# Adaptive Cardiac Resynchronization Therapy Effect on Electrical Dyssynchrony (aCRT-ELSYNC): A randomized controlled trial

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**BACKGROUND** Adaptive cardiac resynchronization therapy (aCRT) is known to have clinical benefits over conventional CRT, but the mechanisms are unclear.

**OBJECTIVE** Compare effects of aCRT and conventional CRT on electrical dyssynchrony.

**METHODS** A prospective, double-blind, 1:1 parallel-group assignment randomized controlled trial in patients receiving CRT for routine clinical indications. Participants underwent cardiac computed tomography and 128-electrode body surface mapping. The primary outcome was change in electrical dyssynchrony measured on the epicardial surface using noninvasive electrocardiographic imaging before and 6 months post-CRT. Ventricular electrical uncoupling (VEU) was calculated as the difference between the mean left ventricular (LV) and right ventricular (RV) activation times. An electrical dyssynchrony index (EDI) was computed as the standard deviation of local epicardial activation times.

**RESULTS** We randomized 27 participants (aged 64 ± 12 years; 34% female; 53% ischemic cardiomyopathy; LV ejection fraction 28% ± 8%; QRS duration 155 ± 21 ms; typical left bundle branch block [LBBB] in 13%) to conventional CRT (n = 15) vs aCRT (n = 12). In atypical LBBB (n = 11; 41%) with S waves in $V_5$-$V_6$, conduction block occurred in the anterior RV, as opposed to the interventricular groove in strict LBBB. As compared to baseline, VEU reduced post-CRT in the aCRT (median reduction 18.9 [interquartile range 4.3–29.2 ms; $P = .034$]), but not in the conventional CRT (21.4 [-30.0 to 49.9 ms; $P = .525$]) group. There were no differences in the degree of change in VEU and EDI indices between treatment groups.

**CONCLUSION** The effect of aCRT and conventional CRT on electrical dyssynchrony is largely similar, but only aCRT harmoniously reduced interventricular dyssynchrony by reducing RV uncoupling.

**KEYWORDS** AV optimization; Bundle branch block; CRT; Dyssynchrony; ECGI; Electrocardiographic imaging; Heart failure; Noninvasive mapping; Randomized controlled trial; Ventricular conduction abnormalities

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## Introduction

The adaptive cardiac resynchronization therapy (aCRT) algorithm has been developed to optimize cardiac resynchronization therapy (CRT) delivery by avoiding right ventricular (RV) pacing and providing concomitant dynamic atrioventricular (AV) and ventriculo-ventricular (VV) adjustments through the measurement of intracardiac conduction parameters.[1] A randomized controlled trial comparing

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## KEY FINDINGS

- This is the first randomized controlled trial that studied a detailed, noninvasively reconstructed map of electrical epicardial activation in patients undergoing cardiac resynchronization therapy (CRT), aiming to study mechanisms of CRT effect.
- The observed statistical power was less than planned. The observed statistical power was insufficient to detect differences in the change of electrical dyssynchrony between treatment groups.
- Only adaptive CRT but not conventional CRT harmoniously reduced interventricular dyssynchrony by reducing right ventricular uncoupling. Reduction of right ventricular uncoupling is one of the mechanisms behind the adaptive CRT effect.
- This study did not find a significant correlation between metrics of electrical dyssynchrony measured on a surface electrocardiogram and the epicardial surface.

aCRT and conventional CRT showed that aCRT is safe and at least as effective as conventional CRT.[2] A higher percentage of left ventricular (LV) pacing was associated with superior clinical outcomes, including decreased risk of death, heart failure (HF) hospitalizations,[3] and 30-day readmissions.[4] Further analysis comparing aCRT to the historic conventional CRT controls showed that the proportion of clinical responders to aCRT was higher by 12%.[5] Notably, aCRT reduced the occurrence of atrial fibrillation (AF) by continuously adjusting AV intervals.[6–9]

However, aCRT's impact on electrical dyssynchrony is not entirely clear. Experimental studies in left bundle branch block (LBBB)-failing hearts showed that biventricular (BiV) pacing, but not LV pacing, decreased electrical dispersion.[10] Further measurements aCRT's effect on electrical dyssynchrony, such as epicardial activation map analysis and novel vectorcardiographic (VCG) metrics, have not previously been assessed. A better understanding of the mechanisms behind aCRT is essential for further improvement in CRT delivery and clinical outcomes.

