

Fusion pacing algorithm to improve synchrony in chronically paced patients

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ABSTRACT

The cardiac resynchronization therapy (CRT) development was fundamental to improve the treatment of patients with heart failure (HF) and intracardiac electric block. Despite all this importance, up to 30% of the patients remain labeled as non-responders. An important question is whether reprogramming of CRT to increase electrical synchrony translates into echocardiographic improvement. New automatic algorithms have been developed to allow fusion of the triple wavefronts: intrinsic, right ventricular (RV)-paced, and left ventricular (LV)-paced. We aimed to assess whether programming with one of these new algorithms is associated with QRS complex duration (QRSd) and improvement in echocardiographic parameters compared to routine CRT programming in patients with chronically implanted devices. We also analyzed the specific data of patients with underlying right bundle branch block (RBBB), traditionally poor CRT responders, optimized using the fusion pacing algorithm and compared with patients who had standard of care CRT implant without fusion pacing algorithm.

Patients at a single tertiary cardiac center with a previously implanted CRT defibrillator or pacemaker with programmable fusion pacing algorithm were recruited. All patients underwent routine electrocardiogram (ECG)-based optimization during a regular device clinic visit. This analysis only included patients who were able to be programmed with the new automatic algorithm (i.e., in sinus rhythm with intrinsic atrioventricular conduction at implant). Echocardiography was performed and NYHA functional class was assessed prior to and 6 months after optimization.

For the chronically paced patients (manuscripts 1 and 2), 34 of 64 consecutive potentially eligible patients who underwent assessment were able to undergo fusion pacing programming, and therefore included. The mean age was 74 ± 9 years, 41% were female and 59% had ischemic cardiomyopathy. The mean intrinsic conduction QRSd was 163 ± 24 ms with intrinsic conduction,

152±25 ms with existing CRT programming and 138±23 ms with fusion pacing programming. At 6-month follow-up, optimization was associated with a significant increase in left ventricular ejection fraction (LVEF; mean 36.5%±13.3% versus 30.9%±13.3%; $P < 0.001$) as well as a reduction in the severity of mitral regurgitation (MR; mean grade 0.5±1.0 versus 0.9±1.0; $P < 0.001$) compared to existing CRT programming.

For the RBBB analysis (manuscript 3), we included 8 patients that had the fusion pacing programming and compared to 16 patients from a historical cohort who received a device without fusion pacing capability. In the first group, we found that the mean intrinsic conduction QRSd was 155±13 ms, the mean nominally-paced QRSd was 156±15 ms (Δ QRSd 1.3±11.6 ms; $P = 0.77$) and the fusion optimized paced QRSd was 135±14 ms (Δ QRSd -20.0±20.4 ms; $P = 0.03$ and Δ QRSd -21.3±16.3 ms; $P = 0.008$; when compared to intrinsic conduction and nominal pacing, respectively). In the second group, the mean QRSd with nominal pacing was 160±24 ms (Δ QRSd 3.8±33.4 ms; $P = 0.66$; compared to intrinsic conduction). Regarding echocardiography parameters, in the first group the baseline LVEF (%) was 22.1±11.5 and 27.8 ± 8.6 ($P = 0.047$) after 6 months of follow-up. In the second, the baseline LVEF (%) was 27.2±10.6 and after 6 months of follow-up was 25.0 ± 10.0 ($P = 0.45$).

Atrioventricular (AV) delay optimization to maximize fusion pacing significantly reduced the QRS duration, improved LVEF and mitral regurgitation severity in patients with existing CRT devices. Similar findings were also seen among patients with underlying RBBB when compared to patients without fusion pacing capability.

This is the first study to assess the effects of the fusion pacing in chronically implanted patients. Moreover, study data showed that the use of regular ECG is cheap, fast, reliable, and easily

reproducible to optimize these special devices. The QRS narrowing was correlated with echocardiography improvement.

