Novel Device-Based Algorithm Provides Optimal Hemodynamics During Exercise in Patients With Cardiac Resynchronization Therapy

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Background: An adaptive cardiac resynchronization therapy (aCRT) algorithm has been described for synchronized left ventricular (LV) pacing and continuous optimization of cardiac resynchronization therapy (CRT). However, there are few algorithmic data on the effect of changes during exercise.

Methods and Results: We enrolled 27 patients with availability of the aCRT algorithm. Eligible patients were manually programmed to optimal atrioventricular (AV) and interventricular (VV) delays by using echocardiograms at rest or during 2 stages of supine bicycle exercise. We compared the maximum cardiac output between manual echo-optimization and aCRT-on during each phase. After initiating exercise, the optimal AV delay progressively shortened (P<0.05) with incremental exercise levels. The manual-optimized settings and aCRT resulted in similar cardiac performance, as demonstrated by a high concordance correlation coefficient between the LV outflow tract velocity time integral (LVOT-VTI) during each exercise stage (Ex.1: r=0.94 P<0.0008, Ex.2: r=0.88 P<0.001, respectively). Synchronized LV-only pacing in patients with normal AV conduction could provide a higher LVOT-VTI as compared with manual-optimized conventional biventricular pacing at peak exercise (P<0.05).

Conclusions: The aCRT algorithm was physiologically sound during exercise by patients.

Key Words: Algorithms; Cardiac resynchronization therapy; Exercise tests; Heart failure; Optimization

Cardiac resynchronization therapy (CRT) is an efficient therapeutic strategy for heart failure (HF) patients with reduced left ventricular (LV) ejection fraction (EF) and cardiac dyssynchrony who are unresponsive even with adequate medication. CRT improves symptoms, reduces hospitalizations for HF, and increases survival in such patients, but approximately one-third of patients may not obtain any improvement in their clinical status even after initiating biventricular (BiV) pacing.1–3 There can be many post-implant factors that contribute to a suboptimal response, among which suboptimal atrioventricular (AV) timing could be a common reason.4 Although optimization of the AV and interventricular (VV) delay during BiV pacing could be 1 solution to maximize the acute hemodynamic effect of CRT,5,6 a single AV and VV optimization at rest could be considered to have only limited meaning for improving the clinical prognosis.7 One explanation could be that the physiological conduction may vary dramatically depending on the patient’s exercise level,8,9 and therefore, the optimal AV and VV timings are frequently changing. Recently, several studies used echocardiography to examine the effect of exercise on the optimal AV delay in CRT patients and their results suggest that AV optimization during exercise improves the cardiac performance in CRT patients.8,10–11 Based on these findings, an algorithm that can provide ambulatory CRT optimization and more physiologic pacing has been developed.

The effectiveness of the AdaptivCRT algorithm (aCRT, Medtronic, Mounds View, MN, USA) has been published.12 The algorithm automatically adjusts the pacing mode or AV/VV pacing intervals every minute based on the intrinsic AV conduction. When normal AV conduction occurs, synchronized LV-only pacing is provided and withholds right ventricular (RV) pacing. During periods of prolonged

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AV conduction, the algorithm continuously optimizes the AV and VV intervals. The aCRT algorithm has been demonstrated to decrease the risk of HF hospitalization as compared with echocardiography-optimized BiV pacing, and especially when the percent synchronized LV-only pacing exceeds more than 50%, a significant reduction in death or HF hospitalizations has been shown. Furthermore, the aCRT is also reported to reduce the risk of developing atrial fibrillation. To date, few studies have been conducted regarding the effect of its validity during exercise-induced changes. Thus, the goal of this study using exercise stress echocardiography was to identify whether this algorithm could provide hemodynamically reasonable and beneficial effects when compared with conventional echocardiographic AV and VV optimization during exercise.

Methods

Study Population
Patients with HF previously implanted with a CRT device were recruited. The eligibility for CRT was based on international guidelines, including advanced HF (NYHA functional class II, III, or IV), depressed LV function (LVEF ≤35%), and a wide QRS complex (>120 ms) on ECG. Inclusion criteria were as follows: able to complete a supine bicycle exercise stress protocol, in sinus rhythm at baseline, and received a CRT device equipped with the aCRT algorithm. Exclusion criteria were patients with atrial fibrillation, prior valvular surgery, significant sinus node dysfunction, and absence or lack of intrinsic AV conduction or pacing dependence. The study protocol was approved by the institutional research ethics committee and all patients provided written informed consent.