To investigate the effect of aCRT on electrical dyssynchrony, we conducted a randomized controlled trial (RCT), "Adaptive CRT Effect on Electrical Dyssynchrony" (aCRT-ELSYNC; ClinicalTrials.gov Identifier: NCT02543281). We hypothesized that (1) aCRT (as compared to conventional CRT) provides a superior degree of reduction of electrical dyssynchrony 6 months post-CRT, and (2) the surface electrocardiogram (ECG)/VCG metric, sum absolute QRST integral (SAIQRST),[11,12] is a superior estimate of electrical dyssynchrony as compared to QRS duration. The secondary objective was to determine if aCRT is associated with improvement in the quality of life and other clinically important outcomes.

## Methods

The research reported in this paper adhered to the CONSORT guidelines. Detailed description of the Methods is provided in the Supplemental Material. We conducted a single-center, double-blind, 1:1 parallel-group assignment RCT. The study was approved by the Oregon Health & Science University (OHSU) Institutional Review Board, and it was monitored by the Data and Safety Monitoring Board. All study participants signed written informed consent before entering the study. All OHSU patients who were scheduled for CRT device implantation at OHSU were considered for participation. Exclusion criteria were permanent AF, existing CRT system or pacemaker, estimated glomerular filtration rate $<30$ mL/min, any acute condition, and a high likelihood of death during 1 year after enrollment. The study participants were implanted with a commercially available, clinically indicated Medtronic (Minneapolis, MN) CRT device with aCRT algorithm. The aCRT intervention arm had adaptive BiV and LV pacing programmed ON, while the conventional CRT control arm had nonadaptive CRT programmed ON. The participants, implanting team, and study investigators assessing outcomes were blinded to the intervention.

### Primary endpoints

For the first hypothesis, the primary endpoint was defined as a change in electrical dyssynchrony metrics measured on epicardial activation map and surface ECG 6 months post-CRT, as compared to pre-CRT.

For the second hypothesis, the primary endpoint was defined as a correlation between the surface ECG metrics of dyssynchrony (SAIQRST, in comparison to QRS duration and QRS area) and electrical dyssynchrony metrics measured on the epicardial activation map, assessed prior to CRT implantation.

We employed an electrocardiographic imaging (ECGI)[13,14] approach to build an epicardial activation map,[15] as described in the Supplemental Material (Figure 1). To obtain the solution of the inverse problem, we used the SCIRun problem-solving software developed at the Center for Integrative Biomedical Computing (University of Utah, Salt Lake City, UT).[16] The study participants underwent recording of unipolar ECG potentials on the body surface using the ActiveTwo biopotential measurement system (BioSemi, Amsterdam, the Netherlands) with 128 Ag/AgCL electrodes.[17] Two cardiologists (RP, MF) reviewed cardiac computed tomography / cardiac magnetic resonance images and identified interventricular and AV grooves. The resolution of the ventricular mesh was $3.2 \pm 1.1$ mm, with $3961 \pm 658$ nodes. A normal sinus beat (baseline) or a paced beat (follow-up) was selected for analyses. The baseline recordings were performed median 7 days (range 1–69 days) before device implantation.

The RV activation time (RVAT), LV activation time (LVAT), and global total activation time were measured.[18,19] Electrical dyssynchrony on the epicardial activation map was

