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Frequency and causes of QRS prolongation during exercise electrocardiogram testing in biventricular paced patients with heart failure

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Introduction

Cardiac resynchronization therapy-defibrillator (CRT-D) implantation is associated with improvements in heart failure (HF) symptoms and all-cause mortality in patients with symptomatic HF, prolonged QRS duration (QRSd), and left ventricular ejection fraction (EF) $\leq$35%.[1–3] Up to 30% of patients fail to experience improvement in HF symptoms after CRT-D implantation.[4] Greater QRSd reduction during CRT pacing is associated with improved likelihood of echocardiographic reverse remodeling after implantation of biventricular (BIV) pacemakers or defibrillators.[5] In some cases, patients have improvement in resting HF symptoms after CRT-D implantation but continue to experience HF symptoms during physical exertion. "Optimal" CRT-D programming varies considerably between patients and within individual patients at rest vs during exercise.[6] Most CRT-D devices are programmed empirically, without knowledge of the patient's individualized optimal settings, because CRT optimization at rest and exercise is time-consuming and expensive and there remains a lack of consensus regarding the best optimization technique.[7] The purpose of this study was to examine the frequency and causes of QRSd prolongation during supervised electrocardiogram (ECG) exercise testing among a group of patients with prior CRT-D implantation.

Case report

Study population

This is a retrospective analysis of patients who received a de novo CRT-D implantation at Duke University Medical Center between April 2006 and September 2015. Patients were included if they had an echocardiogram performed within 365 days prior to CRT-D implantation demonstrating a left ventricular EF of $\leq$35%, had a digital ECG at baseline ($\leq$180 days prior to CRT implantation) demonstrating a QRSd $\geq$120 ms, and underwent a clinically indicated exercise stress test after CRT-D implantation. Patients were excluded if the resting stress test ECG showed no CRT pacing or if the exercise ECG was too noisy to interpret. PR, QRS, and QT intervals were measured manually using electronic calipers at a sweep speed to 50 mm/s and a gain of 15 mm/mV. The study was approved by the Duke Institutional Review Board.

Patients were longitudinally followed using remote patient monitoring or in-clinic device interrogation and reports were stored in PDF format. Device programming was performed at the discretion of the implanting operator or following physician based on the patient's expected or recorded physical activity, age, observed or expected maximum heart rate (HR), and atrioventricular (AV) conduction time.

Baseline characteristics of the study population were reported using frequencies with percentages for categorical variables and means with standard deviations or medians with interquartile range for continuous variables. Statistical analyses were performed in JMP Pro Version 13.1 (SAS, Cary, NC).

A total of 1001 patients underwent CRT-D implant during the study period; 83 patients underwent exercise ECG stress testing after CRT-D implant. Of these, 25 patients were excluded because resting ECG demonstrated no CRT pacing and 1 patient was excluded because resting and exercise stress ECGs demonstrated noise that prevented accurate measurement, leaving a total of 57 patients available for analyses.

Baseline patient characteristics

Patient characteristics at the time of stress testing are shown in Table 1. The median time from CRT-D implant to stress testing was 2.3 (0.7–5.9) years. The median age was 60 (53–69) years, 63% of patients were male, and the majority

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KEY TEACHING POINTS

- Patients with ongoing heart failure symptoms after cardiac resynchronization therapy-defibrillator (CRT-D) implantation frequently demonstrated exercise-induced electrocardiogram (ECG) evidence of suboptimal CRT pacing during clinically indicated stress testing. Despite the high frequency of abnormal findings, the use of exercise ECG testing in CRT-D recipients was infrequent.
- Common mechanisms of QRS prolongation during exercise included an exercise heart rate exceeding the programmed upper tracking rate, progressive competitive native atrioventricular (AV) nodal conduction with bundle branch block due to suboptimal AV interval programming, and switching from left ventricle–only to biventricular (BIV) pacing at heart rates above 100 beats per minute. Device reprogramming could improve CRT pacing during exercise in these patients.
- Approximately half of all patients with QRS prolongation during exercise had no obvious discernible mechanism. More research is needed to understand possible changes in ventricular activation that occur during exercise in patients undergoing BIV pacing.

took a beta blocker on the day of stress testing. Echocardiography was assessed after CRT-D implantation in 36 of 57 patients. The EF improved after CRT-D implantation by ≥5% in 17 of 36 patients (47%) and the left ventricular end-systolic volume improved by ≥15% in 16 of 36 patients (44%). Patients achieved a median BIV pacing percentage of 99% (97%–100%) but were relatively sedentary with a median physical activity of 2.6 (1.1–4.4) hours per day (Table 2).