The aCRT Algorithm
The aCRT algorithm is designed to automatically adjust the pacing mode by evaluating the intrinsic AV conduction every minute. During a normal AV conduction interval (intrinsic AV ≤200 ms during sinus rhythm, or AV ≤250 ms during atrial pacing) and a heart rate that did not exceed 100 beats/min, the synchronized LV-only pacing provides an atrial to RV sense interval of ≥40 ms (adaptive LV). Contrarily, during a prolonged AV conduction interval, the BiV pacing adjusts the AV and VV timing based on the intervals of the atrial to RV sense, atrial to P-wave end, and RV sense to QRS end (adaptive BiV). Once the algorithm is activated, the algorithm-determined pacing mode or AV/VV delays are delivered immediately.

Echocardiographic Imaging and CRT Optimization
The echocardiographic images were recorded with a Vivid E9 ultrasound system (VingMed Ultrasound, General Electric, Milwaukee, WI, USA) equipped with a 3.5-MHz imaging probe and offline cine-loop analysis software. The images were acquired in a semi-supine position at rest and supine during exercise.

Pulsed-wave Doppler images of the transmitral flow velocity were recorded by placing the sample volume at the...
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Marker signals were continuously viewed and recorded throughout the study. Blood pressure and 12-lead ECG were recorded at 1-min intervals. The 12-lead ECGs were assessed for an appropriate BiV or synchronized LV capture throughout the test. In all eligible patients the devices were programmed to the atrial tracking mode (DDD), the aCRT algorithm (aCRT-on) was activated before the study, and a full baseline echocardiographic examination was performed. Next, the aCRT algorithm was de-activated (aCRT-off) and resting AV/VV echo-optimization was applied according to the previously mentioned method. The heart rate at the end of this phase was defined as the baseline heart rate and an exercise test was initiated while remaining in the aCRT-off mode.

The patients underwent supine bicycle exercise at a fixed workload (10W) and the resistance of the bicycle was continually adjusted; the patients were coached to remain alert to the pedaling speed as necessary in order to obtain the target heart rate. After achieving a first target heart rate of 10 beats/min above baseline or at 2 min from the beginning of the exercise (Ex.1), echocardiographic AV

**Exercise and the Study Protocol**

Prior to acquiring the echocardiographic images, a device interrogation was performed and the intra-device ECG/
optimization was performed by the same method as performed at rest. After optimizing the AV delay, the VV intervals were programmed starting with an interval of 0 ms, which was increased iteratively by 10 ms (=LV pacing preceding the RV pacing by 10 ms) intervals up to 50 ms and the LVOT-VTI at each setting was recorded. Next, the aCRT algorithm was activated (aCRT-on) and pulsed-wave Doppler images of the transmitral flow velocity and LVOT-VTI were recorded. After completing the first exercise stage and once more turning off the aCRT algorithm (aCRT-off), the patients began the second stage of the exercise protocol with a target heart rate of 20 beats/min, which increased to 80.8±9.4 beats/min during Ex.2. Before initiating the exercise, 18 (66%) patients were programmed to the adaptive BiV mode and 9 (33%) subjects to the adaptive LV mode. Interestingly, during exercise, 2 patients converted to an adaptive LV from an adaptive BiV, and conversely 3 patients converted to an adaptive BiV from

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>All patients (n=27)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>69±11</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>22 (81)</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>13 (48)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>16 (56)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>7 (26)</td>
</tr>
<tr>
<td>CKD, n (%)</td>
<td>14 (52)</td>
</tr>
</tbody>
</table>

**Treatments**

- β-blocker, n (%) 26 (96)
- ACE inhibitor, n (%) 20 (74)
- Diuretics, n (%) 17 (63)
- Amiodarone n (%) 7 (26)

**Pre-CRT**

- NYHA functional class (II/III/IV) (%) 7/89/4
- ORS duration (ms) 154±26
- LBBB, n (%) 22 (81)
- LVEF (%) 26±8
- LVEDV (mL) 186±89
- LVESV (mL) 136±79

**Post-CRT**

- ΔNYHA class −1.0±0.9
- LVEF (%) 33±14
- LVEDV (mL) 175±59
- LVESV (mL) 122±51

Data are n (%) or mean±SD. ACE, angiotensin-converting enzyme; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; LBBB, left bundle branch block; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association.