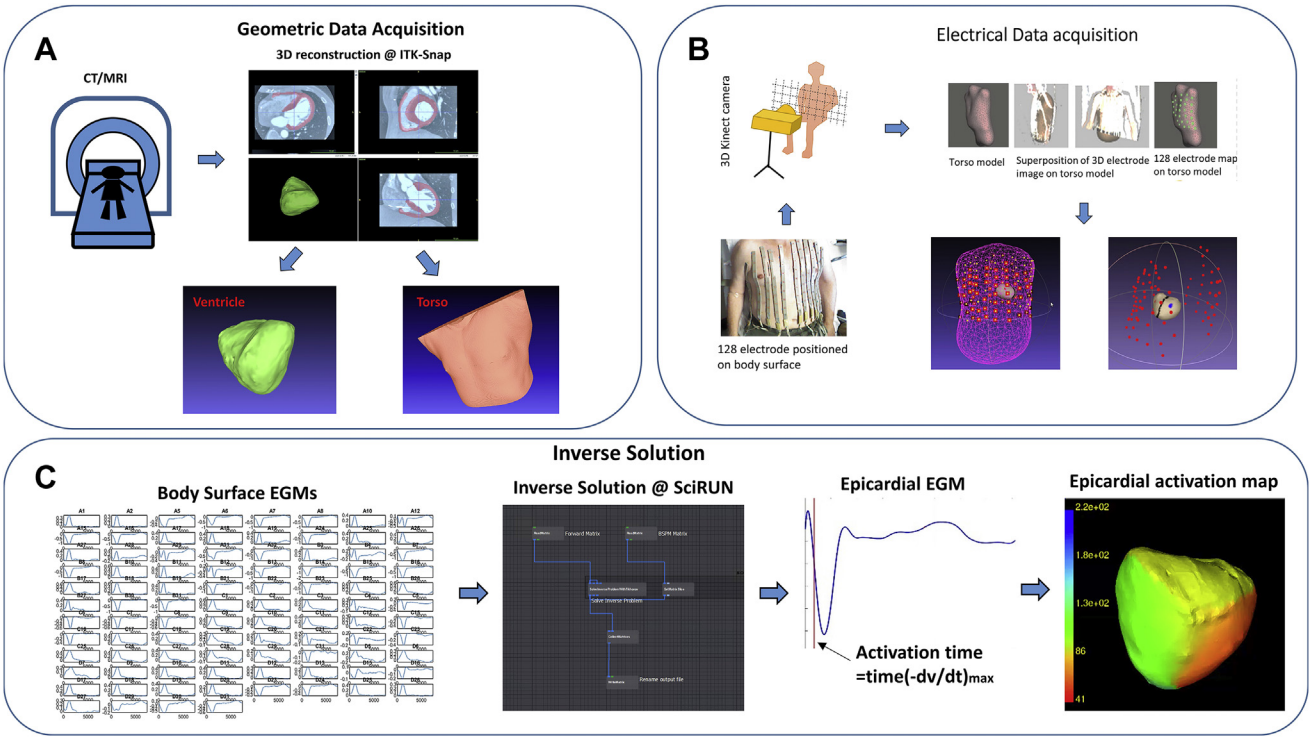


**Figure 1** Study workflow. **A:** Computed tomography (CT) scan or cardiac magnetic resonance (CMR) provided the geometry of the ventricles and the torso. Images underwent segmentation, structure identification, geometric modeling, and meshing. The 3-D meshes of the ventricles and torso were created. **B:** Body surface potential (BSP) was recorded using the 128 electrodes. Three-dimensional photography was used to record the electrodes locations on a torso. The torso geometric models based on the 3-D photography and CT/CMR were co-registered. **C:** Epicardial electrogram (EGM) reconstruction using the SCIRun inverse solution module. Local activation for each epicardial node was obtained as the point of the steepest downward slope (minimum dV/dt) of the corresponding EGM. An epicardial activation map was generated.

measured by ventricular electrical uncoupling (VEU), calculated as the difference between the mean LV and RV activation times. Positive VEU indicated LV uncoupling (delay) from the RV, whereas negative VEU indicated RV uncoupling (delay) from the LV.[19] An electrical dyssynchrony index (EDI)[20] was computed as the standard deviation (SD) of activation times throughout the entire ventricular epicardium ($EDI_V$), LV epicardium ($EDI_{LV}$), and RV epicardium ($EDI_{RV}$).

Assessment of the baseline QRS duration and morphology (ventricular conduction abnormality) was performed using clinical 12-lead ECG recorded before CRT implant, stored in the electronic medical record.

Electrical dyssynchrony on surface ECG was also measured by SAIQRST.[11,12] In addition, we measured QRS area[21] as previously described[22,23] (Supplemental Figure 1).

## Secondary clinical endpoints

The secondary clinical endpoints were assessed by the research team members blinded to the randomization assignment. The clinical composite outcome was defined as worsened if a study participant (1) died from any cause, or (2) experienced HF hospitalization within 6 months post-CRT. In addition, secondary endpoints included quality-of-life assessment by the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and 36-Item Short Form Survey (SF-36) questionnaire. The 6-minute walk distance was measured.

## Statistical analysis

We conducted an intention-to-treat analysis. Wilcoxon (Mann-Whitney) rank sum exact test was used to compare continuous variables that were summarized as the median and interquartile range (IQR). Fisher exact test was used to compare categorical variables. Wilcoxon matched-pairs signed rank test was used to compare changes from the baseline to 6 months post-CRT. Spearman correlation statistics were computed to study an association between epicardial and surface ECG measures of dyssynchrony. Two-sided exact $P$ values were reported. $P < .05$ was considered statistically significant. Statistical analyses were performed using STATA MP 16.1 (StataCorp LLC, College Station, TX).

