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# A novel algorithm increases the delivery of effective cardiac resynchronization therapy during atrial fibrillation: The CRTee randomized crossover trial



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**BACKGROUND** Cardiac resynchronization therapy (CRT) requires a high percentage of ventricular pacing (%Vp) to maximize its clinical benefits. Atrial fibrillation (AF) has been shown to reduce %Vp in CRT due to competition with irregular intrinsic atrioventricular (AV) conduction. We report the results of a prospective randomized crossover trial evaluating the amount of effective CRT delivered during AF with a novel algorithm (eCRTAF).

**OBJECTIVE** The purpose of this study was to determine whether eCRTAF increases the amount of effective CRT delivered during AF compared to a currently available rate regularization algorithm.

**METHODS** Patients previously implanted with a cardiac resynchronization therapy-defibrillator and with a history of AF and intact AV conduction received up to 4 weeks of control (Conducted AF Response) and up to 4 weeks of eCRTAF in a randomized sequence. The percent effective CRT (%eCRT) pacing, which excludes beats without left ventricular capture, %Vp, and mean heart rate (HR) were recorded during AF and sinus rhythm.

**RESULTS** The eCRTAF algorithm resulted in a significantly higher %eCRT during AF than control ( $87.8\% \pm 7.8\%$  vs  $80.8\% \pm 14.3\%$ ;  $P < .001$ ) and %Vp during AF than control ( $90.0\% \pm 5.9\%$  vs  $83.2\% \pm 11.9\%$ ;  $P < .001$ ), with a small but statistically significant increase in mean HR of 2.5 bpm ( $79.5 \pm 9.7$  bpm vs  $77.0 \pm 9.9$  bpm;  $P < .001$ ).

**CONCLUSION** In a cohort of CRT patients with a history of AF, eCRTAF significantly increased %eCRT pacing and %Vp during AF with a small increase in mean HR. This algorithm may represent a novel noninvasive method of significantly increasing effective CRT delivery during AF, potentially improving CRT response.

**KEYWORDS** Atrial fibrillation; Biventricular pacing; Cardiac resynchronization therapy; Effective pacing; Heart failure

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## Introduction

Cardiac resynchronization therapy (CRT) provides significant benefits in both morbidity and mortality for heart failure (HF) patients with reduced ejection fraction and a wide QRS. Achieving these benefits requires a high percentage of ventricular pacing (%Vp). Retrospective analyses have shown that even small reductions in CRT pacing are associated with increased morbidity and mortality.<sup>1–3</sup> The reduced efficacy

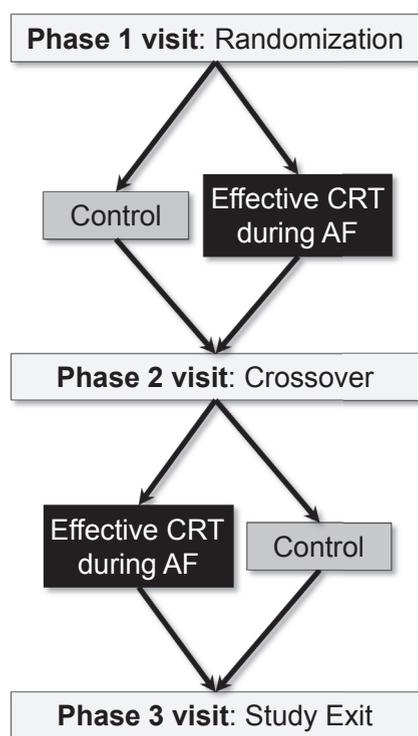
of CRT in some patients with atrial fibrillation (AF) has been attributed to reduced %Vp due to competition with irregular intrinsic atrioventricular (AV) conduction, which can lead to pacing-refractory myocardium. Some CRT devices use rate regularization algorithms during AF (Conducted AF Response [CAFR]—Medtronic plc; Ventricular Rate Regulation—Boston Scientific) to modulate pacing rate in an attempt to reduce the loss of %Vp.<sup>4</sup> However, the performance of these algorithms has not been evaluated in a CRT patient population.

