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Effect of Closed Loop Stimulation versus Accelerometer on Outcomes with Cardiac Resynchronization Therapy: The CLASS Trial

Short Title: Closed loop stimulation vs accelerometer in CRT

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identifier: NCT02693262

Abstract

Purpose: Chronotropic incompetence (CI) in patients with heart failure is common and associated with impaired exercise intolerance and adverse outcomes. This study sought to determine the effects of closed loop stimulation (CLS) rate-adaptive pacing on functional capacity in patients with heart failure with reduced ejection fraction (HFrEF) and CI implanted with cardiac resynchronization therapy (CRT) devices.

Methods: A randomized, blinded, cross-over designed trial enrolled patients with HFrEF and CI implanted with a Biotronik CRT-D to complete a quality of life questionnaire, 6-minute walk distance (6MWD), and cardiopulmonary exercise testing after two programmed periods: one-week period of CLS and one-week period of standard accelerometer (DDDR).

Results: Nine patients (6 males, mean age 71.4 years, 7 with New York Heart Association Class III, mean ejection fraction 39$\pm$8%) were enrolled. Quality of life trended higher in CLS as compared to DDDR (550.8$\pm$123.9 vs 489.3$\pm$164.9, p=0.06). There were no differences between CLS and DDDR in 6MWD (293.1$\pm$90.2 m vs 315.1$\pm$95.5 m, p=0.52), peak heart rate (HR) 110.7$\pm$14.7 bpm vs 109.7 bpm$\pm$14.1, p=0.67), or peak VO2 (12.3$\pm$4.9 ml/kg/min vs 12.9$\pm$5.9, p=0.47). As tests were submaximal as indicated by low respiratory exchange ratios (0.98$\pm$0.11 vs 1.0$\pm$0.8, p=0.35), VE/VCO$_2$ slope also showed no difference between CLS and DDDR (35.8$\pm$5.6 vs 35.4$\pm$5.7, p=0.65). Five patients (56%) preferred CLS programming (p=1.0).

Conclusion: In patients with HFrEF and CI implanted with a CRT-D, peak

HR, peak VO2 and 6MWD were equivalent, while there was a trend toward

improved quality of life in CLS as compared to DDDR.

Clinical Trial Registration: URL: https://www.clinicaltrials.gov. Unique identifier: NCT02693262

INTRODUCTION

Chronotropic incompetence (CI), broadly defined as the inability to increase heart (HR) during exercise to meet metabolic demands, is common in patients with heart failure (HF) and contributes to exercise intolerance [1]. Several studies have shown CI in patients with HF is an independent predictor of cardiovascular adverse events and mortality [2, 3]. Contractility reserve is diminished in patients with heart failure, thus cardiac output becomes increasingly dependent on heart rate response during exercise. Consequently, those with concomitant CI have reduced exercise capacity compared to patients with HF without CI [4, 5].

Cardiac resynchronization therapy (CRT) in selected patients with HF with reduced ejection fraction (HFrEF) improves exercise capacity, quality of life (QoL), and mortality [6, 7]. Rate-adaptive pacing, a pacemaker feature that restores physiological HR response to exercise, may be a potentially effective treatment for CI, particularly in patients implanted with CRT. In those with HFrEF and severe CI implanted with CRT, Tse et al. showed an improvement in exercise capacity using the most common form of rate-adaptive pacing, an accelerometer-based sensor that responds to body movements [8]. Closed-loop stimulation (CLS) is an alternative rate-adaptive pacemaker feature that responds to beat-to-beat intracardiac impendence measurements, a feature that may allow for a more physiological response to all forms of exercise and emotional situations compared to an accelerometer.

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Therefore, the aim of this study is to compare the effects of CLS versus standard accelerometer rate-adaptive pacing on subjective symptoms and clinical outcomes, as assessed by QoL questionnaire, six-minute walk distance, and cardiopulmonary exercise testing.

METHODS

Study Population

Patients with HFrEF and CI implanted with a CRT with defibrillator (CRT-D) (Biotronik, Lake Oswego, OR) capable of CLS programming were eligible for this study. CI was defined as blunted atrial sensing histogram or significant burden of atrial pacing on device interrogation that would justify a treating clinician to enable a rate–adaptive pacing feature. Inclusion criteria included age ≥18 years and at least three months post-implantation of a CRT-D device. Patients were excluded in case of pregnancy, decompensated heart failure, unable to perform exercise testing, and current persistent or permanent atrial fibrillation.