# Results

## Study population

The study flowchart is shown in Figure 2. Enrollment in the study was completed between June 22, 2015, and October 10, 2018. All study participants had LV lead successfully implanted within the epicardial venous system. Out of 32 enrolled participants, 27 were randomized, and 5 were included in the registry arm. All randomized participants and 4 out of the 5 registry participants completed the 6-month follow-up visit procedures.

The clinical characteristics of the study participants are shown in Table 1. One-third of the participants were female,

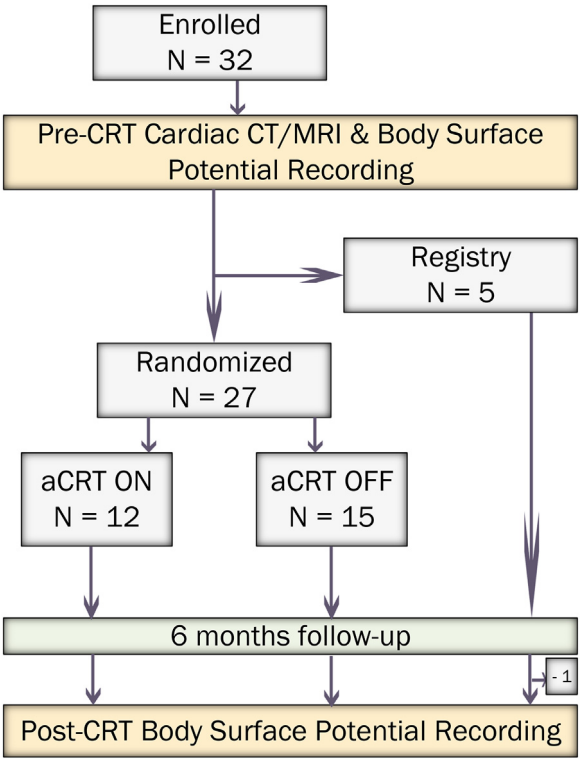


**Figure 2** Study flowchart.

and approximately half had ischemic cardiomyopathy. Out of randomized participants, 15% (n = 4) met strict LBBB criteria (broad notched or slurred R without Q and S waves in leads I, aVL, $V_5$, and $V_6$; intrinsicoid deflection in $V_5$-$V_6$ >60 ms; Supplemental Figure 2), 41% (n = 11) met LBBB criteria used in the main CRT trials (RsR′ in $V_6$ and rS/QS in $V_1$-$V_2$) and had prominent S waves in $V_5$-$V_6$ (Supplemental Figure 3), and 44% (n = 12) had interventricular conduction delay with QRS duration above 150 ms. Nearly all participants were on angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and beta-blockers. Study groups were well balanced.

During the 6-month study period, aCRT arm participants experienced LV-only pacing median 92.6% (IQR 23.3%-96.6%) of the time. ECGI analysis was performed during LV-only pacing in 9 out of 12 (75%) aCRT arm participants.

## Effect of aCRT on ventricular epicardial activation maps and electrical dyssynchrony

Representative examples of ventricular activation maps are discussed in the Supplemental Material (Supplemental Figures 2–5). The electrical activation sequence was patent specific.

At baseline, there were no differences in the dyssynchrony metrics between treatment groups (Table 2 and Supplemental Table 1). Post-CRT, total activation time, LVAT, and RVAT were reduced significantly and similarly in both groups. Baseline VEU ranged from negative 85 to positive 72 ms, indicating that the study participants had dyssynchrony owing to both LV and RV uncoupling, without significant differences between treatment groups. As compared to a baseline, post-CRT, VEU significantly decreased only in the aCRT group, but not in the conventional CRT arm. Post-CRT, aCRT significantly reduced RV uncoupling. This is illustrated by changes in VEU in each study participant (Figure 3). Harmonious VEU reduction was observed in the aCRT group, in contrast to the conventional CRT arm, demonstrating discordant and inconsistent changes in VEU. However, there was no statistically significant difference in the degree of VEU reduction between treatment groups (Table 2).

Both aCRT and conventional CRT resulted in a significant reduction of both intraventricular and interventricular dyssynchrony as measured by EDI indices, without differences between treatment groups.

## Effect of aCRT on surface ECG and VCG

QRS area and SAIQRST significantly decreased post-CRT in both groups, whereas QRS duration changes were borderline. However, no significant differences were found in QRS duration, QRS area, and SAIQRST between the 2 treatment groups at baseline or after therapy (Supplemental Table 2).

## Correlation of the dyssynchrony measured on surface ECG and epicardial surface

There was no statistically significant correlation between any of the epicardial and surface ECG measures of dyssynchrony found in all (including registry) study participants at baseline (Table 3).

