiV capture. However, the programmed percentages used in these studies have been arbitrary (13). Rather than rely on the percentage pacing measures obtained from the CRT device alone, we deter-

mined the actual percentage of completely BiV captured beats using a 12-lead Holter monitor. This concept has neither been previously quantified nor correlated with outcome.

In studying patients who had a >90% BiV pacing from CRT devices, we selected a group that would be expected to respond. We used the cutoff of >90% BiV pacing as recorded by CRT counters in all patients. Although arbitrary, this number was higher than that used in a previous study (13) and it was reasonable to assume that this high pacing percentage would be adequate to achieve response. Improvement in clinical response was instead explained by higher percentage of paced beats with effective BiV capture, rather than the simple counts of pacing delivery. In addition, reverse remodeling was shown only among responders with higher percentages of fully paced beats.

The management options for patient with permanent AF and HF include optimum rate control, cardioversion and maintenance of sinus rhythm, or AVJ ablation with permanent pacing. In patients in whom a rate control strategy is used, the best way to achieve rate control of AF for effective CRT remains unclear. This rate control may be difficult to achieve during activity even in the presence of beta-blockers. In patients with permanent AF who undergo CRT without AVJ ablation, few studies have suggested that cardioversion and aggressive rhythm control result in better clinical outcomes (14,15). However, maintenance of sinus rhythm using antiarrhythmic drugs in the setting of AF and HF does not improve survival or other important end points (16), and maintenance of sinus rhythm will likely be very difficult in this setting. Because antiarrhythmic drugs are only partially effective in the maintenance of sinus rhythm and are associated with long-term adverse effects, catheter ablation may offer another approach for achieving sinus rhythm in these patients (17–19), but this approach has not been tested in large number of patients. An AVJ ablation with insertion of a permanent pacemaker theoretically ensures 100% ventricular capture. It renders the patient pacemaker dependent and forces consistent capture. This approach provides adequate rate control and also maintains a regular rhythm, thus providing additional benefit on ventricular function.

There are limited data from prior studies on the optimal management of permanent AF and HF in patients receiving CRT. The MUSTIC (MUltisite STimulation in Cardiomyopathies) trial showed similar improvement in the 6-min walk test in class III HF patients after CRT whether they were in sinus rhythm or in AF (8). The study enrolled 64 patients, but only 37 patients completed both crossover phases, limiting the impact of the results. In addition, all patients with AF in the MUSTIC study were required to have a slow ventricular rate occurring spontaneously or after AVJ ablation. This may have selected patients who were likely to have a high degree of effective ventricular capture. Delnoy et al. (20) compared the efficacy of CRT in 96 patients with chronic AF and 167 patients with sinus rhythm. Overall mortality and rates of hospitalization were similar in both groups. However, among patients with chronic AF, 22% had AVJ ablation and nearly 50% the patients were in spontaneous or cardioverted sinus rhythm. Khadjooi et al. (21) studied 295 patients (209 in sinus rhythm, 66 in permanent AF, and 20 in paroxysmal AF) who underwent CRT therapy without AVJ ablation. Both the AF and the sinus rhythm groups derived similar improvement in NYHA functional class, 6-min walk test, and quality-of-life scores. Echocardiographic improvements were also comparable. In patients with HF and permanent AF, rhythm regularization with AVJ ablation improved exercise capacity and quality of life with BiV pacing (22). Similarly, Gasparini et al. (13) showed that in patients with HF and permanent AF, only patients who underwent AVJ ablation showed a significant increase of ejection fraction, reverse remodeling effect, and improved exercise tolerance. In contrast, no improvements were observed in AF patients who did not undergo AVJ ablation. The long-term effect on mortality and hospitalizations was subsequently assessed in the follow-up of 1,285 consecutive patients (1,042 in sinus rhythm, 243 in AF) who underwent CRT therapy (23). At nearly 3 years of follow-up, all-cause mortality and cardiac mortality were similar in the sinus rhythm group and the AF group. Within the AF group, total mortality was significantly better in the AVJ ablation group compared with the AF drug-treated group. These data suggest that patients with AF and HF may do better with the "ablate and pace" strategy; however, this is not standard practice at this time because this would create the large number of pacemaker-dependent HF patients. In addition, a small but variable rate of spontaneous conversion of AF to sinus rhythm has been reported after CRT (24,25). The relatively low response rate among patients with HF and permanent AF in our study suggests that regardless of the treatment method used, 100% effective BiV capture, rather than a high percentage of pacing, should be the goal.

**Study limitations.** The relative small sample size is a limitation of the study. Patients were enrolled consecutively and not randomized. The inclusion criteria for this study specified the stringent requirement of triple therapy including amiodarone for optimal rate control, >90% BiV capture, and no AVJ ablation, and thus a group with maximal medical management and presumably an optimized opportunity to respond to CRT. Although responders and nonresponders differed only in the percentage of effective and ineffective pacing, there may have been unmeasured factors that may have influenced response. Echocardiographic volumes on all patients would have enabled the assessment of the importance of full BiV capture to achieve reverse remodeling. We cannot be certain whether our results would apply to other patients with AF, HF, and CRT.

## Conclusions

Device-based pacing counters overestimate the degree of genuine effective BiV pacing in a significant number of

patients with permanent AF undergoing CRT therapy. Only patients with a high percentage of demonstrated complete capture responded clinically to CRT or had reverse remodeling. Thus, the goal of CRT in these patients is near 100% effective BiV capture as assessed on 12-lead Holter monitor, potentially achieved by medical therapy or AVJ ablation.

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**Key Words:** Holter monitoring ■ atrial fibrillation ■ cardiac resynchronization therapy.