RÉSUMÉ

Le développement de la thérapie de resynchronisation cardiaque (TRC) était fondamental pour améliorer le traitement des patients souffrant d'insuffisance cardiaque (IC) et de bloc électrique intracardiaque. Malgré toute cette importance, jusqu'à 30% des patients restent étiquetés comme non-répondeurs. Une question importante est de savoir si la reprogrammation de la TRC pour augmenter la synchronie électrique se traduit par une amélioration échocardiographique. De nouveaux algorithmes automatiques ont été développés pour permettre la fusion des fronts d'onde triples: intrinsèque, ventriculaire droit (VD) et ventriculaire gauche (VG). Nous avons cherché à évaluer si la programmation avec l'un de ces nouveaux algorithmes est associée à la durée complexe QRS (QRSd) et à l'amélioration des paramètres échocardiographiques par rapport à la programmation de routine TRC chez les patients avec des dispositifs implantés de manière chronique. Nous avons également analysé les données spécifiques des patients avec un bloc de branche droit (BBD) sous-jacent, des répondeurs TRC traditionnellement pauvres, optimisés à l'aide de l'algorithme de stimulation de fusion et comparés avec des patients qui avaient un implant TRC standard de soins sans algorithme de stimulation de fusion.

Les patients d'un seul centre cardiaque tertiaire avec un défibrillateur TRC ou un stimulateur cardiaque préalablement implanté avec un algorithme de stimulation par fusion programmable ont été recrutés. Tous les patients ont subi une optimisation de routine basée sur l'électrocardiogramme (ECG) lors d'une visite clinique régulière de l'appareil. Cette analyse n'a inclus que les patients qui ont pu être programmés avec le nouvel algorithme automatique (c'est-à-dire en rythme sinusal avec conduction auriculo-ventriculaire intrinsèque à l'implant). Une échocardiographie a été réalisée et la classe fonctionnelle NYHA a été évaluée avant et 6 mois après l'optimisation.

Pour les patients à rythme chronique (manuscripts 1 et 2), 34 des 64 patients consécutifs potentiellement éligibles qui ont subi une évaluation ont pu subir une programmation de stimulation de fusion, et donc inclus. L'âge moyen était de 74 ± 9 ans, 41% étaient des femmes et 59% avaient une cardiomyopathie ischémique. La conduction intrinsèque QRSd moyenne était de 163 ± 24 ms avec la conduction intrinsèque, de 152 ± 25 ms avec la programmation TRC existante et de 138 ± 23 ms avec la programmation de stimulation de fusion. À 6 mois de suivi, l'optimisation était associée à une augmentation significative de la fraction d'éjection ventriculaire gauche (FEVG; moyenne $36,5\% \pm 13,3\%$ versus $30,9\% \pm 13,3\%$; $P < 0,001$) ainsi qu'à une réduction de la sévérité de la mitrale régurgitation (MR; grade moyen $0,5 \pm 1,0$ versus $0,9 \pm 1,0$; $P < 0,001$) par rapport à la programmation TRC existante.

Pour l'analyse BBD (manuscrit 3), nous avons inclus 8 patients qui avaient la programmation de stimulation de fusion et comparé à 16 patients d'une cohorte historique qui ont reçu un dispositif sans capacité de stimulation de fusion. Dans le premier groupe, nous avons constaté que le QRSd de conduction intrinsèque moyen était de 155 ± 13 ms, le QRSd moyen à stimulation nominale était de 156 ± 15 ms (Δ QRSd $1,3 \pm 11,6$ ms; $P = 0,77$) et le QRSd stimulé par fusion optimisé était de 135 ± 14 ms (Δ QRSd $-20,0 \pm 20,4$ ms; $P = 0,03$ et Δ QRSd $-21,3 \pm 16,3$ ms; $P = 0,008$; par rapport à la conduction intrinsèque et à la stimulation nominale, respectivement). Dans le deuxième groupe, le QRSd moyen avec stimulation nominale était de 160 ± 24 ms (Δ QRSd $3,8 \pm 33,4$ ms; $P = 0,66$; comparé à la conduction intrinsèque). En ce qui concerne les paramètres échocardiographiques, dans le premier groupe, la FEVG initiale (%) était de $22,1 \pm 11,5$ et $27,8 \pm 8,6$ ($P = 0,047$) après 6 mois de suivi. Dans la seconde, la FEVG initiale (%) était de $27,2 \pm 10,6$ et après 6 mois de suivi était de $25,0 \pm 10,0$ ($P = 0,45$).

