Clinical response with adaptive CRT algorithm compared with CRT with echocardiography-optimized atrioventricular delay: a retrospective analysis of multicentre trials

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Aims
Adaptive cardiac resynchronization therapy (aCRT) is a novel algorithm for CRT pacing that provides automatic ambulatory selection between synchronized left ventricular (LV) or bi-ventricular (BiV) pacing and optimization of atrioventricular (AV) and inter-ventricular (VV) delays based on periodic measurement of intrinsic conduction. We aimed to compare the clinical response between aCRT and standard CRT in historical trials.

Methods and results
The treatment arm of the aCRT trial was compared with a pooled historical control (HC) derived from the CRT arms of four clinical trials (MIRACLE, MIRACLE ICD, PROSPECT, and InSync III Marquis) with respect to the proportion of patients who had an improved clinical composite score (CCS) at the 6-month follow-up. Patients in the HC underwent echocardiography-guided AV optimization after the implant. A propensity score model was used to adjust for 22 potential baseline confounders of the effect of CRT. Patients were stratified into quintiles according to the propensity score and the adjusted absolute treatment effect was obtained by averaging estimates across these quintiles. The propensity score model included 751 patients (aCRT: 266, historical trials: 485). The adjusted absolute difference in percent improved in CCS between the aCRT and HC arms was 11.9% [95% confidence interval (CI): 2.7–19.2%] favouring aCRT. The patients in the aCRT group were significantly more likely to have an improved CCS than the patients in the HC (odds ratio = 1.65, 95% CI: 1.1–2.5).

Conclusion
The aCRT algorithm may be associated with additional improvement in clinical response compared with historical CRT with echocardiographic AV optimization.

Keywords
Cardiac resynchronization therapy • Pacing • Optimization

Introduction
Cardiac resynchronization therapy (CRT) alleviates symptoms, improves cardiac function, exercise capacity,1,2 and survival3 in systolic heart failure (HF) patients with wide QRS durations.4 However, approximately one-third of the CRT recipients do not report clinical improvement.3 Individual patient characteristics, such as severity and type of electrical conduction abnormalities,5 mechanical dysfunction, and scar burden6 have been shown to predict CRT outcomes. Cardiac resynchronization therapy benefit can be maximized through optimization of pacing site location7 or device pacing parameters.8

Multiple single-centre studies have shown that haemodynamic optimization of the ventricular pacing chamber, atrioventricular (AV) and inter-ventricular (VV) delays can improve cardiac function,5 increase exercise capacity,10 or alleviate HF symptoms.11 However, benefit of in-office optimization has not been confirmed in multicentre randomized trials.12,13 One potential explanation is that optimal

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Clinical response with adaptive CRT

What’s new?

- Adaptive cardiac resynchronization therapy (aCRT) algorithm is a novel algorithm for individualized CRT pacing. The algorithm withstands right ventricular pacing when intrinsic electrical conduction to the right ventricle is normal. Another unique aspect of the algorithm is ambulatory adjustment of CRT pacing parameters based on electrical conduction.
- This study compares clinical response rate observed in aCRT trial with historical CRT trials. Adaptive CRT trial was a prospective, multicentre, randomized, double-blind clinical trial that demonstrated safety and efficacy of the aCRT algorithm. The practical implications of the algorithm include increase in the longevity of the implantable device and substitution of a manual device optimization process with an automatic ambulatory algorithm.
- Our study establishes a hypothesis that aCRT algorithm may be superior to echocardiographic atrioventricular optimization post-implant. This hypothesis needs to be proven in a prospective study.

Device AV and VV delays change with activity and exercise. A more recent multi-center study of an ambulatory sensor-based optimization algorithm demonstrated significant symptomatic benefit at 1-year follow-up.

Adaptive CRT (aCRT) is a novel algorithm which, while ambulatory, periodically measures intrinsic conduction and dynamically adjusts CRT pacing parameters. If the conduction interval from the right atrium to the right ventricle is normal (AV ≤ 200 ms during sinus rhythm) the algorithm provides left ventricular (LV)-only pacing. Data from acute and chronic studies have shown that LV-only pacing is most favourable if PR interval does not exceed 200 ms. The AV delay is adjusted to produce an appropriate degree of fusion with the activation propagating through the still preserved portions of the His-Purkinje network. Haemodynamic studies have demonstrated that in patients with normal AV conduction, LV pacing with fusion resynchronizes ventricular contraction better than simultaneous bi-ventricular (BiV) pacing. If intrinsic AV conduction interval is prolonged (AV > 200 ms during sinus rhythm), the algorithm provides BiV pacing. In this case, the AV delay is adjusted to pace the ventricles after the completion of the P-wave in the far-field electrogram which is recorded and processed by the device. The rationale is to adjust for the inter-atrial conduction delay and optimize LV filling. The details of the algorithm have been published previously. Safety and efficacy of the aCRT algorithm has been demonstrated in the prospective, multicentre, randomized, double-blind aCRT trial. The goal of this analysis was to compare the aCRT algorithm with CRT as administered in historical trials.