The trial was funded by Biotronik (Lake Oswego, OR). It was registered at www.clincaltrials.gov (NCT02693262) and was approved by the Institutional Review Board of University of California, San Diego. All patients provided written informed consent.

Study Design

The CLASS trial was a double-blinded, single cross-over, randomized clinical trial testing two rate-adaptive pacing modes: CLS versus standard accelerometer (DDDR). During the initial visit, demographic information,

medical history, and medication prescriptions were recorded. Baseline device interrogation was performed to ensure appropriate sensing and pacing function of the leads. The devices were then programmed to no rate response (DDD mode) for a one-week wash-out period. Patients were then randomized via hand-picked blinded numbers and programmed to either CLS or DDDR. Both modes were programmed to "medium" and were not modified during study period. After one week, patients then returned to complete the RAND 36-Item Short Form Health Survey (RAND-36), six-minute walk test (6MWD), and cardiopulmonary exercise testing (CPET). Following the CPET, all patients were then crossed over to the other pacing mode. After one week of programming in the alternate mode, the RAND-36, 6MWD, and CPET were completed as previously described and a blinded assessment of the patient's preferred pacing modality (between CLS versus DDDR) was obtained. The study design is illustrated in Figure 1.

The RAND-36 is a generic 36-item questionnaire that measures eight health-related domains stratified by physical health (physical functioning, role limitations due to physical health, pain, and general health) and emotional health (vitality, role limitations due to emotional problems, social functioning, and mental health). Higher scores represent a more favorable health status. The RAND-36 is a widely used QoL survey and has well-documented reliability exceeding 0.80 and validity 0.80 – 0.90 [9].

The 6MWD is a standardized field test to evaluate functional exercise performance. Subjects are instructed to walk as far as possible in

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6 minutes on a flat surface. The 6MWD has been shown to be a reliable test with intra-class correlation coefficient of 0.90 in patients with heart failure [10]. Distance walked in meters and rate of perceived exertion on the Borg scale were collected. Noninvasive blood pressure was measured before and after the test.

All patients underwent a symptom-limited CPET on a standard treadmill according to the Naughton protocol [11]. During the test, patients inspired room air through a low-resistance mask, and expired oxygen and carbon dioxide partial pressures were measured with a gas analyzer (MedGraphics, St Paul, MN, USA). Measurements of oxygen consumption (VO_2), carbon dioxide production (CO_2), minute ventilation (V_E), tidal volume (V_T), end-tidal carbon dioxide tension (P_{ETCO2}), end tidal oxygen tension (P_{ETO2}), respiratory rate, and HR were recorded every 30 seconds during exercise. The patient's RPE on the Borg scale and V_E/V_{CO2} ratio (minute ventilation/carbon dioxide production) were recorded at each stage and at peak exercise. All patients were encouraged to exercise to maximal effort. Standard 12-lead electrocardiogram and non-invasive blood pressures were obtained before and immediately after the test.

The parameters measured included: peak HR (beats per min), peak oxygen uptake (peak VO_2, measured in ml/kg/min), HR reserve (peak HR – resting HR), anaerobic threshold (AT, L/min), oxygen pulse (ml/beat), and respiratory exchange ratio (RER). The RER, defined as VCO_2/VO_2, is an objective measure to classify patient motivation and maximal effort achievement at ratio > 1.05. CI during the CPET was defined by a <80% HR reserve. The Wilkoff equation, known as the metabolic-chronotropic

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relationship (MCR), was used to evaluate the prevalence of CI during exercise [12]. The MCR adjusts for age and functional capacity, and thus can be used during submaximal exercise testing. The MCR is calculated by the ratio of actual HR_{stage}/estimated HR_{stage}, where $HR_{stage} = [(220 – age – HR_{rest})] \times (METS_{stage} – 1)/(METS_{peak} – 1) + HR_{rest}$. An MCR value ≤ 0.80 is considered indicative of CI.