Accurately determining the amount of CRT being delivered is made even more difficult because standard device pacing counters cannot distinguish left ventricular (LV) pacing that is delivered to refractory myocardium (i.e., pseudofusion) from LV pacing that succeeds in depolarizing a significant portion of the LV (i.e., effective CRT pacing). A new device-based diagnostic, percent effective CRT (%eCRT) pacing, quantifies actual CRT delivery using beat-to-beat

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**Figure 1** Flow diagram for the study design. AF = atrial fibrillation; CRT = cardiac resynchronization therapy.

analysis of the paced morphology of the unipolar LV electrogram. This diagnostic has been validated against the 12-lead ECG and has been shown to accurately identify 98.2% of effectively paced beats.<sup>5</sup> When applied to a general CRT patient population in an observational study (N = 57), the diagnostic demonstrated that %Vp overestimated %eCRT pacing by an average of  $7.3\% \pm 22.2\%$  ( $P < .05$ ).<sup>6</sup>

A novel algorithm has been developed that increases the amount of effective CRT delivered during AF (eCRTAF). Using the %eCRT diagnostic, it monitors beat-to-beat LV capture during AF and adjusts pacing rate to maximize %eCRT pacing while minimizing any increase in pacing rate. We report the results of a prospective randomized crossover trial evaluating the amount of effective CRT delivered during AF with this new algorithm.

## Methods

The CRTee download study was a prospective randomized crossover study enrolling CRT patients with a history of AF. The study compared a commercially available algorithm (CAFR) with a novel algorithm (EffectivCRT during AF [eCRTAF]). The primary endpoint was %eCRT during AF, with additional endpoints of %Vp during AF and mean heart rate (HR) during AF. Cardiovascular adverse events (AEs) also were recorded. An additional acute comparison of no algorithm, CAFR, and eCRTAF was performed in those subjects who were in AF at the time of the office visit.

## Subjects

Participants provided fully informed written consent and were enrolled by site personnel trained in the study and designated for this task.

The study recruited patients with a previously implanted Medtronic Viva or Brava cardiac resynchronization therapy-defibrillator (CRT-D) device. The inclusion/exclusion criteria included the following:

### Inclusion

- A Viva or Brava device had been implanted for at least 30 days
- AF burden: At least 6 days with at least 4 hours of AF during a 4-week period occurring within 90 days *or* clinical diagnosis of permanent AF (when no device data were available)
- Demonstrated history of being able to complete the LV Capture Management nightly test
- Less than or equal to 97% Vp during AF.

### Exclusion

- AV nodal ablation
- Complete or third-degree heart block
- Myocardial infarction within 30 days

## Study design

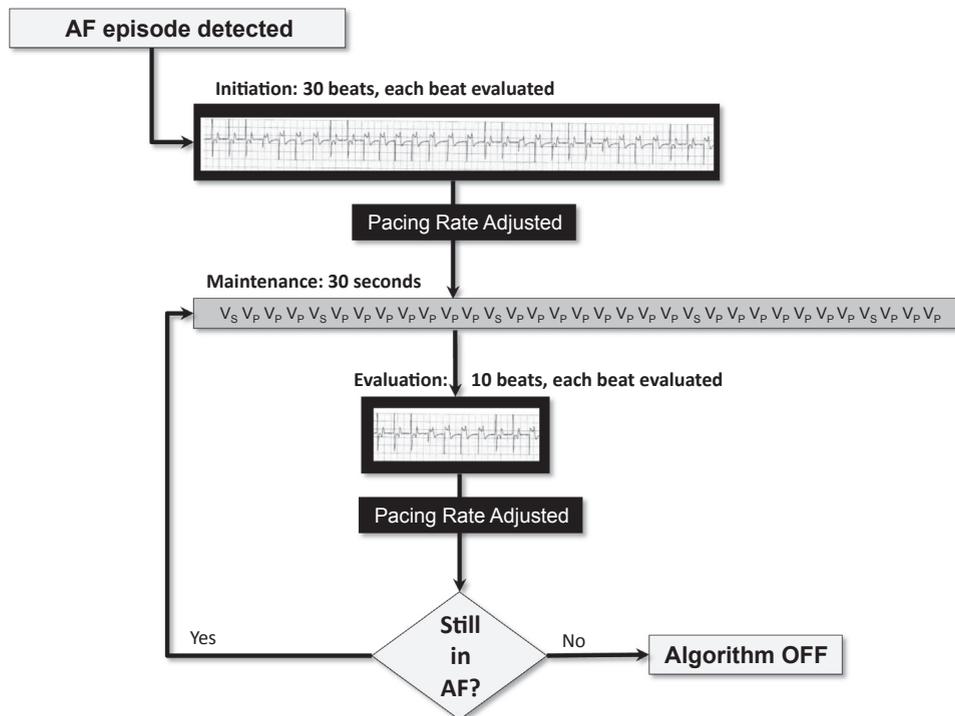
The study outline is shown in Figure 1. Baseline data were collected at the phase 1 visit, and the eCRTAF algorithm and the ambulatory diagnostics of %eCRT pacing were downloaded to the CRT-D devices using a modified model 2090 programmer. The patient was then randomized 1:1 to either control (i.e., CAFR algorithm) or eCRTAF first. Randomization allocations were stratified by site and generated by the study sponsor. Each week, the subject completed a remote transmission. The phase 2 visit was scheduled when the programmed algorithm had been active for at least 2 hours or 4 weeks had passed, whichever came first. At the phase 2 visit, the patient was crossed over to the alternative algorithm, and the transmission process was repeated. After collecting at least 2 hours of data under the programmed algorithm (or 4 weeks had passed), the phase 3 visit was scheduled. The phase 3 visit could have been the exit visit, or, if desired, the eCRTAF algorithm could have remained on for up to 4 months postrandomization. This additional time of algorithm operation outside of the randomized phases was not included in the primary analysis of the trial.