Methods

Patient population

The treatment group in this analysis was the treatment arm of the aCRT trial. Details of the aCRT trial design and main results have been published previously. Briefly, the trial enrolled patients who did not have permanent atrial tachyarrhythmias and were clinically indicated for implantation of a de novo CRT-D system. The clinical indication was New York Heart Association (NYHA) functional Class III or IV HF symptoms, left ventricular ejection fraction (LVEF) ≤ 35% and QRS duration ≥ 120 ms while on optimal medical therapy. During the baseline visit, which occurred within 30 days prior to the implant, demographic and medical history data were collected, full echocardiographic imaging of cardiac function was performed, global clinical status evaluated, distance walked in 6 min measured, and quality-of-life score assessed using Minnesota Living with HF questionnaire. Within 2 weeks after the CRT-implantable cardioverter defibrillator (ICD) implant, the patients were randomized to either receive the aCRT algorithm (treatment arm) or undergo echocardiographic optimization of AV and VV delays (control arm). The primary endpoint of the study was the proportion of patients with improvement in clinical composite score (CCS) at 6 months after the randomization. The CCS was developed by Packer and has been used in multiple CRT trials. It is an aggregate measure of deaths, hospitalizations, changes in NYHA, and patient’s global assessment, and classifies patients as improved, unchanged, or worsened.

The historical control (HC) group in this analysis was derived from the CRT arms of four multicentre clinical trials conducted by Medtronic: MIRACLE, MIRACLE ICD, PROSPECT, and InSync III Marquis. These trials enrolled patients clinically indicated for CRT, had similar sets of inclusion/exclusion criteria, collected similar set of baseline patient characteristics as the aCRT study, and had CCS at 6-month follow-up as one of the pre-specified endpoints. Patients with atrial tachyarrhythmias were excluded from these trials. After the baseline evaluation, the patients were implanted with CRT devices which were programmed to deliver atrial-synchronized simultaneous BiV pacing. The device AV delays were optimized within 2 weeks after the implant using echocardiographic Ritter’s or iterative methods designed to maximize LV filling. The device VV delays in the HC group were not optimized, i.e. BiV pacing was simultaneous (VV = 0). For InSync III Marquis only, the CRT arm with simultaneous BiV pacing was included in the analysis, since BiV pacing in the rest of the trials was simultaneous.

Statistical analysis

Stratification by propensity score was performed in order to adjust for the differences in baseline patient characteristics between aCRT and HC. Twenty-two potential baseline confounders of the effect of CRT, which are presented in Table 1, were considered. Dichotomous variables, which are reported as number (percent) with condition, were compared using the χ² test, while continuous variables, which are reported as mean (standard deviation) were compared using the t-test. To better visualize the imbalance between the groups, a standardized difference defined as the mean difference expressed as a percentage of the average of the standard deviations was calculated in addition to the P values. A standardized difference of greater than 10% was considered as a meaningful imbalance between the groups. The propensity score for an individual is the probability of being in the treatment group given the profile of his/her baseline characteristics. The propensity score was determined for each patient using a multivariate logistic regression model with the treatment assignment (aCRT vs. HC) as response variable and the 22 potential baseline confounders as independent variables. All patients were stratified by their propensity score into five quintiles. Patients with missing baseline covariates and HC patients with lower propensity scores than any aCRT patients were excluded from the analysis. The interaction between the treatment groups and the quintiles was checked using ANOVA for continuous variables and a logistic regression model for dichotomous variables. The adjusted absolute treatment effect

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(percentage of patients improved and worsened in CCS) was obtained by averaging the treatment effects across the quintiles. The odds ratio (OR) for improved CCS between groups was also determined. The 95% confidence interval (CI) for the adjusted absolute treatment effect was calculated using a bootstrap method with 10,000 replications. Subgroups of patient baseline characteristics were examined while adjusting for the propensity score in the model. The same methods were used to compare the echo-optimized (control) arm of the aCRT trial with HC. All analyses were performed using SAS software (version 9.2, SAS Institute).