Statistical Analysis

Continuous variables are presented as median and interquartile range. Categorical variables are listed as frequencies or percent. Intragroup differences were compared by paired *t*-testing and Friedman's test. Comparisons between peak heart rate in both study arms and beta blocker dose was performed using the Kruskal-Wallis test. A $p \leq 0.05$ was considered statistically significant. All analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Study Population

A total of 12 patients with HFrEF and CI implanted with a CRT-D were enrolled into the trial. Three patients withdrew prior to randomization. Baseline characteristics of the final cohort are shown in Table 1. The 9 patients had a median age of 69 years (interquartile range [IQR]: 63.5 – 76.5) and 5 (56%) were male. The median time from CRT implant was 154 (IQR: 96 – 217) days. All patients had LVEF $\leq 35\%$ at the time of implantation with median of 29.5% (IQR 23.5 – 35.0). Seven (78%) patients had New York Heart Association (NYHA) Class III symptoms, while

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two (22%) had NYHA Class II symptoms. Six (67%) patients had ischemic cardiomyopathy. Indications for CRT-D implantation included LBBB with QRS > 120 ms (N=5, 56%), non-LBBB and QRS >120 (N=2 (18%), and depressed LVEF with high right ventricular pacing burden (N=2, 18%). Two (18%) patients had history of paroxysmal atrial fibrillation with no evidence of atrial fibrillation on device interrogation during the study period. All patients were prescribed a beta blocker and angiotensin-converting enzyme inhibitor, angiotensin receptor antagonist, or angiotensin receptor neprilysin inhibitor. All patients were prescribed carvedilol (mean dose 10.1± 6.6 mg twice daily). Two patients were prescribed anti-arrhythmic therapy (amiodarone for history of ventricular tachycardia and sotalol for history of atrial fibrillation).

Within the cohort, median baseline atrial pacing burden was 58% (49.5 – 97.0), while median baseline LV pacing burden was 99% (96.5 – 100). There were no differences in percentage of atrial pacing (p=0.24) or LV pacing (p=0.54) across the study period (Figure 2).

Outcomes

Quality of Life

Overall, the quality of life (QoL) of subjects as measured by the RAND-36 was higher in patients with CLS programming as compared to DDDR with a trend toward significance (550.8 ± 123.9 vs 489.3 ± 164.9, p = 0.06). There were no significant differences when QoL scores were stratified by physical health (CLS 253.5 ± 77.0 vs DDDR 224.0 ± 104.2, p = 0.16). Quality of life scores were significantly higher with CLS vs DDDR

when stratified by emotional health (303.0 ± 54.5 vs 257.3 ± 76.3, p = 0.02).

6MWD

There were no differences in 6MWD distance between the two groups (293.1 ± 90.2 for CLS and 315.1 ± 95.5, p = 0.52 for DDDR). Also, the rate of perceived exertion on the Borg scale was low with no difference between groups (1.39 ± 1.45 for CLS and 2.28 ± 2.33 for DDDR, p = 0.21).

CPET

There were no significant differences between peak HR (CLS 110.7 ± 14.7 vs DDDR 109.7 ± 14.1, p = 0.67) or HR reserve (CLS 39.1 ± 17.7 vs DDDR 38.7 ± 16.4, p = 0.88) between the two pacing modalities. The mean MCR was < 0.80 in both groups without significant difference (CLS: 48.3 ± 22.3 vs 50.2 ± 24.1, p = 0.27). Only one patient (9%) did not exhibit chronotropic incompetence during CPET as defined by MCR. There was no association between beta blocker dose and peak HR while patients were programmed to each mode (CLS: p = 0.10 and DDDR: p = 0.16). There were no differences in peak VO_2 between CLS and DDDR (12.3 ± 4.9 vs 12.9 ± 5.9, p = 0.47). Given that the tests were submaximal as indicated by low RERs (CLS 0.98 ± 0.11 vs DDDR 1.0 ± 0.8, p = 0.35) with only 2/9 (22.2) achieving RER >1.05, there were no changes in VE/VCO_2 slope (CLS 35.8 ± 5.6 vs DDDR 35.4 ± 5.7, p = 0.653), a parameter considered independent of subject effort. Furthermore, there were no differences in anaerobic threshold (CLS 0.72 ± 0.9 vs DDDR 0.82 ± 0.1, p

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= 0.27) or oxygen pulse (CLS 9.8 $\pm$ 3.1 vs 10.3 $\pm$ 4.4, p = 0.47). Study endpoints are shown in Figure 3.