## CAFR (control)

CAFR is an algorithm that was designed to regularize the ventricular response to AF. Medtronic CRT devices have this algorithm programmed on by default because it tends to increase pacing. When the device is not trying to track the atrium, the algorithm measures the variability of the intervals between ventricular events (both paced and sensed) and dynamically adjusts the pacing rate. The algorithm is not able to distinguish between paces that were delivered but did not capture and those that did capture. This was used as control because it is active by default in the CRT-D devices used in the study.

## EffectivCRT during AF (eCRTAF)

The eCRTAF algorithm is designed to maximize percent LV capture while minimizing the increase in pacing rate. It



**Figure 2** Flow diagram for the EffectivCRT during AF (eCRTAF) algorithm. AF = atrial fibrillation.

operates only during mode switch or VVIR pacing mode. It consists of 3 phases: initiation, maintenance, and evaluation (Figure 2).

During the initiation phase, the algorithm evaluates eCRT on 30 consecutive beats, adjusting the pacing rate after each beat to achieve the minimum pacing rate that maximizes eCRT pacing as quickly as possible. Ventricular sensed events or ineffective LV pacing results in small increases in the pacing rate, whereas effectively paced ventricular events result in small decreases in pacing rate. After the initiation phase, the algorithm enters a maintenance phase during which the pacing rate is maintained for 30 seconds. After the maintenance phase, while continuing at the current pacing rate the algorithm moves to a brief evaluation phase of 10 beats. Each beat is assessed for effectiveness, and, at the end of the evaluation phase, a pacing rate is determined based on the number of ventricular sensed events, and effective and ineffective paced beats. After the evaluation phase, the algorithm returns to the maintenance phase and then continues to cycle between evaluation and maintenance phases until the end of the AF episode.

The eCRTAF algorithm includes 4 safety features to limit increases in HR. First, there is a programmable maximum pacing rate. Second, during a daily test, the device confirms that it can deliver effective CRT pacing with a short sensed or paced atrioventricular interval or an accelerated rate during a non-tracking mode, in both biventricular and LV-only modes. If effective CRT pacing cannot be achieved, the algorithm is disabled for the day. Third, the algorithm is suspended if the pacing rate reaches the programmed maximum rate and the device still detects ineffective capture in 4 of 5 paced beats. Finally, the proportion of sensed or ineffective CRT paced beats required to increase pacing rate increases as the pacing rate rises. This makes the algorithm progressively less aggressive as the pacing rate increases.

### Data collection

During each phase of the study, eCRT pacing was evaluated continuously during AF (or while the device was in VVIR mode). If the subject was in normal sinus rhythm, eCRT pacing was evaluated every hour for 100 consecutive beats at 25 minutes past the hour. The accumulated %eCRT pacing was defined as follows:

$$\%eCRT = \frac{\text{effective CRT paced beats}}{\text{effective CRT paced beats} + \text{ineffective CRT paced beats} + \text{ventricular sensed events}}$$

Ventricular sense response beats were treated as sensed beats. Separate metrics of %eCRT pacing and %Vp were maintained for time spent in AF and sinus rhythm. Device counters and diagnostics were downloaded at each clinic visit. %Vp and mean HR since last interrogation were recorded.

During the phase 1 office visits, if the subject was in AF, %eCRT pacing and pacing rate were assessed over 3-minute periods with no algorithm, with CAFR, and with eCRTAF. The order of CAFR and eCRTAF was randomized, and each algorithm had its own control period with no algorithm.

### Study oversight

The study was approved by the local institutional review board or the Medical Ethics Committee and the national regulatory body for each country in which the study was conducted.

AEs were adjudicated by the Adverse Event Adjudication Committee. The committee consisted of 3 physicians not involved in the study. All AEs and deaths were reviewed by the committee and evaluated for relatedness to the algorithm as well as category, such as cardiovascular or noncardiovascular.