Stress testing

The indication for stress testing was evaluation of ongoing HF symptoms in 46 patients, symptoms of cardiac ischemia in 5 patients, and other indications in 6 patients (Table 3). Stress testing was ordered by a primary care provider in 1 patient, a cardiologist in 14 patients, an HF specialist in 36 patients, and an electrophysiologist in 6 patients. The median exercise time was 414 (259–540) seconds. Patients obtained a median peak HR of 125 (110–138) beats per minute (BPM) and had a median maximum metabolic equivalent of 6.7 (4.4–8.4). The peak heart rate exceeded the programmed upper tracking rate in 22 of 49 (45%) patients programmed to DDD or DDDR mode.

Table 1 Demographic and clinical information obtained at the time of exercise stress test

Age, years	60 (53–69)
Sex, male	36 (63)
Diabetes	20 (35)
Hypertension	32 (56)
Ischemic heart disease	22 (39)
Atrial fibrillation	17 (30)
Underlying QRS duration, ms	162 (146–178)
Underlying PR interval, ms	176 (156–190)
Underlying QRS morphology	
LBBB	36
RBBB	6
IVCD	3
RV paced	12
Beta blocker taken on day of stress	
Yes	45 (79)
No	9 (16)
Missing	3 (5)
Antiarrhythmic drug taken on day of stress	
Amiodarone	9 (16)
Class III	5 (9)
None	43 (75)
Pre-biventricular ICD ejection fraction, %	22 (18–29)
Resting ejection fraction on stress test, %	35 (20–50)
Change in ejection fraction from pre-biventricular ICD to stress test, %	4 (0–15)

All values are given as n (%) or median (interquartile range).
ICD = implantable cardioverter-defibrillator; IVCD = nonspecific intraventricular conduction delay LBBB = left bundle branch block; RBBB = right bundle branch block; RV = right ventricle.

ECG findings

The median resting CRT paced QRSd was 152 ms (140–175 ms). The median change in QRSd from underlying conduction to resting CRT pacing was -12 ms (-25 ms to +17 ms). At peak exercise, QRSd increased in 37 patients, remained

Table 2 Biventricular implantable cardioverter-defibrillator device programming at the time of exercise stress test

Days from device interrogation to stress test	-22 (-82 to +6)
Pacing mode, n (%)	
DDD	32 (56)
DDDR	17 (30)
VVIR	8 (14)
Paced AV delay, ms	140 (130–160)
Sensed AV delay, ms	100 (100–120)
Rate-adaptive AV delay	
Yes	35 (61)
No	10 (18)
Unknown	12 (21)
Adaptive CRT programmed ON	15 (27)
Lower rate, BPM	60 (50–60)
Upper tracking rate, BPM	130 (130–135)
Upper sensor rate, BPM	130 (120–130)
Patient activity (hours/day)	2.6 (1.1–4.4)
Biventricular pacing, %	98.7 (97–100)

All values are given as n (%) or median (interquartile range).
AV = atrioventricular; BPM = beats per minute; CRT = cardiac resynchronization therapy.

Table 3 Results of exercise stress testing

Indication for stress test	
Heart failure	46
Ischemia symptoms	5
Other	6
Time from implant to stress test, years	2.3 (0.7–5.9)
Stress protocol	
Bruce	12
Ekelund	22
Modified Naughton	19
Other	4
Maximum METs	6.7 (4.4–8.4)
Peak heart rate (BPM)	125 (110–138)
Resting BIV-paced QRSd (ms)	152 (140–175)
Peak exercise QRSd (ms)	160 (152–176)
Change in QRSd from rest to peak exercise (ms)	10 (-7 to +28)
Resting BIV-paced PR interval (ms)	154 (140–171)
Peak exercise PR interval (ms)	132 (119–160)
Change in PR interval from rest to peak exercise (ms)	-14 (-40 to +8)
Resting QT interval (ms)	454 (420–480)
Peak exercise QT interval (ms)	374 (354–400)
Change in QT interval from rest to peak exercise (ms)	-66 (-98 to -48)

All values are given as n (%) or median (interquartile range).

BIV = biventricular; BPM = beats per minute; METs = metabolic equivalents.

unchanged in 3 patients, and decreased in 17 patients. The median change in QRSd at peak exercise compared to rest was +10 ms (-7 ms to +28 ms). Twenty-nine patients (50%) had an increase in QRSd of ≥10 ms and 20 patients (34%) had an increase in QRSd of ≥20 ms from rest to peak exercise (Figure 1). Fifteen patients had a gradual increase in QRSd from rest to peak exercise, the cause of which could not be determined. Eleven patients had a sudden increase in QRSd with change in QRS morphology as the exercise HR exceeded the upper tracking rate; 9 patients had a sudden, initially intermittent increase in QRSd with a change in QRS morphology below the upper tracking rate with loss of ventricular pacing output as the PR interval became shorter than the sensed AV delay. Among these 9 patients, 6 had either a rate-adaptive AV interval feature or Adaptive CRT (Medtronic plc, Dublin, Ireland) programmed on. Two patients had a sudden increase in QRSd with change in QRS morphology after the HR exceeded 100 BPM and had Adaptive CRT programmed on, consistent with automated change from left ventricle–only pacing to BIV pacing with the Adaptive CRT algorithm. Examples of ECG changes associated with each cause are shown in Figure 2. Among those patients with a sudden change increase in QRSd during exercise testing (n = 22), the median time from QRSd increase to peak exercise was 94 (18–278) seconds.