## Secondary outcomes

There were no deaths and HF hospitalizations during 6 months of follow-up. There were no differences in the 6-minute walk distance between treatment groups. Baseline and post-CRT 6-minute walk distance did not differ either (Supplemental Table 3). Overall, MLHFQ score improved from baseline (median 46 [IQR 20–68]) to post-CRT (median 27 [IQR 11–48]); $P$ = .003. However, there were no differences between treatment groups.

On average, role limitations owing to physical health improved with CRT (from median 0 [IQR 0–63] to median 100 [IQR 0–100]; $P$ = .004). The energy/fatigue score improved from median 30 (IQR 20–53) to median 55 (IQR 35–70); $P$ = .004. There was no pre- vs post-CRT difference in other SF-36 indicators and no difference in any SF-36 indicators between treatment groups.

# Discussion

Our double-blind RCT showed that the effect of aCRT and conventional CRT on electrical dyssynchrony is largely similar, with both significantly reducing electrical dyssynchrony overall. We did not find differences between aCRT and conventional CRT in the degree of reduction of LV and RV inter- and intraventricular electrical dyssynchrony 6 months post-CRT. However, only aCRT but not

**Table 1** Baseline clinical and demographic characteristics of the study participants

| Characteristic | All (n = 32) | Conventional CRT (n = 15) | Adaptive CRT (n = 12) | *P* value | Registry (n = 5) |
|---|---|---|---|---|---|
| Age (SD), y | 64.4 (11.5) | 65.3 (12.2) | 62.2 (10.3) | .373 | 67.3 (13.6) |
| Female, n (%) | 11 (34.4) | 5 (33.3) | 4 (33.3) | 1.000 | 2 (40.0) |
| White, n (%) | 31 (96.9) | 15 (100) | 11 (91.7) | .444 | 5 (100.0) |
| Body mass index (SD), kg/m$^2$ | 31.3 (7.4) | 30.2 (4.3) | 33.1 (9.1) | .683 | 30.2 (10.8) |
| Ischemic cardiomyopathy, n (%) | 17 (53.1) | 9 (60.0) | 5 (41.7) | .449 | 3 (60.0) |
| Myocardial infarction history, n (%) | 9 (28.1) | 4 (26.7) | 3 (25.0) | .408 | 2 (40.0) |
| Revascularization history, n (%) | 15 (46.9) | 8 (53.3) | 5 (41.7) | 1.000 | 2 (40.0 |
| 3-vessel disease, n (%) | 8 (25.0) | 4 (26.7) | 3 (25.0) | .691 | 1 (20.0) |
| NYHA class II, n (%) | 21 (65.6) | 9 (60.0) | 8 (66.7) | 1.000 | 4 (80.0) |
| NYHA class III, n (%) | 11 (34.4) | 6 (40.0) | 4 (33.3) | 1.000 | 1 (20.0) |
| QRS duration (SD), ms | 155.1 (20.9) | 151.3 (24.3) | 160.6 (19.0) | .379 | 153.1 (20.9) |
| QTc interval (SD), ms | 492.5 (40.6) | 492.0 (45.0) | 496.1 (35.1) | .943 | 485.6 (47.2) |
| PR interval (SD), ms | 181.2 (22.9) | 187.6 (21.6) | 176.6 (21.0) | .419 | 170.0 (35.4) |
| Strict LBBB, n (%) | 4 (12.5) | 1 (6.7) | 3 (25.0) | .294 | 0 |
| IVCD, n (%) | 28 (87.5) | 14 (93.3) | 9 (75.0) | .542 | 5 (100.0) |
| Upgrade from ICD, n (%) | 1 (3.1) | 0 | 1 (8.3) | .444 | 0 |
| Atrial fibrillation history, n (%) | 7 (21.9) | 3 (20.0) | 2 (16.7) | 1.000 | 2 (40.0) |
| Diabetes, n (%) | 7 (21.9) | 4 (26.7) | 2 (16.7) | .662 | 2 (20.0 |
| Hypertension, n (%) | 24 (75.0) | 11 (73.3) | 8 (66.7) | 1.000 | 5 (100.0) |
| COPD, n (%) | 4 (12.5) | 3 (20.0) | 1 (8.3) | .605 | 0 |
| Never-smoker, n (%) | 20 (62.5) | 7 (46.7) | 8 (66.7) | .642 | 5 (100.0) |
| Beta-blockers, n (%) | 31 (96.9) | 14 (93.3) | 12 (100.0) | 1.000 | 5 (100.0) |
| ACEI or ARB, n (%) | 28 (87.5) | 13 (86.7) | 10 (83.3) | 1.000 | 5 (100.0) |
| LVEF (SD), % | 28.4 (8.0) | 26.0 (8.6) | 29.7 (7.5) | .486 | 32.3 (6.4) |
| LVDDi (SD), cm/m$^2$ | 3.2 (0.5) | 3.3 (0.6) | 3.1 (0.4) | .261 | 3.1 (0.3) |
| LVSDi (SD), cm/m$^2$ | 2.7 (0.5) | 3.0 (0.5) | 2.7 (0.4) | .133 | 2.6 (0.2) |