L'optimisation du délai auriculo-ventriculaire (AV) pour maximiser la stimulation de fusion a considérablement réduit la durée du QRS, amélioré la FEVG et la gravité de la régurgitation

mitrale chez les patients avec des dispositifs TRC existants. Des résultats similaires ont également été observés chez les patients avec BBD sous-jacent par rapport aux patients sans capacité de stimulation de fusion.

Il s'agit de la première étude à évaluer les effets de la stimulation de fusion chez les patients implantés de manière chronique. De plus, les données de l'étude ont montré que l'utilisation d'un ECG régulier est bon marché, rapide, fiable et facilement reproductible pour optimiser ces dispositifs spéciaux. Le rétrécissement du QRS était corrélé à l'amélioration de l'échocardiographie.

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CONTRIBUTION OF AUTHORS

Pedro Yuri Paiva Lima is the first author for Chapters 1 through 7. For all chapters, he led the creative process, protocol development, methodology, results, conclusions, discussion, writing, and editing throughout. Dr Alturki: assistance with statistics and creation of Kaplan-meier curves (figure 2), for chapters 3, 4 and 5 (manuscript #1, 2 and 3). Drs. Hadjis, Bernier and Joza: assistance with procedural guidance and editing/review of manuscript. Dr. Essebag: assistance with protocol development and procedural guidance, and editing/review of manuscript.

CHAPTER 1: INTRODUCTION

Cardiac resynchronization therapy improves cardiovascular outcomes in patients with heart failure (1). However, a significant proportion, around 30% of patients, who receive CRT do not improve and are deemed non-responders (2). While there have been significant efforts identifying predictors of response to CRT prior to device implantation such as LBBB and a prolonged QRSd, optimal programming of CRT has not yet been fully elucidated. Given individual variations in ventricular activation sequences, a one-size fits all approach to CRT programming may be sub-optimal.

The ideal method to optimize CRT post-implantation is controversial. Echocardiography has traditionally been considered the gold standard for CRT optimization (3). However, 58% of the investigators surveyed do not optimize the device after implantation because this method requires complex adjustments that demand expertise, and it is time-consuming (4). The use of ECG would therefore be an inexpensive and practical process for CRT optimization (5). Narrowing of QRS complex with biventricular pacing (the paced QRSd) has been shown to correlate with clinical and echocardiographic improvement (6,7). One study has also reported that the ECG-based optimization using the measurement of the narrowest QRS is comparable to echocardiography-based optimization regarding LV reverse remodeling (8).

The efficacy of fusion pacing has been evaluated in previous studies using an algorithm to allow LV pacing and intrinsic conduction fusion. These studies confirmed the non-inferiority of the fusion pacing algorithm compared to echocardiography biventricular optimization regarding clinical and mechanical parameters (9), as well as a composite of death or heart failure hospitalizations (10). Other authors studied the effect of the triple front waveform allowing the fusion between the intrinsic conduction, left ventricular pacing (LVp) and right ventricular pacing

(RVp) and how to perform measurements for ECG-based optimization in order to allow triple wavefront fusion (11). In 2017, Varma et al. used the device's algorithm to perform an ECG-based optimization, revealing a narrowing of the QRS in well selected LBBB patients (12). Despite all these studies and the apparent clinical, echocardiographic, and electrocardiographic improvement, the fusion pacing with intrinsic and LV pacing or triple wavefront pacing was never tested in chronically paced patients.

Another subgroup related with limited CRT response are the non-LBBB patients. Several studies had reported limited success to resynchronization in this specific population (13-15). The mechanism involved in the rate of non-responder and the potential benefit of fusion pacing was never assessed in this population.