### Data and statistical analysis

The primary objective of the study was to demonstrate that, during AF, %eCRT with eCRTAF applied was noninferior to when CAFR was applied. If this objective was met, the superiority objective could be evaluated to determine whether, during AF, %eCRT with eCRTAF applied was greater than when CAFR was applied. The lower confidence limit for the difference between treatment and control had to exceed the noninferiority margin of  $-2\%$  in order to meet the primary objective. To meet the superiority objective, the lower confidence limit for the difference had to exceed  $0\%$ . For both objectives, the 1-side type I error rate was controlled

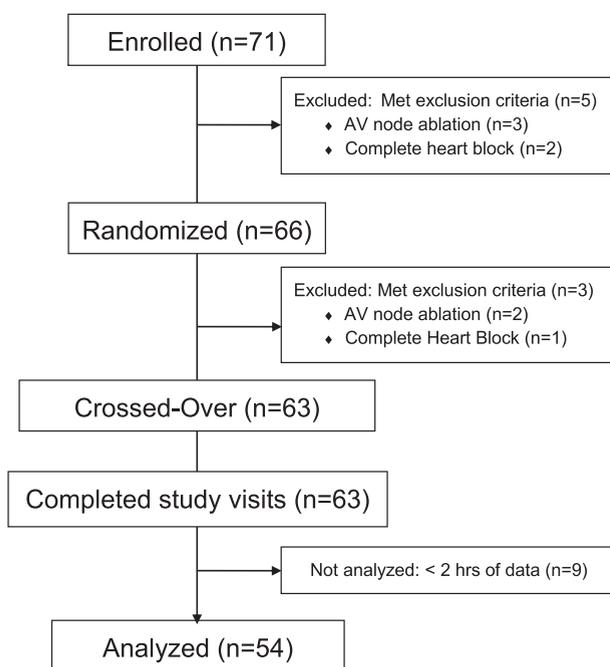
at the 0.025 level. Sample size was driven by the more stringent superiority objective; with 80% power, assumed true difference of 6% and standard deviation of 15%, and a planned interim analysis at 60% of accrual, a total sample size of 54 subjects with paired data was required.

For continuous variables, mean  $\pm$  SD are reported. For categorical variables, frequency and percentage are reported. The %Vp, %eCRT pacing, and mean HR during AF were compared between eCRTAF and control (CAFR) using paired *t* tests.  $P < .05$  was considered significant. Each subject needed to have at least 2 hours of data in each phase of the study (eCRTAF and control) to be considered a complete dataset included in the final analysis.

A multivariate regression analysis was performed to identify factors that might be associated with greater increases in %eCRT pacing. The factors that were explored included age, gender, HF etiology, New York Heart Association functional class, AF classification, AF medications, programmed lower pacing rate, and programmed upper tracking rate at baseline, HR during AF under control, and % pacing during AF under control. The final model was selected using a backward elimination method keeping all factors with  $P < .2$  in the model. All analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC).

### Results

Seventy-one subjects were enrolled in the study from 22 centers in the United States, Europe, and the Middle East between October 2014 and January 2016. Follow-up was completed in January 2016. Of the 66 subjects randomized,