The median change in PR interval from rest to peak exercise was -14 ms (-40 ms to +8 ms), while the median change in QT interval was -66 ms (-98 ms to -48 ms). All patients in the study (57/57) received CRT-D device follow-up in our center after stress testing. Seven of 37 patients (19%) with QRSd prolongation at peak exercise had their upper tracking rate or AV intervals reprogrammed within 1 year of their stress test.

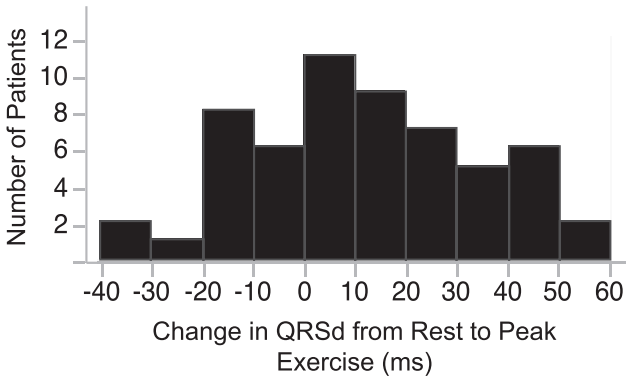

Figure 1 Frequency of change in QRS duration by 10-millisecond intervals.

Discussion

We used stress ECG data to examine the frequency and causes of QRSd prolongation during exercise after CRT-D implantation. Our population was composed of patients who initially met Class I or II indication for CRT-D implantation[8,9] with pre-implantation QRSd prolongation, subsequently received a high BIV pacing percentage, and demonstrated resting ECG evidence of successful CRT. Almost half of the subjects demonstrated >5% improvement in resting EF or >15% reduction in left ventricular end-systolic volume, suggesting that they obtained benefit from CRT-D implantation. Despite objective evidence of CRT-D "response," the device-derived activity monitoring data showed that the patients remained relatively sedentary after CRT-D implantation and ongoing HF symptoms were the indication for stress testing in the majority of cases.

The majority of the study population took beta-blocker prescriptions on the day of their stress test, limiting the likelihood of developing sinus tachycardia or accelerated AV nodal conduction with exertion. Despite this, the majority of studied patients attained a peak heart rate that exceeded their programmed upper tracking rate or developed competing AV nodal conduction with underlying bundle branch block.

In our study, only 7 of 39 patients with QRSd prolongation during stress testing received CRT programming changes to improve CRT pacing during exercise. It is possible that QRSd prolongation was not noted during the stress ECG interpretation. In our study few of the exercise tests were ordered by an electrophysiologist, and the treating electrophysiologist may not have been aware of the results. Given the frequency of QRSd prolongation among CRT-paced patients and the fact that the majority of identified cases could potentially have been corrected with device reprogramming, review by the treating electrophysiologist should be encouraged. Alternatively, the development of automated device features to identify exercise-induced loss of CRT and iterative automated device reprogramming to improve CRT pacing during exercise may provide improvement of CRT delivery during varying physiological conditions.