## Results

The number of patients included in the aCRT and HC groups were 318 and 1003, respectively (Figure 1). Table 1 presents the comparison of the 22 baseline confounders between the aCRT and HC groups. The patients in the aCRT group had smaller LV volumes, narrower QRS duration, lower prevalence of ischaemic cardiomyopathy and coronary artery disease, and higher utilization of beta-blockers. The final propensity score model included 751 patients: 266 in the aCRT group and 485 in the HC control (Figure 1). Stratification into the propensity score quintiles balanced out all baseline confounders except age (P = 0.059) and LVEF (P = 0.084) (see Supplementary material online, Table S1). Both variables were included along with the propensity score in a logistic regression model estimating the treatment effect. Comparison of the 6-month CCS outcomes within each quintile and the overall difference between aCRT and HC are shown in Table 2. Adaptive CRT group had a higher proportion of improved patients and lower proportion of worsened patients in all but the fourth quintile. The adjusted absolute difference in percentage of patients improved in CCS between the aCRT and HC arms was 11.9% (95% CI: 2.7% to 19.2%) significantly favouring aCRT. However the adjusted difference in percent worsened CCS between the aCRT and HC arms did not have a significant difference (--4.7%, 95% CI: --19.2% to 10.0%).

### Table 1 Comparison of baseline characteristics between aCRT and HC patients

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>aCRT n</th>
<th>Mean (SD)/count (%)</th>
<th>HC n</th>
<th>Mean (SD)/count (%)</th>
<th>Comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>318</td>
<td>65.4 (11.2)</td>
<td>1003</td>
<td>66.4 (11.1)</td>
<td>0.157</td>
</tr>
<tr>
<td>Male gender</td>
<td>318</td>
<td>221 (69.5%)</td>
<td>1003</td>
<td>724 (72.2%)</td>
<td>0.355</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>318</td>
<td>29.1 (5.8)</td>
<td>961</td>
<td>28.1 (5.9)</td>
<td>0.008</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>318</td>
<td>1.99 (0.24)</td>
<td>961</td>
<td>1.95 (0.25)</td>
<td>0.003</td>
</tr>
<tr>
<td>Heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA Class II</td>
<td>318</td>
<td>4 (1.3%)</td>
<td>1003</td>
<td>0 (0.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA Class III</td>
<td>318</td>
<td>300 (94.3%)</td>
<td>1003</td>
<td>934 (93.1%)</td>
<td>0.445</td>
</tr>
<tr>
<td>NYHA Class IV</td>
<td>318</td>
<td>14 (4.4%)</td>
<td>1003</td>
<td>69 (6.9%)</td>
<td>0.113</td>
</tr>
<tr>
<td>History of ischaemic cardiomyopathy</td>
<td>318</td>
<td>143 (45.0%)</td>
<td>1003</td>
<td>604 (60.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of CAD</td>
<td>318</td>
<td>139 (43.7%)</td>
<td>1003</td>
<td>546 (54.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Minnesota living with HF score</td>
<td>286</td>
<td>48.5 (24.1)</td>
<td>949</td>
<td>44.3 (26.2)</td>
<td>0.015</td>
</tr>
<tr>
<td>Six-minutes hall walk (m)</td>
<td>312</td>
<td>276.9 (127.5)</td>
<td>975</td>
<td>276.5 (117.3)</td>
<td>0.961</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>318</td>
<td>24.7 (6.6)</td>
<td>857</td>
<td>24.2 (8.5)</td>
<td>0.260</td>
</tr>
<tr>
<td>LV end-diastolic diameter (cm)</td>
<td>309</td>
<td>6.6 (0.9)</td>
<td>709</td>
<td>7.3 (1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV end-diastolic volume (mL)</td>
<td>304</td>
<td>202.3 (70.9)</td>
<td>862</td>
<td>273.0 (109.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV end-systolic diameter (cm)</td>
<td>309</td>
<td>5.7 (1.0)</td>
<td>703</td>
<td>6.5 (1.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV end-systolic volume (mL)</td>
<td>304</td>
<td>147.9 (61.4)</td>
<td>863</td>
<td>206.4 (97.2)</td>
<td>&lt;0.001</td>
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<tr>
<td>Electrocardiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>316</td>
<td>154.3 (21.0)</td>
<td>1001</td>
<td>161.4 (24.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of any degree AV block</td>
<td>318</td>
<td>94 (29.6)</td>
<td>1001</td>
<td>366 (36.3)</td>
<td>0.024</td>
</tr>
<tr>
<td>History of LBBB</td>
<td>318</td>
<td>240 (75.5%)</td>
<td>1003</td>
<td>743 (74.1%)</td>
<td>0.620</td>
</tr>
<tr>
<td>History of RBBB</td>
<td>318</td>
<td>29 (9.1%)</td>
<td>1003</td>
<td>99 (9.9%)</td>
<td>0.693</td>
</tr>
<tr>
<td>History of AF</td>
<td>318</td>
<td>56 (17.6%)</td>
<td>1003</td>
<td>194 (19.3%)</td>
<td>0.492</td>
</tr>
<tr>
<td>History of ventricular arrhythmias</td>
<td>318</td>
<td>136 (42.8%)</td>
<td>1003</td>
<td>383 (38.2%)</td>
<td>0.145</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On ACE inhibitor/ARB</td>
<td>318</td>
<td>274 (86.2%)</td>
<td>1003</td>
<td>884 (88.1%)</td>
<td>0.351</td>
</tr>
<tr>
<td>On beta blocker</td>
<td>318</td>
<td>289 (90.9%)</td>
<td>1003</td>
<td>787 (78.5%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Continuous variables are reported as mean (SD), while dichotomous variables are reported as number with condition (%).