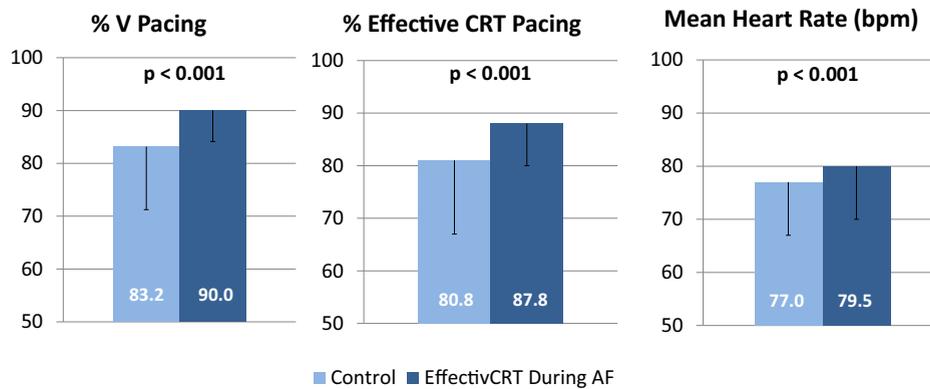


**Figure 3** Cohort distribution of study participants.

**Table 1** Subject demographics at the time of enrollment (N = 54)

Male	50 (92.6)
Age (years)	71.0 $\pm$ 10.5
Left ventricular ejection fraction (%)	28.8 $\pm$ 8.1
Intrinsic QRS duration (ms)	157.3 $\pm$ 36.4
Heart rate (bpm)	76.1 $\pm$ 10.6
New York Heart Association functional class	
I	6 (11.1)
II	22 (40.7)
III	16 (29.6)
Not available	10 (18.5)
Left bundle branch block	26 (48.1)
Coronary artery disease	28 (51.9)
Ischemic cardiomyopathy	21 (38.9)
AV conduction status	54 (100)
First-degree block	3 (5.6)
Second-degree block	0 (0)
Third-degree block	0 (0)
Atrial fibrillation	54 (100)
Permanent	28 (51.9)
Persistent	21 (38.9)
Paroxysmal	5 (9.3)
Rate/rhythm control drugs	54 (100)
Class III antiarrhythmic drug	7 (13.0)
Beta-blocker	51 (94.4)
Calcium channel blocker	4 (7.4)
Cardiac glycoside	27 (50.0)

Values are given as n (%) or mean  $\pm$  SD.



**Figure 4** Effect of treatment (EffectivCRT during AF [eCRTAF]) on percent ventricular pacing (% V pacing) (left), % effective CRT pacing (middle), and mean heart rate (right). Light blue bars indicate control (Conducted AF Response [CAFR]). Dark blue bars indicate eCRTAF. Error bars indicate standard deviation. AF = atrial fibrillation; CRT = cardiac resynchronization therapy.

63 completed all study visits, and 54 had sufficient data ( $\geq 2$  hours in each phase) available for analysis (Figure 3).

The characteristics at the time of enrollment of the 54 subjects included in the analysis are given in Table 1. Twenty-eight (52%) were in permanent AF, defined as a clinical diagnosis of permanent AF and continuous AF in the 7 most recent days of device trend data for subjects with an atrial lead ( $n = 20$ ) or as a clinical diagnosis of permanent AF for subjects with no atrial lead ( $n = 8$ ). Subjects with at least 24 hours of AF for at least 7 consecutive days but who did not meet the criteria for permanent AF were categorized as persistent. Subjects with paroxysmal AF were those who had AF but not for 7 consecutive days at any time. All subjects were taking at least one of the following categories of drugs for rate or rhythm control: beta-blockers,  $Ca^{2+}$  channel blockers, cardiac glycosides, or class III antiarrhythmic drugs.

### Primary results

During AF, the eCRTAF algorithm resulted in a significantly higher %eCRT than control ( $87.8\% \pm 7.8\%$  vs  $80.8\% \pm 14.3\%$ ;  $P < .001$ ), meeting both the primary objective of non-inferiority and the secondary objective of superiority. %Vp was also significantly higher during AF ( $90.0\% \pm 5.9\%$  vs  $83.2\% \pm 11.9\%$ ;  $P < .001$ ), and there was a small but statistically significant increase in mean HR of 2.5 bpm ( $79.5 \pm 9.7$  bpm vs  $77.0 \pm 9.9$  bpm;  $P < .001$ ) (Figure 4). As expected, there were negative correlations between mean HR and %eCRT and between mean HR and %VP (Pearson correlation coefficient  $-0.75$  and  $-0.68$ , respectively). In addition, 5 subjects went from  $<90\%$  eCRT during control to  $>90\%$  eCRT during eCRTAF. Five more subjects improved from  $<95\%$  eCRT during control to  $>95\%$  eCRT during eCRTAF. Of the 54 patients, 42 showed an increase in % eCRT with eCRTAF. Of the remaining 12 patients, 4 had a decrease in eCRT of  $<1\%$ , another 6 had a decrease  $\leq 3\%$ , and the remaining 2 had reductions of 3.3% and 7.6%.

### Subgroup analyses

Subjects with lower %Vp during the control (CAFR) phase showed a greater increase in %eCRT with eCRTAF than