The statistical analyses were performed with JMP 12 software (SAS Institute, Inc., Cary, NC, USA).

### Results

#### Study Population

As our cohort of CRT patients, a total of 27 patients were enrolled. Their baseline characteristics are summarized in Table 1. Most were men with moderate HF, a prolonged QRS with left bundle branch block (LBBB), equivalent representation of ischemic and non-ischemic, and a severely reduced LVEF. The majority of the patients were prescribed negative chronotropic agents such as β-blockers or amiodarone. At the 6-month follow-up, the mean NYHA functional class improved from 3.0±0.3 to 2.0±0.7 (P<0.001) and the LVEF from 25±8.4 to 32.9±14.1 (P<0.003). All eligible patients had their atrial leads placed in the right atrial appendage and the RV lead in the RV apex. The LV lead was placed in an anterolateral (n=8), lateral (n=11) or posterior (n=8) cardiac vein.

#### Exercise Tolerance and the Pacing Mode

All patients were able to successfully complete the protocol of the first exercise stage (Ex.1), but 3 patients could not achieve the target heart rate in the second exercise stage (Ex.2) because of reported symptoms of fatigue and inability to increase their heart rate. The resting heart rate was 74.3±9.0 beats/min, which increased to 80.8±9.4 beats/min during Ex.1 and 89.6±8.3 beats/min during Ex.2. Before initiating the exercise, 18 (66%) patients were programmed to the adaptive BiV mode and 9 (33%) subjects to the adaptive LV mode. Interestingly, during exercise, 2 patients converted to an adaptive LV from an adaptive BiV, and conversely 3 patients converted to an adaptive BiV from...
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Pacing at a VV delay of 0 ms and successfully converted to an effective LV pacing at a VV delay of up to 20 ms during exercise.

Correlation Between Manual Echo-Optimization and aCRT
In the overall patients, the baseline mean LVOT-VTI for the manual echo-optimized settings and aCRT was 12.5 ± 3.0 cm and 12.5 ± 3.1 cm, respectively (P=0.8). During Ex.1, the LVOT-VTI for the manual echo-optimized settings and aCRT was 14.2 ± 3.5 cm and 14.2 ± 4.0 cm, respectively (P=0.9), and 13.8 ± 3.0 cm and 14.5 ± 3.3 cm (P=0.005) during Ex.2. There were no significant differences in the heart rate between that at the time of the maximal LVOT-VTI with a manual echo-optimized setting and that of the aCRT both during Ex.1 (80.8 ± 9.9 beats/min and 81.2 ± 9.2 beats/min, respectively; P=0.9) and Ex. 2 (89.6 ± 8.5 beats/min and 89.6 ± 7.6 beats/min, respectively; P=0.95). Surprisingly, the manual echo-optimized setting and aCRT resulted in a similar cardiac performance, as demonstrated by a high concordance correlation coefficient between the LVOT-VTI with a manual echo-optimized setting and aCRT for each exercise stage (baseline: r=0.95, P<0.001, Ex.1: r=0.94 P=0.0008, Ex.2: r=0.88, P<0.001, respectively) (Figure 4A). Similarly, only among the patients with an adaptive BiV pacing mode, there was a high concordance correlation coefficient between the manual echo-optimized setting and BiV pacing at a VV delay of 0 ms and successfully converted to an effective LV pacing at a VV delay of up to 20 ms during exercise.

### Optimal AV/VV Delay and the LV Filling Time at Rest and During Exercise
At baseline, the mean optimal AV delay was 116.3 ± 27.2 ms. During exercise, the optimal AV delay was significantly reduced to 95.8 ± 23.9 ms during Ex.1 (mean difference 20.7 ms; 95% CI 29.6–11.9 ms; P<0.0001), and progressively shortened to 90.9 ± 18.0 ms during Ex.2 (mean difference from Ex.1: 8.2 ms; 95% CI 15.8–0.6 ms; P=0.018) (Figure 3). There was no significant difference in the LV filling time at rest (pre-optimization 442 ± 88 ms; post-optimization 438 ± 19 ms; P=0.6). After initiating the exercise, the LV filling time significantly decreased from 438 ± 19 ms to 365 ± 25 ms (P<0.01); however, a corresponding increase was observed in the mean LV filling time from 365 ± 75 ms to 386 ± 84 ms following the AV optimization at peak exercise (P<0.01).