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; COPD = chronic obstructive pulmonary disease; IVCD = interventricular conduction delay; LBBB = left bundle branch block; LVDDi = left ventricular end-diastolic internal dimension index; LVEF = left ventricular ejection fraction; LVSDi = left ventricular end-systolic internal dimension index; NYHA = New York Heart Association.

conventional CRT harmoniously reduced interventricular dyssynchrony by reducing RV uncoupling. The observed differences in the effect of aCRT and conventional CRT on interventricular dyssynchrony suggest that a reduction of RV uncoupling together with adaptive AV optimization are the mechanisms behind the previously reported clinical benefit of aCRT.[3,4,6–9]

Adaptive CRT can exert its physiologic effects via 2 mechanisms: one involving the effect of the fusion of LV pacing with intrinsic RV activation on electrical dyssynchrony, and the other via adaptive AV optimization. Moreover, there is a complex interaction between interventricular dyssynchrony and AV optimization.[24,25] Our RCT showed that aCRT reduced RV uncoupling by significantly changing VEU, thereby reducing interventricular dyssynchrony, a known critical predictor of CRT response.[26,27] In the previous studies, VEU was strongly associated with clinical outcomes.[19] The magnitude of change in VEU has been shown to be the primary driver of acute hemodynamic CRT response.[28]

Our results support previous experimental and clinical studies[10,29] indicating similar effects of LV and BiV pacing on LV intraventricular dyssynchrony. It should be noted that in our study, the protocol did not mandate the placement of the LV lead in the location corresponding to the latest activation. It is known that the degree of interventricular dyssynchrony depends on the location of LV and RV pacing, and the complex interaction of pacing sites with the heterogeneous substrate in CRT recipients.[30] Nevertheless, the aCRT-ELSYNC RCT results suggest that both reduction of RV uncoupling and adaptive AV optimization are responsible for the previously reported advantages of aCRT over conventional CRT: higher likelihood of CRT response[5] and reduction of AF occurrence.[6–9] Our results are consistent with previous observations concluding that an optimal AV delay is necessary for effective fusion of LV pacing with intrinsic excitation and the most advantageous reduction of interventricular dyssynchrony.[30]

In our study population, only a few participants met strict LBBB criteria, and nearly half of the participants had an S wave in $V_5$-$V_6$, which explains why we observed both RV and LV uncoupling.[19] The presence of an S wave in $V_5$-$V_6$ has previously been associated with poor CRT response, HF rehospitalizations, and all-cause mortality.[31] Biventricular and RV enlargement and apical location of the LV posterior fascicular branch were suggested as possible mechanisms behind atypical LBBB with S wave in $V_5$-$V_6$. Our observation that conduction block in such atypical LBBB occurred in the anterior RV, as opposed to the interventricular groove in those who met the strict LBBB criteria, suggests yet another possible mechanism. Longitudinal dissociation of the His bundle and predestined conduction cables suggest that proximal conduction block of fibers that