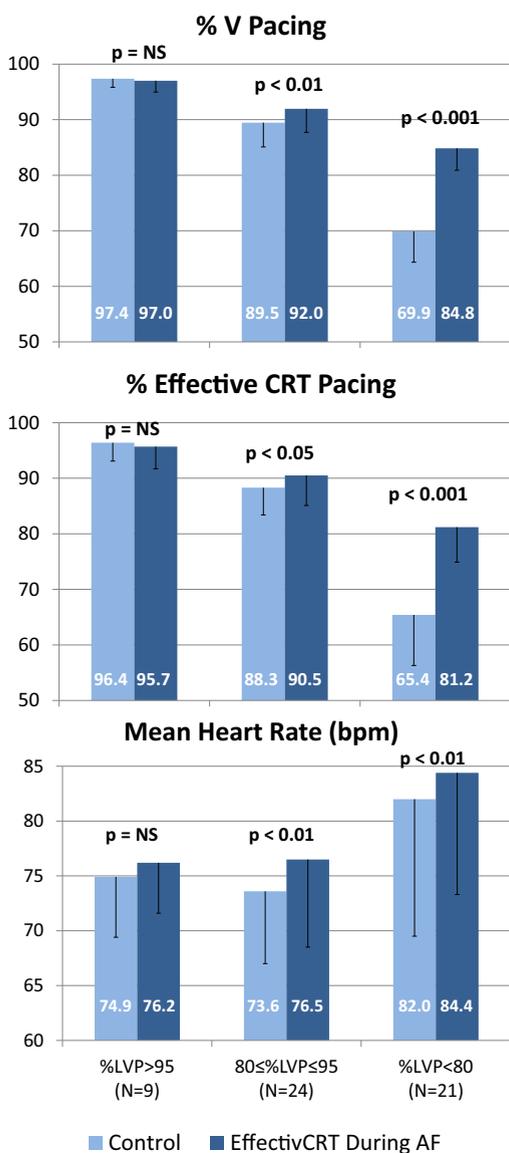
those who were already achieving a high %Vp (Figure 5). Subjects who received  $< 80\%$  Vp during control showed the greatest increase in both %Vp ( $14.9\% \pm 5.5\%$ ;  $P < .001$ ) and %eCRT ( $15.7 \pm 6.9\%$ ;  $P < .001$ ) with eCRTAF compared to control. There was also an increase in mean HR of 2 bpm from 82 to 84 bpm ( $P < .01$ ) in these subjects from control to eCRTAF. Subjects with %Vp between 80% and 95% during control showed a  $2.2 \pm 4.2$  point increase in %eCRT with eCRTAF ( $P < .05$ ). There was no significant difference in %eCRT or HR with eCRTAF in subjects with  $>95\%$  Vp during control.

In a multivariate analysis, lower %Vp during control continued to result in a greater impact of the algorithm ( $P < .001$ ). This is consistent with the univariate analysis shown in Figure 5. In addition, a higher HR during control significantly reduced the increase in %eCRT with the algorithm ( $P < .05$ ). Finally, having paroxysmal AF (as opposed to persistent or permanent AF) significantly increased the likelihood of a greater increase in %eCRT with the algorithm ( $P < .01$ ). None of the other factors considered had a significant effect.

Acute testing data were available from 42 subjects comparing no algorithm to CAFR and from 39 subjects comparing no algorithm to eCRTAF. CAFR increased % eCRT pacing from  $66\% \pm 35\%$  (no algorithm) to  $79\% \pm 20\%$  ( $P < .001$ ). eCRTAF increased %eCRT pacing from  $67\% \pm 37\%$  (no algorithm) to  $87\% \pm 17\%$  eCRT pacing ( $P < .001$ ). Although these tests were brief, the acute results for CAFR ( $79\% \pm 21\%$ ) and eCRTAF ( $87\% \pm 16\%$ ) are consistent with the primary results of the study ( $81\% \pm 14\%$  for CAFR/control and  $88\% \pm 8\%$  for eCRTAF).

### Safety

The algorithm performed as expected and did not result in any unexpected device issues. There were 7 cardiovascular-related AEs during eCRTAF and 3 during CAFR ( $P = .37$ ). AEs included shortness of breath ( $n = 4$ ), hypotension ( $n = 2$ ), implantable cardioverter-defibrillator shock for rapidly conducted AF ( $n = 1$ ), fatigue ( $n = 1$ ), and ventricular arrhythmia ( $n = 2$ ). None of the AEs that occurred



**Figure 5** Results subgrouped by percent ventricular pacing (%Vp) under control (top), % effective CRT (middle), and mean heart rate (bottom). Light blue bars indicate control (Conducted AF Response [CAFRR]). Dark blue bars indicate EffectivCRT During AF (eCRTAF). Error bars indicate standard deviation.

during the study were adjudicated to be related to either the algorithm or any increase in pacing rate.

## Discussion

On average, the eCRTAF algorithm resulted in a 7% absolute increase in eCRT pacing and %Vp during AF while increasing the mean HR by 2.5 bpm. The algorithm had an even greater effect in subjects with lower %Vp during AF while in the control arm.

Two algorithms currently are available in CRT devices to increase pacing during AF, but both were designed for and tested in a bradycardia pacemaker population. Ventricular Rate Regulation (VRR, Boston Scientific) has not been evaluated in a CRT patient population; however, in a pacemaker

population with AF, the algorithm was shown to increase %Vp from 38% to 58%.<sup>7</sup> The rate regularization algorithm in Medtronic devices (CAFR) was used as the control in this study. On average, CAFR achieved 80.8% ± 14.3% eCRT pacing and 83.2% ± 11.9% Vp during AF. Limited data are available regarding delivery of CRT during AF in CRT patients without such an algorithm. Based on the limited acute data from this study, the eCRTAF algorithm may produce large increases in %Vp and %eCRT when compared to patients without a rate regularization algorithm.