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CAD, coronary artery disease; RBBB, right bundle branch block.

*The standardized difference in percentage is mean difference expressed as a percentage of the average of the standard deviations.
The patients in the aCRT group were significantly more likely to have an improved CCS than the patients in the HC (OR = 1.65, 95% CI: 1.1–2.5). The odds of an improved CCS, adjusted for the propensity score, were compared between aCRT and HC (Figure 2) by subgroups, but none of the interactions were statistically significant. When the echo-optimized arm (n = 160) of the aCRT trial was compared with the HC the adjusted absolute difference in percent of patients improved and worsened in CCS was 6.9% (95% CI: −4.5–17.5%) and 4.3% (95% CI: −10.3–14.7%), respectively.

**Discussion**

The present study compared the clinical outcome of patients who received CRT with aCRT algorithm to CRT with echocardiographic AV delay optimization in historical trials. The analysis showed that, on average, the proportion of clinical responders to CRT was higher by an absolute 11.9% with aCRT. These results suggest that aCRT algorithm may provide additional improvement in clinical response to CRT.
higher than that observed in previously published CRT trials. Patients with an improved CCS observed in this trial appeared significantly to improve cardiac haemodynamics in CRT patients acutely.8,9 The optimization of AV delays in CRT patients alleviates HF symptoms11 and increases exercise capacity10 compared with nominal programming. Several single-centre studies have suggested that echocardiographic optimization of AV and VV delays resulted in higher improvement in the CCS (75 vs. 65%, P = 0.03) and more patients improved in NYHA class (75 vs. 58%, P = 0.01) at 6-month follow-up compared with optimization of the AV delay alone. Our comparison of the echocardiographically optimized arm of the aCRT trial to the HC also indicated a 6.9% increase in the CCS responder rate, although this effect was not statistically significant. Finally, almost all prior trials to date have only investigated optimization performed at a single point in time. However, device settings optimal during an in-office evaluation at rest may not be optimal at later times when the patient is active15 or when chronic changes in cardiac structure and function take place.33 In contrast to the abovementioned algorithms, aCRT is device-based and, similar to other physiological pacing algorithms, adjusts pacing settings in ambulatory conditions, which may result in greater efficacy of the therapy. For instance, a recent randomized study of ambulatory optimization using an accelerometer sensor16 showed an additional 14% improvement in clinical response compared with empirical programming. In addition to ambulatory AV and VV optimization, the aCRT algorithm avoids right-ventricular (RV) pacing in patients with normal AV conduction. In previous single-centre studies, ventricular pacing with optimal fusion has been associated with superior RV34 and ILV22 function and greater reverse remodelling35 compared with BiV pacing. In the aCRT trial, a significantly higher percentage of patients with left bundle branch block (LBBB) and normal AV conduction who received primarily LV-only pacing had an improved CCS than comparable patients from the echo-optimized arm.25