**Table 2** Comparison of ventricular epicardial activation metrics of electrical dyssynchrony

| | Conventional CRT (n=15) | $P_{pre\text{-}post}$ | Adaptive CRT (n=12) | $P_{pre\text{-}post}$ | *P* value |
|---|---|---|---|---|---|
| Baseline TAT median (IQR), ms | 192 (154-213) | - | 190 (172 to 215) | - | .801 |
| Post-CRT TAT median (IQR), ms | 111 (94-126) | - | 101 (98 to 134) | - | .674 |
| Difference TAT median (IQR), ms | -69 (-54 to -124) | .0002 | -78 (-54 to -111) | .0005 | .857 |
| Baseline LVAT median (IQR), ms | 172 (138-213) | - | 187 (172 to 213) | - | .622 |
| Baseline mean RV time median (IQR), ms | 169 (127-198) | | 158 (142 to 184) | | .829 |
| Post-CRT mean RV time median (IQR), ms | 105 (91-133) | | 107 (100 to 148) | | .347 |
| Difference mean RV time median (IQR), ms | -48 (0107 to -3) | .003 | -47 (-59 to -23) | .002 | .614 |
| Baseline mean LV time median (IQR), ms | 160 (136-214) | | 132 (121 to 151) | | .083 |
| Post-CRT mean LV time median (IQR), ms | 106 (79-141) | | 108 (93 to 132) | | .905 |
| Difference mean LV time median (IQR), ms | -50 (-83 to -14) | .003 | -27 (-36 to -8) | .043 | .183 |
| Baseline LVAT median (IQR), ms | 172 (138-213) | - | 187 (172 to 213) | - | .622 |
| Post-CRT LVAT median (IQR), ms | 104 (87-126) | - | 100 (93 to 131) | - | .895 |
| Difference LVAT median (IQR), ms | -58 (-36 to -124) | .0004 | -75 (-48 to -110) | .0005 | .782 |
| Baseline RVAT median (IQR), ms | 187 (141-211) | - | 185 (153 to 202) | - | .895 |
| Post-CRT RVAT median (IQR), ms | 110 (87-126) | - | 102 (89 to 125) | - | .783 |
| Difference RVAT median (IQR), ms | -60 (-22 to -111) | .0006 | -83 (-60 to -91) | .0005 | .406 |
| Baseline VEU median (IQR), ms | +2.3 (-34.8 to 17.2) | | -28.4 (-40.3 to -11.2) | | .183 |
| Post-CRT VEU median (IQR), ms | -3.3 (-13.3 to 18.0) | | -9.1 (-18.2 to 4.7) | | .347 |
| Difference VEU median (IQR), ms | 21.4 (-30.0 to 49.9) | .525 | 18.9 (4.3 to 29.2) | .034 | .719 |

CRT = cardiac resynchronization therapy; LVAT = left ventricular activation time; $P_{pre\text{-}post}$ = *P* value for difference baseline – post-CRT; RVAT = right ventricular activation time; TAT = total activation time; VEU = ventricular electrical uncoupling.

form downstream branches of both right and left bundles may produce atypical LBBB with S wave in $V_5$-$V_6$.

Similar to previous studies,[19] we observed considerable heterogeneity in epicardial activation sequences. As observed in previous studies,[28] RV pacing and BiV pacing prolongs RVAT and increases RV uncoupling. In contrast, single-site LV pacing with fusion reduces RV uncoupling and interventricular dyssynchrony in a wide range of LBBB morphologies, including interventricular conduction delay and atypical LBBB with S wave in $V_5$-$V_6$, as demonstrated in this RCT.

The aCRT-ELSYNC RCT results did not find a significant correlation between metrics of electrical dyssynchrony measured on a surface ECG and the epicardial surface;

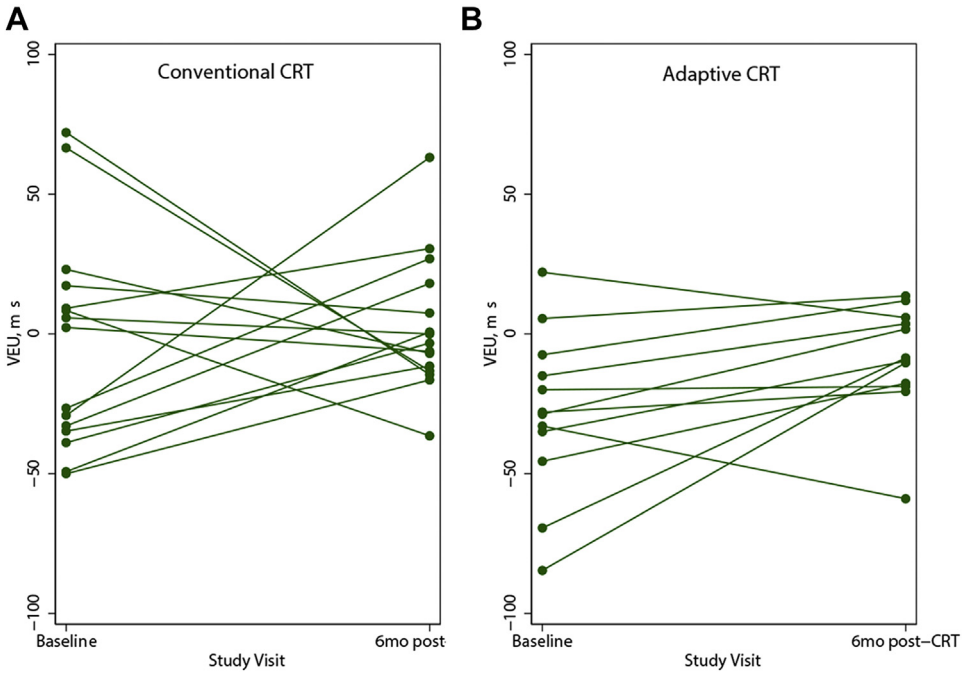


**Figure 3** Change in the ventricular electrical uncoupling (VEU) between 2 study visits (*green line*) in every randomized study participant (*green dot*), in (**A**) conventional cardiac resynchronization therapy (CRT) and (**B**) adaptive CRT arms.