Although there are data on the optimal %Vp for CRT during AF, there are no similar data for %eCRT during AF. Because each beat classified as effective CRT is a V pace beat by definition, loss of %eCRT will be at least as clinically important as loss of %Vp. However, establishing a %eCRT threshold for optimal CRT will require additional clinical data.

Several retrospective analyses demonstrated that small decreases in %Vp (1%–3%) are associated with a significant increase in mortality.<sup>1–3</sup> Koplan et al<sup>2</sup> showed that a decrease of as little as 1%–4% in ventricular pacing was associated with a significant negative impact on survival free from HF hospitalization and all-cause mortality. In addition, a history of AF was a significant independent predictor of mortality in CRT patients. Hayes et al<sup>1</sup> showed in a retrospective study of >36,000 CRT patients that a reduction from 1% to 5% in ventricular pacing was associated with increased mortality. Their analysis also showed AF had an additive negative effect on mortality. The magnitude of the increase in %Vp in the current study (7%) suggests that this algorithm could have a significant clinical benefit in CRT patients with high AF burden.

Multivariate analysis suggests that the biggest impact of the algorithm may be in patients with paroxysmal AF, although the small number of subjects (n = 5) makes it difficult to extrapolate these results. However, this is a plausible correlation, as a retrospective analysis of >12,000 CRT subjects with AF demonstrated that those with paroxysmal AF saw the greatest drop in %Vp during AF compared to those with persistent or permanent AF.<sup>8</sup> Because low %Vp during AF was also a strong predictor of response in the multivariate analysis, its correlation with paroxysmal AF provides an explanation for why this group may see the largest effect.

Our data show that with the eCRTAF algorithm, 5 subjects improved from <90% to >90% eCRT, and an additional 5 subjects improved from <95% to >95% eCRT. Moreover, in the cohort receiving <80% Vp during control, the algorithm improved %eCRT by a mean of 16%. The ability to deliver more eCRT during AF may lead to better resynchronization and consequently reduce HF symptoms. AV junctional ablation (AVJA) is associated with improved outcomes in observational trials of patients with permanent AF who did not experience clinical improvement and/or an adequate biventricular pacing percentage with rate limiting drugs,<sup>9–13</sup> but there are no randomized controlled trials of AVJA for this indication. The eCRTAF algorithm has the potential to increase biventricular capture during AF without AVJA. This could improve outcomes in patients not previously known to have AF and avoid the need for AVJA in others

by achieving high rates of biventricular capture. It may also help to identify others for whom AVJA is the only appropriate way to achieve sufficient biventricular capture.

When considering the applicability of this algorithm to the general CRT patient population, it is important to keep in mind that, although most CRT patients do not have AF at initial implant, many will develop AF over the course of their disease. A recent retrospective analysis by Hayes et al<sup>14</sup> suggests that as many as 30% of CRT patients will experience clinically significant AF ( $\geq 1$  day of atrial tachycardia/AF for  $>6$  hours) within 2 years of implant.

Because the eCRTAF algorithm involves additional processing, the impact on device longevity may be a concern. According to the manufacturer, a patient with permanent AF (worse-case scenario) will experience a 2%–3% decrease in device longevity. A 2.5-bpm increase in pacing rate will have an additional 1%–2% impact on device longevity.

### Study limitations

The majority of the subjects included in this study had permanent or persistent AF. Given the small number of paroxysmal AF subjects in the study, additional clinical data are needed to confirm the preliminary findings about the algorithm behavior in this group. In addition, the comparison of the new algorithm to a control of no rate regularization algorithm at all was only performed with a small acute dataset. The difference in a chronic ambulatory setting remains to be determined.

It is possible that greater variation in RR intervals during AF or an increased number of premature ventricular contractions was associated with lower %VP, but this information was not collected in this study. It also is possible that the algorithm would be more effective during regular tachycardias such as atrial flutter, but this study was unable to evaluate this possibility.

Finally, this study did not evaluate long-term clinical events, so additional investigation is needed to demonstrate whether a higher %eCRT pacing would result in improved clinical outcomes.

### Conclusion

In a cohort of CRT subjects with high AF burden, eCRTAF was shown to significantly increase %eCRT pacing during AF from 80.8% to 87.8% ( $P < .001$ ) and %Vp during AF from 83.2% to 90.0% ( $P < .001$ ) while increasing mean HR by an average of 2.5 bpm ( $P < .001$ ). Given the significant proportion of CRT patients who will develop AF over their disease course, this algorithm could represent a noninvasive, low-risk strategy to increase CRT delivery during AF, potentially improving CRT response and preventing adverse outcomes.