Patient Preference

At the end of the blinded study, five (56%) patients preferred CLS over DDDR (p=1.0). Two patients who had higher QoL scores during CLS favored DDDR, while one patient with slightly higher QoL during DDDR favored CLS.

DISCUSSION

The present study is the first to examine the effects of CLS on objective and subjective clinical outcomes in patients with HFrEF and CI implanted with CRT-D. Several key findings regarding the effects of rate-adaptive pacing with CLS programming as compared to standard accelerometer on exercise capacity and QoL in patients were demonstrated. First, there was a trend toward improved QoL with a significant improvement in emotional health with CLS as compared to DDDR. Secondly, there was no difference in 6MWD between the groups. Lastly, there were no differences in treadmill CPET measurements, including peak HR or peak VO_2. Taken together, peak HR and exercise capacity were equivalent between CLS and DDDR, although the trend in improvement in QoL suggests a subjective benefit of CLS rate-adaptive pacing.

In patients with HF, up to two-thirds of patients have concomitant CI.[13] As the ability to maintain stroke volume during exercise diminishes with HF, augmentation of HR becomes a major determinant of cardiac

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output. There exists a linear relationship with HR and VO_2 in patients with HF, in which a 2 to 6 bpm increase in HR is associated with a 1 ml/kg/min increase in VO_2 during exercise [14]. Therefore, the augmentation of HR response via programmed rate-adaptive pacing has gained increased recognition as a therapeutic target.

A few small crossover-designed trials have examined the effects of rate responsive pacing via accelerometer in those with HF, CI and CRT. In a study of 20 patients, Tse et al demonstrated significantly higher peak HR and VO_2 (approximate increase of 30 bpm and 2.0 ml/kg/min, respectively) during exercise with the accelerometer on compared to off in only the 11 patients with severe CI (age-predicted max HR < 70%) [8]. The 9 patients with mild CI did not have improvements in exercise capacity with rate-adaptive pacing. However, contradictory findings were observed in subsequent studies. Van Thielen et al studied 14 patients with severe CI (age-predicted max HR <70%) using echocardiography and CPET [15]. Despite an increase in peak HR with rate response on as compared to off, there were no differences in peak VO_2. Furthermore, Sims et al demonstrated an improvement in 6MWD (mean increase 18 m), while peak VO_2 did not improve in 13 patients with CI and CRT with accelerometer on compared to off [16].

We expand on the previous studies as the first trial to examine the role of CLS versus accelerometer driven rate-adaptive pacing on exercise capacity in those with HF, CRT, and CI. CLS is a rate-response algorithm that responds to changes in cardiac contractility via right ventricular impedance measurements on a beat-to-beat basis. With increased

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sympathetic activity, the CLS algorithm immediately senses changes in cardiac contractility and responds by increasing HR. As compared to an accelerometer, it does not rely on body motion, but rather it reacts to physiological input, such as increased sympathetic activity from mental stress and all types of exercise. In our study, we did not observe significant differences in parameters of peak HR or peak VO_2 on a treadmill CPET between CLS and DDDR modes. Several reasons may explain the equivalent results. Given the premature cessation of exercise as evidenced by low RER in both groups, sinus node activation via rate-adaptive pacing may not have been maximal, thus true peak HR may not have been elucidated. Also, the results suggest that CLS and DDDR modes perform equally well with HR response on a treadmill. Whether CLS results in superior HR response on a stationary bike, in which anterior-posterior movement is minimal, remains unknown. Furthermore, one week of CLS programming may not result in a "training" effect difference that will be measurable via CPET. Lastly, improving HR response alone may not be sufficient to increase peak VO_2, which is dictated by HR, stroke volume and arterio-venous oxygen difference. A multifactorial approach to improve central (HR and SV) factors and peripheral delivery and extraction, all of which are limited in patients with HF, such as exercise training along with CLS programming, may result in measurable differential effects between programmed modes [17].

We observed a trend toward improved QoL measures in the CLS arm. Although a small sample size, the trend may provide insight into previous studies examining the role of mental stress in CLS. Coenen et al.