**Table 3** Correlation matrix for baseline (n = 32) electrical dyssynchrony metrics measured on the reconstructed epicardial activation map and body surface ECG

| | Spearman ρ coefficient | | | |
|---|---|---|---|---|
| | VEU | $EDI_V$ | $EDI_{LV}$ | $EDI_{RV}$ |
| QRS duration | 0.059 | 0.334 | 0.267 | 0.241 |
| *P* value | .752 | .062 | .140 | .283 |
| QRS area | -0.047 | 0.091 | 0.261 | -0.114 |
| *P* value | .797 | .622 | .150 | .536 |
| SAIQRST | 0.021 | 0.120 | 0.175 | 0.037 |
| *P* value | .908 | .064 | .340 | .839 |

EDI = electrical dyssynchrony index throughout the entire ventricular epicardium ($EDI_V$), left ventricle epicardium ($EDI_{LV}$), and right ventricle epicardium ($EDI_{RV}$); VEU = ventricular electrical uncoupling.

however, both sets of metrics showed a significant reduction in the degree of dyssynchrony 6 months post-CRT. This finding highlights the differences between the 2 approaches and their complementary value. The ECGI method[14] utilized in this study is built on a pericardial potential source model, showing the distribution of electrical potentials on the pericardial surface of the heart. In contrast, surface ECG metrics of electrical dyssynchrony (QRS duration, QRS area,[21] and SAIQRST[11,12,18]) are global metrics of electrical dyssynchrony, a sum of dyssynchrony through endocardium, midmyocardium, epicardium, and both ventricles. Through results from the epicardial activation map metrics, we could appreciate the variation in LV activation patterns at baseline and the reduction in VEU in only the aCRT group. From the surface ECG, the QRS area and SAIQRST significantly decreased post-CRT in both groups. Using both metrics allows for a comprehensive evaluation of electrical dyssynchrony, with both showing an overall reduction in electrical dyssynchrony post-CRT.[32,33]

A weak correlation between ECGI measures of electrical dyssynchrony and QRS duration has been previously reported.[19,30] Similarly to many previous ECGI studies,[19,20,28] we observed highly variable patterns of epicardial activation and response to LV and BiV pacing, highlighting the importance of individualized planning of both RV and LV lead placement and assessment of the pacing effect. Studies using an ECG belt showed that electrical dyssynchrony measured on the body surface could provide a good prediction of hemodynamic CRT response[34] and LV remodeling,[35] helping to optimize LV lead location. Simple VCG metrics (SAIQRST and QRS area) showed an advantage over QRS duration for the prediction of CRT response.[11,12,21] Experimental studies showed limitations of ECGI-derived dyssynchrony indices, which had only a moderate agreement with directly measured interventricular dyssynchrony.[36] Available resources might dictate the choice regarding method of assessment of electrical dyssynchrony (VCG, ECG belt, ECGI) in clinical practice. Further development of these methods of assessment of electrical dyssynchrony is essential to equip physicians in a wide range of practice settings.

## Limitations

The number of enrolled and randomized participants was modest. However, this is the first RCT to date that studied detailed, noninvasively reconstructed epicardial mapping of electrical activation abnormalities in patients undergoing CRT. The observed statistical power was less than planned. The observed statistical power was insufficient to detect differences in the change of electrical dyssynchrony between treatment groups. Lead placement was not standardized or guided by the study protocol; this requires further study. As we reconstructed activation on the epicardial surface only, the lack of information about septal and mid-myocardial activation limited assessment of the dyssynchrony by ECGI.

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## Disclosures

The study was partially supported by Medtronic, Inc, as a physician-initiated study (LGT).

## Authorship

All authors attest they meet the current ICMJE criteria for authorship.

## Patient Consent

All study participants signed written informed consent before entering the study.

## Ethics Statement

The research reported in this paper adhered to the CONSORT guidelines. The study was approved by the Oregon Health & Science University Institutional Review Board, and it was monitored by the Data and Safety Monitoring Board.

## Appendix

### Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2021.06.006.

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