**Study limitations**

This analysis is limited by its retrospective nature. A prospective comparison is needed to corroborate our observations and rule out the possibility that they were observed due to chance. Propensity score adjustment was therefore used to eliminate the imbalance in 22 potential baseline confounders. The propensity score is a widely accepted approach for reducing bias in observational studies.17 The confounders were selected from the baseline variables available for all trials, which, according to the published clinical evidence, were known to affect clinical response. Not all potential confounders were included in the model; therefore, the observed differences in clinical improvement may be the consequence of the differences between the two populations that were not adjusted by our propensity model. For instance, apical location of the LV pacing site has been shown to result in worse CRT outcomes.36 For MIRACLE and MIRACLE-ICD trials, the pacing site information was missing for ~90% of patients. Examination of the data from the rest of the trials showed that the majority (from 88.5% in PROSPECT to (Figure 3). In the present study, a propensity score model was employed to compare the outcomes of these trials while controlling for potential baseline imbalances. The analysis showed that after adjusting for these imbalances patients in the aCRT group had a significantly higher likelihood of responding to CRT than HC. Multiple factors could have contributed to this result. Firstly, utilizing a standardized optimization protocol may have helped to improve reproducibility and efficacy of the optimization procedure in the aCRT trial. Secondly, optimization of VV delay on top of the AV delay may have conferred additional benefits. For instance, in InSync III Marquis trial29 echocardiographic optimization of AV and VV delays resulted in higher improvement in the CCS (75 vs. 65%, P = 0.03) and more patients improved in NYHA class (75 vs. 58%, P = 0.01) at 6-month follow-up compared with optimization of the AV delay alone. Our comparison of the echocardiographically optimized arm of the aCRT trial to the HC also indicated a 6.9% increase in the CCS responder rate, although this effect was not statistically significant. Finally, almost all prior trials to date have only investigated optimization performed at a single point in time. However, device settings optimal during an in-office evaluation at rest may not be optimal at later times when the patient is active15 or when chronic changes in cardiac structure and function take place.33 In contrast to the abovementioned algorithms, aCRT is device-based and, similar to other physiological pacing algorithms, adjusts pacing settings in ambulatory conditions, which may result in greater efficacy of the therapy. For instance, a recent randomized study of ambulatory optimization using an accelerometer sensor16 showed an additional 14% improvement in clinical response compared with empirical programming. In addition to ambulatory AV and VV optimization, the aCRT algorithm avoids right-ventricular (RV) pacing in patients with normal AV conduction. In previous single-centre studies, ventricular pacing with optimal fusion has been associated with superior RV34 and ILV22 function and greater reverse remodelling35 compared with BiV pacing.
97.4% in InSync III Marquis) of the LV pacing sites was in non-apical locations and there was no notable difference in the distribution of LV pacing sites between the trials. There may have been significant discrepancies in the classification of LV pacing site locations between the trials due to lack of a standardized approach. Another example of a confounder that was not included in the model is renal dysfunction, which was assessed differently in the considered trials (as a binary variable or through serum creatinine) or not assessed at all. Other possible confounders, such as potential improvement in the quality of health care from the time of older to the time of more recent trials, have not been taken into account, although the model adjusted for the baseline use of beta blockers and ACE inhibitors/angiotensin receptor blockers. A significant number of patients were excluded due to missing some baseline data. In HC ($n=432$) and aCRT ($n=52$) patients, who were excluded from the analysis due to missing baseline data, the percentages with improved CCS were 57.6 and 63.5%, respectively. Since the HC group had a higher percentage of subjects with missing data (43.1%) compared with the aCRT group (16.4%), the CCS score in our analysis might be biased towards greater improvement in the HC group prior to adjusting for the propensity score. The analysis was focused on CCS, since it was the primary endpoint of the aCRT trial. Other outcomes, such as HF hospitalizations, functional, structural, and quality-of-life measures, were not ascertained.

Conclusions

Ambulatory optimization of CRT settings provided by the aCRT algorithm was associated with an additional 11.9% improvement in clinical response compared with a HC receiving CRT with echocardiographic optimization of the AV delay. The current study suggests that aCRT algorithm may provide additional clinical benefit compared with CRT with single AV delay optimization post-implant. This hypothesis needs to be proven in prospective randomized trials.

Supplementary material

Supplementary material is available at Europace online.

Conflict of interest: J.P.S. received research grants from Medtronic, St Jude Medical, Boston Scientific, and Biotronik; received consulting and lecture fees from Boston Scientific, Medtronic, Sorin, and St Jude Medical. W.T.A. received consulting fees from Medtronic, St Jude Medical, and Biotronik. E.S.C. received consulting fees from Medtronic and Boston Scientific. T.R., A.S., and J.A.C. are employees of Medtronic.

References


Figure 3 Percent of patients improved in their clinical composite score over 6-month follow-up in randomized trials.