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randomized 131 patients with CI to either CLS or standard-accelerometer in a cross-over design trail and assessed 6MWD distance and HR response during an arithmetic test [18]. There were no differences in 6MWD distance, while HR was higher in the CLS during the arithmetic test by a mean of 3.0 bpm. Similarly, Chandiramani et al. demonstrated a higher HR response in CLS as compared to accelerometer during mental stress testing (mean, 9.3 bpm) [19] However, whether the increase in HR correlated with improvement in cognition or in mental stress was not studied. To the best of our knowledge, this study was the first to describe the role of CLS on QoL measures. Patient-reported health status is an important and underrecognized measure of cardiovascular health and is an independent predictor of adverse events, including mortality [20]. Importantly, the QoL of the studied cohort was poor overall, as evidenced by low scores in the RAND-36 questionnaire in both arms. When the questionnaire was stratified between physical and emotional health, there was only a statistically significant benefit favoring CLS with emotional health, suggesting that the benefit of CLS may stem from improvement in mental stress, rather than physical limitations. Long-term follow-up is needed to provide insight into whether improvements in quality of life may persist and if it were to translate into increased physical activity levels and improved exercise capacity.

Limitations

Our study should be interpreted in the context of several limitations. First, the small sample size is an important limitation of the study that leads to low statistical power to detect potentially small differences

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between the different rate-adaptive pacing modes; such small differences may have clinically significant effects. Secondly, baseline measurements with rate-adaptive feature programmed off was not performed, therefore it is unknown if CLS and accelerometer resulted in improved exercise capacity relative to no rate-adaptive pacing. Thirdly, pacemaker interrogation was not performed during exercise testing to assess the percent of atrial-pacing during submaximal exercise testing. However, pacemaker interrogation was performed after each week of programmed parameters with no significant differences in pacing rates. Lastly, we relied on a blunted atrial sensing histogram or significant burden of atrial pacing on device interrogation to define CI instead of specific objective criteria. Since no standard definition of CI exists, we believe this method reflects clinical practice and will be more applicable to the general population.

Conclusion

In the first study evaluating CLS in patients with HFrEF and CI implanted with CRT-D in a crossover-designed trial, there were no differences in measures of exercise capacity between CLS and standard accelerometer-based rate-adaptive pacing. We observed a trend toward improved quality of life in those with CLS compared to standard accelerometer-based rate-adaptive pacing. Larger studies of longer duration are needed to evaluate the potential beneficial effect of CLS in those with HF, CI, and psychological distress.

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DECLARATIONS

Ethics Approval: The study was approved by the Institutional Review

Board of University of California, San Diego.

Informed consent: Informed consent was obtained by each participant.

Figure 1.

Title: Study design.

Caption: Abbreviations: CLS, closed loop stimulation; CPET, closed-loop stimulation; QoL, quality of life.

Figure 2:

Title: Percentage of A.) atrial pacing and B.) left ventricular pacing throughout study period.

Central Illustration.

Title: (A) Quality of Life Score as assessed by RAND-36 Questionnaire, (B) six-minute walk distance, and (C-E) cardiopulmonary exercise test results of CLS vs DDDR.

Caption: Abbreviations: 6MWD, 6-minute walk distance.