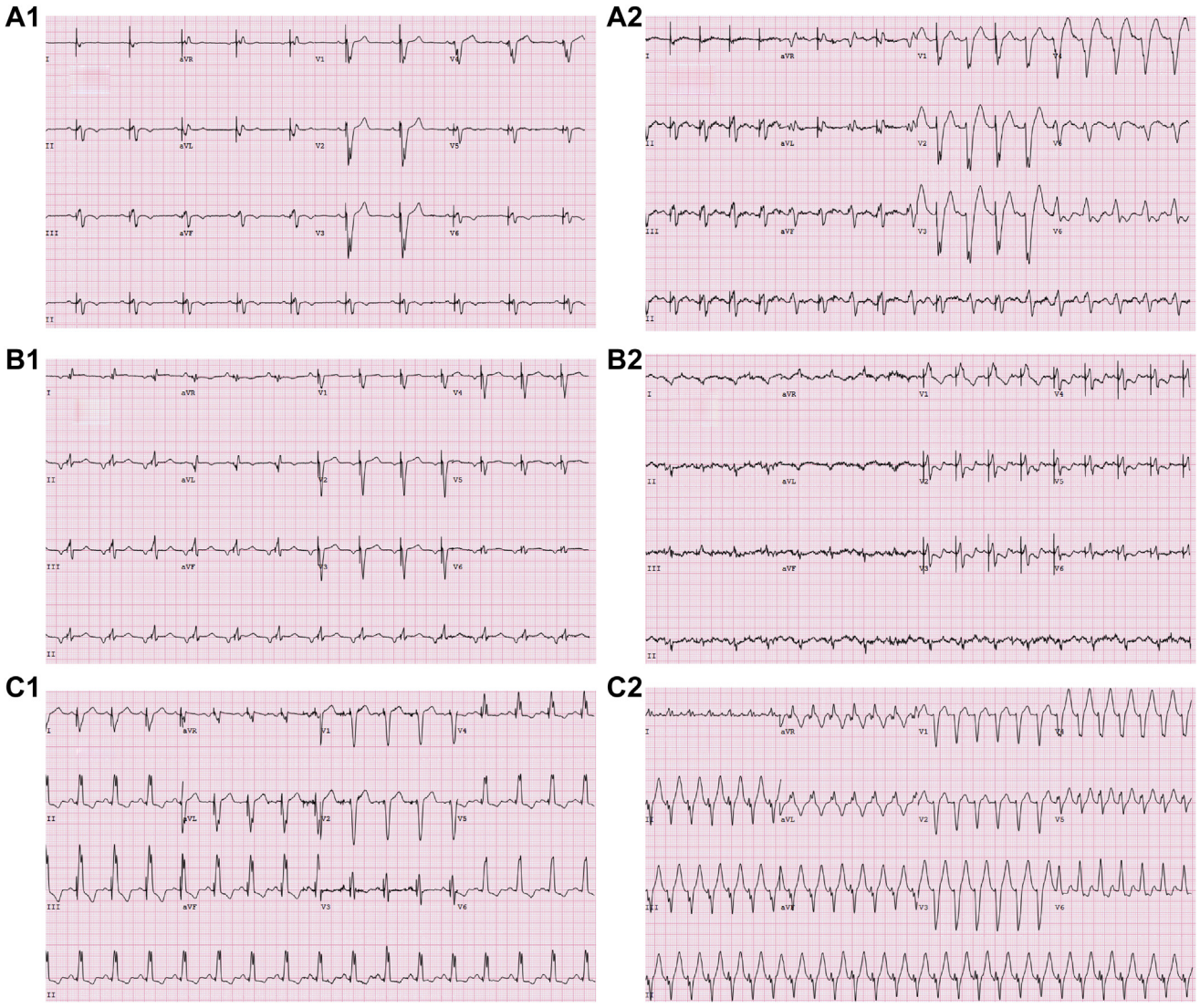

Figure 2 Representative electrocardiogram (ECG) examples highlighting common causes of QRS prolongation with exercise. **A1, B1, C1:** Resting cardiac resynchronization therapy–paced ECGs on 3 patients. **A2:** Intermittent loss of ventricular pacing spikes with associated intermittent QRS prolongation. This resulted from reduction in native PR interval to less than the sensed atrioventricular (AV) delay in a patient without rate-adaptive AV delay programmed on. As the patient continued to exercise, ventricular pacing was lost entirely. **B2:** Ongoing biventricular pacing but with more prolonged QRS duration after the heart rate increases beyond 100 beats per minute. At this rate, the Adaptive CRT (Medtronic plc) algorithm automatically switched from left ventricle only to biventricular pacing, resulting in QRS prolongation. **C2:** Absence of ventricular pacing with underlying left bundle branch block conduction and QRS widening, resulting from an atrial rate exceeding the programmed upper tracking rate.

We noted QRSd reduction in 16 of 57 patients during exercise. Further evaluation of the mechanisms of QRSd reduction during exercise is warranted.

Limitations

The study is limited by the retrospective, single-center design. All patients had a clinical indication for stress testing. It remains unclear how frequently QRSd prolongation occurs during exercise among a less carefully selected CRT population. A prospective study of routine exercise ECG testing in a population of patients with CRT pacing would improve understanding of the incidence among CRT recipients. Stress echocardiography images were available in only 16 of 57 patients, limiting our ability to study associations between exercise-induced QRSd prolongation and ventricular function.

Conclusions

CRT recipients with ongoing symptoms of HF or cardiac ischemia frequently demonstrate prolongation of QRSd during exercise ECG testing, suggesting that CRT pacing may be less effective during exercise compared to rest. The majority of these cases could be corrected with CRT device reprogramming.

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