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### References

- Hayes DL, Boehmer JP, Day JD, Gilliam Iii FR, Heidenreich PA, Seth M, Jones PW, Saxon LA. Cardiac resynchronization therapy and the relationship of percent biventricular pacing to symptoms and survival. *Heart Rhythm* 2011;8:1469–1475.
- Koplan BA, Kaplan AJ, Weiner S, Jones PW, Seth M, Christman SA. Heart failure decompensation and all-cause mortality in relation to percent biventricular pacing in patients with heart failure: is a goal of 100% biventricular pacing necessary? *J Am Coll Cardiol* 2009;53:355–360.
- Ruwald A-C, Kutiyifa V, Ruwald MH, et al. The association between biventricular pacing and cardiac resynchronization therapy-defibrillator efficacy when compared with implantable cardioverter defibrillator on outcomes and reverse remodelling. *Eur Heart J* 2015;36:440–448.
- Tse H-F, Newman D, Ellenbogen KA, Buhr T, Markowitz T, Lau C-P. Effects of ventricular rate regularization pacing on quality of life and symptoms in patients with atrial fibrillation (Atrial fibrillation symptoms mediated by pacing to mean rates [AF SYMPTOMS Study]). *Am J Cardiol* 2004;94:938–941.
- Ghosh S, Stadler RW, Mittal S. Automated detection of effective left-ventricular pacing: going beyond percentage pacing counters. *Europace* 2015;17:1555–1562.
- Hernández-Madrid A, Facchin D, Klepfer RN, Ghosh S, Matía R, Moreno J, Locatelli A. Device pacing diagnostics overestimate effective CRT pacing results of the holter for efficacy analysis of CRT study (OLE CRT study). *Heart Rhythm* 2017;14:541–547.
- Ciaramitaro G, Sgarito G, Solimene F, Maglia G, Vicentini A, Di Donato G, Raciti G, Parrinello G, Del Giudice GB. Role of rate control and regularization through pacing in patients with chronic atrial fibrillation and preserved ventricular function: the VRR study. *Pacing Clin Electrophysiol* 2006;29:866–874.
- Ousdigian KT, Borek PP, Koehler JL, Heywood JT, Ziegler PD, Wilkoff BL. The epidemic of inadequate biventricular pacing in patients with persistent or permanent atrial fibrillation and its association with mortality. *Circ Arrhythm Electrophysiol* 2014;7:370–376.
- Dong K, Shen W-K, Powell BD, Dong Y-X, Rea RF, Friedman PA, Hodge DO, Wiste HJ, Webster T, Hayes DL, Cha Y-M. Atrioventricular nodal ablation predicts survival benefit in patients with atrial fibrillation receiving cardiac resynchronization therapy. *Heart Rhythm* 2010;7:1240–1245.
- Ganesan AN, Brooks AG, Roberts-Thomson KC, Lau DH, Kalman JM, Sanders P. Role of AV nodal ablation in cardiac resynchronization in patients with coexistent atrial fibrillation and heart failure: a systematic review. *J Am Coll Cardiol* 2012;59:719–726.
- Gasparini M, Auricchio A, Metra M, Regoli F, Fantoni C, Lamp B, Curmis A, Vogt J, Klersy C. Long-term survival in patients undergoing cardiac resynchronization therapy: the importance of performing atrioventricular junction ablation in patients with permanent atrial fibrillation. *Eur Heart J* 2008;29:1644–1652.
- Gasparini M, Leclercq C, Lunati M, Landolina M, Auricchio A, Santini M, Boriani G, Lamp B, Proclemer A, Curmis A, Klersy C, Leyva F. Cardiac resynchronization therapy in patients with atrial fibrillation. *JACC Heart Fail* 2013;1:500–507.
- Gasparini M, Steinberg JS, Arshad A, Regoli F, Galimberti P, Rosier A, Daubert JC, Klersy C, Kamath G, Leclercq C. Resumption of sinus rhythm in patients with heart failure and permanent atrial fibrillation undergoing cardiac resynchronization therapy: a longitudinal observational study. *Eur Heart J* 2010;31:976–983.
- Hayes DL, Monteiro JV, Klepfer R, Grenz NA, Tsintzos SI, Eggington S, Shah BR. Prevalence and incidence of atrial fibrillation in a population implanted with cardiac resynchronization therapy devices implanted for at least 30 days: evidence from a prospective clinical trial. Abstract 12995. *Circulation* 2016; 134:A12995.