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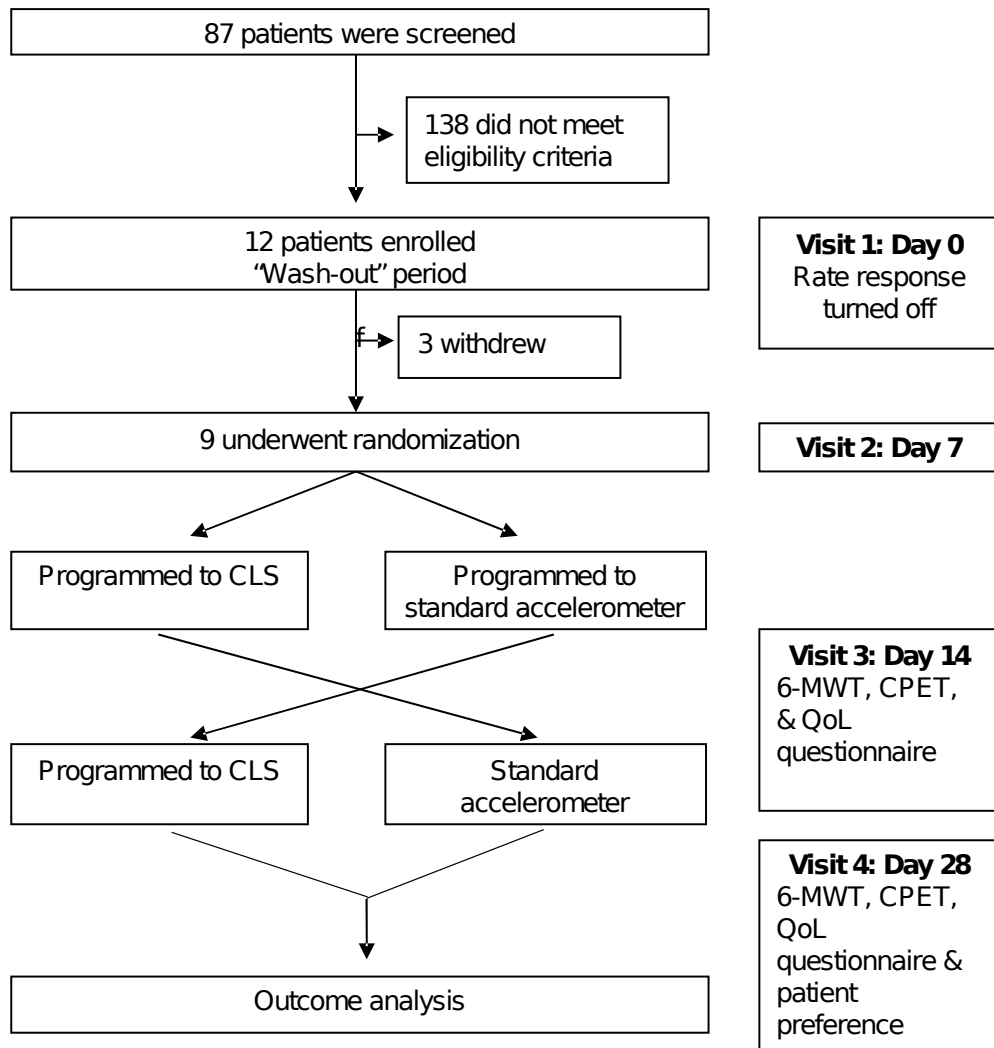
Table 1: Baseline characteristics.