The median VV delay at rest was 0 ms (0–20 ms) and exercise induced a change in the VV delay programming in 13 (48%) patients. The rest-to-peak exercise variations in the optimal VV delay ranged from 0 to 50 ms, with a median value of 20 ms. There were no concordant correlations between the heart rates and optimal VV delays (r=-0.04, P=0.9). Importantly, 2 patients developed ineffective LV pacing at a VV delay of 0 ms and successfully converted to an effective LV pacing at a VV delay of up to 20 ms during exercise.

### Table 2. Pacing Mode of the aCRT Algorithm During Each Phase

<table>
<thead>
<tr>
<th>Pacing mode</th>
<th>Rest (n, %)</th>
<th>Ex. 1 (n, %)</th>
<th>Ex. 2 (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adaptive BiV</td>
<td>18 (66)</td>
<td>19 (70)</td>
<td>17 (71)</td>
</tr>
<tr>
<td></td>
<td>BIV at rest to BIV</td>
<td>16 (69)</td>
<td>BIV at rest to BIV</td>
</tr>
<tr>
<td></td>
<td>LV at rest to BIV</td>
<td>3 (11)</td>
<td>LV at rest to BIV</td>
</tr>
<tr>
<td>Adaptive LV</td>
<td>9 (33)</td>
<td>8 (30)</td>
<td>7 (29)</td>
</tr>
<tr>
<td></td>
<td>BIV at rest to LV</td>
<td>2 (7)</td>
<td>BIV at rest to LV</td>
</tr>
<tr>
<td></td>
<td>LV at rest to LV</td>
<td>6 (22)</td>
<td>LV at rest to LV</td>
</tr>
</tbody>
</table>

aCRT, adaptive cardiac resynchronization therapy algorithm; BiV, biventricular pacing; LV, synchronized left ventricular pacing.

### Figure 3.
Changes in the optimal atrioventricular (AV) delay assessed at baseline and during each exercise phase. Ex., exercise protocol.
In the present study, we showed the hemodynamic validity of the aCRT algorithm during exercise.

Effects of Optimization Performed During Exercise

Normal physiological adaptation to exercise leads to an increase in the heart rate, shortening of the AV node conduction time, and increased myocardial contractility, and therefore, generally results in a shorter AV interval at higher heart rates. Increasing the heart rate plays a major role in producing a cardiac output increase with exercise and the maximum cardiac output depends on the maximum heart rate. However, AV synchrony contributes to the cumulative effects for heart rates up to approximately 80 beats/min and increases the myocardial contractility above 80 beats/min in normal hearts. Accordingly, the significance of AV synchrony for maximizing cardiac performance is well described and is more pronounced in patients with systolic HF. To date, several studies have shown that AV and VV optimization improves LV systolic performance even during exercise. We demonstrated that the optimal AV delay progressively shortened during exercise, and similar findings have been reported by Sun et al., who showed an almost 40% reduction in the programmed AV delay during exercise. They also suggested that the magnitude of the change in the AV delay with increasing heart rates in CRT patients appeared to be significantly greater than the physiological exercise-induced...

**Figure 4.** Comparison of cardiac performance with the aCRT and echo-optimized settings at baseline and during exercise. Plot of the LVOT-VTI at the settings calculated by the aCRT algorithm and settings obtained using the echocardiographic optimization protocol in all subjects (A) and only in those with adaptive BiV pacing (B). aCRT, adaptive cardiac resynchronization therapy algorithm; BiV, biventricular; Ex., exercise protocol; LVOT-VTI, left ventricular outflow tract velocity time integral.
change in the PR intervals observed in healthy subjects. Similarly, Shanmugam et al also reported that over 90% of patients with CRT showed a significant reduction (mean 50 ms) in the optimal AV delay during exercise and they demonstrated a corresponding increase in the LV filling time following AV optimization during exercise as well. Moreover, they successfully showed a 10% improvement in exercise capacity with a programmable rate-adaptive AV delay. Our findings concur with those reports and led us to believe that it may be beneficial to program the device to automatically adjust the AV delay according to the activity level.