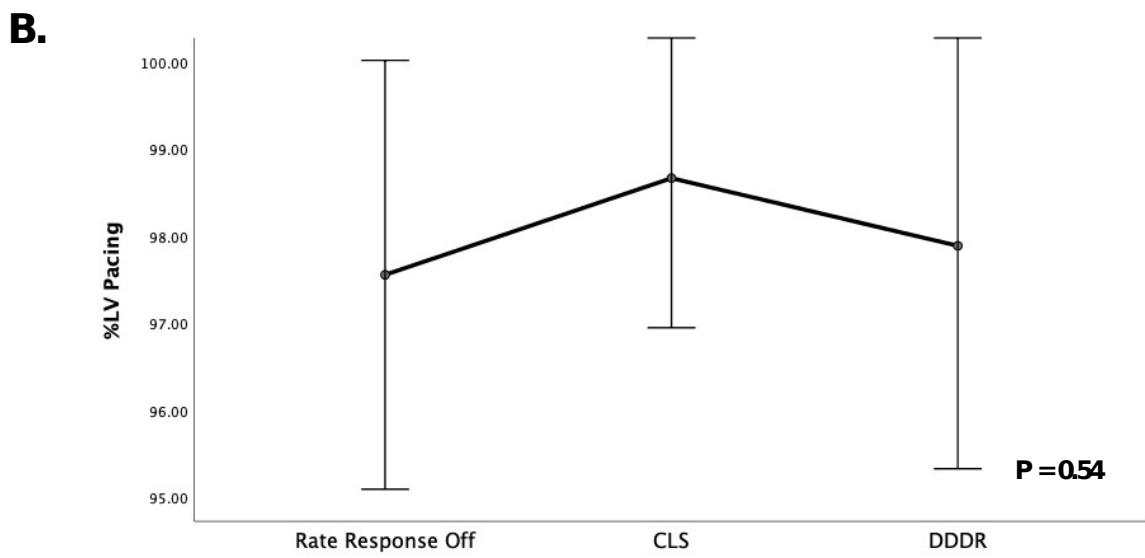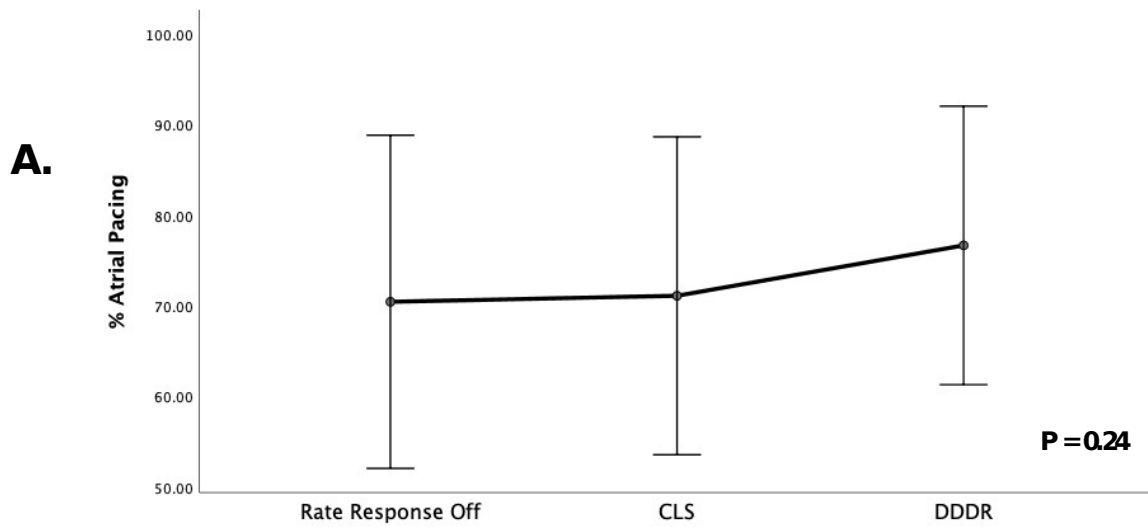| Characteristic	All Patients (N = 9)
Age (yr)	69 (63.5 – 76.5)
Male	5 (56%)
White race	6 (67%)
Days since CRT-D implant	154 (96 – 217)
Body-mass index (kg/m^2)	25 (23.6 – 33.7)
Hypertension	5 (56%)
Diabetes	2 (18%)
Prior cardiac arrest	1 (11%)
Paroxysmal atrial fibrillation	2 (18%)
Systolic blood pressure (mmHg)	130 (122 – 150)
Heart rate (beats/min)	70 (60-72)
Ejection fraction prior to implant (%)	29.0 (23.5 – 35.0)
Ejection fraction at enrollment (%)	37.0 (34.5 – 48.0)
NYHA Class	
II	2 (22%)
III	7 (78%)
Cardiomyopathy etiology	
Ischemic	6 (67%)
Nonischemic	3 (33%)
Reason for CRT-D Implantation	
LBBB and QRS > 120 ms	5 (56%)
Non-LBBB and QRS > 120 ms	2 (18%)
Depressed EF and high RV pacing burden	2 (18%)
Medications	
Beta blocker	8 (88.9%)
ACEi/ARB/ARNI	8 (88.9%)
Anti-arrhythmic therapy	2 (22%)
Atrial pacing (%)	58 (49.5 – 97.0)
LV pacing (%)	99 (96.5 – 100)
Values are presented as median (interquartile range) for continuous and n(%) for categorical variables. Abbreviations: NYHA, New York Heart Association; CRT-D, cardiac resynchronization therapy with defibrillator; LBBB, left bundle branch block;	

ACEi, ACE inhibitor; ARB, angiotension receptor blocker; ARNI, angiotension receptor neprilysin inhibitor; LV, left ventricle.

Figure 1.

Figure 2.

A.

B.

Figure 3.

A. Quality of Life Score

B. 6MWD

C. Peak Heart Rate

D. Peak VO$_2$

E. VE/VCO$_2$ Slope

F. Anaerobic Threshold

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