Furthermore, we demonstrated significant variation in the optimal VV delay between rest and exercise. Unlike the AV delay, the optimal VV delay cannot be considered as correlated to the heart rate and a large variation can be seen between individual subjects. Notably, some patients developed ineffective LV pacing during exercise and this phenomenon may be found in the general population of patients with CRT. Valzania et al showed that the optimal VV delay varied considerably from rest to exercise and a re-assessment during exercise yielded an additional hemodynamic benefit. They also demonstrated the validity of their algorithm, which was based on the intracardiac electrogram method (QuickOptTM), as having a strong agreement with the echo-optimization during exercise regarding the LVOT-VTI. However, the Frequent Optimization Study Using the QuickOpt Method study (FREEDOM) did not show its superiority to conventional methods of optimization when the clinical composite score was compared. Moreover, the SMART-AV study that compared device-based, echo-based, and empirical programming of the AV delay did not show any significant changes in the LV volume and LVEF. Much evidence has suggested that the optimal AV and VV delay varies between rest and exercise, but it could still be challenging to discover an algorithm that can provide an adaptive AV/ VV delay for general patients with CRT.

The aCRT algorithm can provide better clinical outcomes, or at least those as effective as comprehensive echo-optimized BiV pacing, through synchronized LV pacing and continuous optimization. Importantly, this novel algorithm is based on clinical research conducted essentially during the resting phase and thus it has been unclear whether these results can be applied during exercise. As mentioned before, the major role of AV synchrony in contributing to the hemodynamics is during exercise with a heart rate of less than 100 beats/min, and the aCRT algorithm can only provide synchronized LV-only pacing when the heart rate is under 100 beats/min. Thus, our study protocol was designed to target a heart rate under 100 beats/min. In the present study, we provide new information regarding the validity of this algorithm even during low-intensity exercise. Through all the phases, a high correlation was shown between aCRT and echo-optimization regarding the stroke volume among patients with prolonged AV conduction. Furthermore, when normal AV conduction was observed, synchronized LV-only pacing could also provide a better stroke volume compared with echo-optimized BiV pacing during exercise. Synchronized LV-only pacing may prevent RV pacing-induced dyssynchrony and allow for simultaneous RV and LV electrical activation. A previous study on CRT in patients with LBBB and preserved RV conduction showed that the RV dP/dtmax was greater when CRT produced synchronized LV-only pacing. Avoidance of RV pacing can provide superior RV function in patients with sufficiently preserved conduction to the RV. The results of our study indicated that aCRT offered a similar or greater stroke volume compared with real-time echo-optimization both at rest and during exercise, which could be a possible explanation for the better clinical outcomes in some clinical trials of this novel algorithm.

Study Limitations
A potential weakness of this study was that it was conducted at a single center with a relatively small patient cohort and only included sinus rhythm patients with availability of the aCRT algorithm, which could expose the study to a myriad of biases, particularly selection bias and statistical power limitations. A higher prevalence of patients with prolonged AV conduction and moderate to severe HF could be considered as a limitation. Moreover, it is important to emphasize that the stroke volume is affected by multiple factors such as the cardiac pre- or afterload or exercise-induced mitral regurgitation, which make it difficult to clearly distinguish whether or not this additional hemodynamic contribution was only based on pacing settings. Also, it was unclear how the duration of exercise, passage of time, and order of the measurements from aCRT-off to aCRT-on affected the results. Finally, the study design

![Figure 5. Comparison of stroke volume during synchronized LV pacing (adaptive LV) and at the echo-optimized settings at baseline and during exercise. Boxplot (25–75th percentile) and median values (open circles) showing the distribution of the LVOT-VTI during synchronized LV pacing and echo-optimized conventional BiV pacing, both at rest and during exercise. The adaptive LV shows a higher value compared with manual echo-optimized BiV pacing at peak exercise. BiV, biventricular; LVOT-VTI, left ventricular outflow tract velocity time integral.](image-url)
did not intend to determine whether other hemodynamic benefits, excepted for stroke volume, would be observed when using the aCRT algorithm, as well as whether the same was true with much harder exercise or during tachycardia. Therefore, the current data need to be confirmed in a larger number of participants with a wider HF status and AV conduction range, and further studies are needed to evaluate the validity of the aCRT algorithm for other hemodynamic factors or during harder exercise.

Conclusions

Among the study patients with CRT, the optimal AV delay progressively shortened with incremental exercise levels. The aCRT algorithm is a novel device-based algorithm that has a significant correlation to echo-optimization regarding the stroke volume both at rest and during exercise. Once the patients developed a normal AV conduction following exercise, the aCRT algorithm provided an additional hemodynamic benefit through synchronized LV-only pacing.

Conflicts of Interest

Dr. Nakajima received a scholarship from the Japanese Heart Rhythm Society and received speaking honoraria from Medtronic Japan Co., Ltd.

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