During this research project we aimed to determine whether the triple wavefront benefit seen on new device implant equipped with the automatic fusion pacing algorithm could also be reproduced in chronically paced patients. We also evaluated if the fusion pacing algorithm associated with the ECG-based optimization was correlated with QRS narrowing and echocardiographic parameters improvement. Finally, we studied if the triple wavefront fusion pacing algorithm would increase the rate of responders in a non-LBBB population.

CHAPTER 2: REVIEW OF THE LITERATURE

The concept of fusion pacing has been studied since 2003 as an attempt to improve the rate of CRT responders. Verbeek et al. first described in an animal model with induced LBBB the feasibility of fusion between intrinsic AV conduction through the septum, RV and LV pacing when shorter AV delays were programmed. His group also described optimal AV intervals based on different LV lead position. The shorter QRS intervals were found with the combination of LV positioned at the lateral wall and fusion with intrinsic activation (16). In 2005, Gianfranchi et al. reported a case of a patient with a LBBB who had an ECG-based optimization performed using the range of fusion pacing called fusion band. The echocardiographic parameters revealed an improvement when the AV delay was programmed inside the fusion band, allowing fusion with right bundle septal activation (17). The same group performed in 2008 a pilot study with 24 patients applying the concept of fusion band with ECG-based optimization to confirm the fusion, associates with echocardiography measurements. The results confirmed the previous individual findings of diastolic filling time, ejection fraction, myocardial performance index, and mitral regurgitation with shorter AV intervals inside the fusion band (18). Back in 2005, Van Gelder et al. conducted a series of cases to assess the hemodynamic acute effects of different combinations of AV intervals to achieve fusion of biventricular and LV pacing only in De novo CRT implants. Among 34 patients, several AV intervals adjustments were performed and revealed better hemodynamic acute parameters when LV pacing combined with right bundle activation through the septum (19).

In order to have a better understanding of the LV activation during biventricular pacing associated with intrinsic AV septal conduction and LV only pacing also associated with intrinsic conduction, Vatasescu et al. performed a contact-based 3D activation map of the LV during sinus

rhythm, RV pacing and biventricular pacing with septal fusion (triple wavefront activation) in 15 patients under CRT implant. The results pointed to an improvement of LV activation time in the biventricular associated with septal depolarization configuration. The group also suggested to avoid the biventricular pure pacing without fusion due to a worse LV activation time (20).

After all the data supporting the fusion pacing for De novo CRT implants, Wang et al. decided to evaluate the fusion pacing concept in a series of cases of seven CRT non-responders. As the previous studies, ECG-based optimization was performed to confirm the achievement of fusion. All the patients experienced symptoms improvement, QRS narrowing, increasing in LVEF, and reducing in LVESV in a 6-month follow-up (21). Despite the good results seen at both recent implants and non-responders, the question about how the fusion would behave regarding the daily physiologic PR interval variations and how these variations would affect the fusion remained unclear.

The answer to this question came in 2012 when Martin et al. published the first randomized controlled trial to assess the non-inferiority of an automatic algorithm to allow fusion between AV conduction and LV pacing and the standard BIV pacing. The results revealed a 44% reduction in RV pacing and confirmed the hypothesis of non-inferiority of the new algorithm compared to echocardiographic AV and VV intervals optimization. The new algorithm was considered safe and effective for device optimization (22). The subsequent clinical data analysis performed by Birnie et al. demonstrated that higher LVP ($> 50\%$) was correlated with a reduced primary clinical outcome of death and heart failure hospitalizations with additional benefits in the subgroup with normal AV (23). Several authors described methods for AV adjustment to allow fusion pacing and compared the QRS duration, echocardiography parameters, and acute hemodynamics improvement with the nominal device settings. Arbelo et al. described a QRS narrowing compared

with the nominal settings (Δ QRS duration 40 ms $\pm$ 21 ms in the nominal group vs 59 ms $\pm$ 19 ms with the ECG-based optimization group with a p-value < 0.001) and hemodynamic improvement (Δ + dP/dt [mmHg/s]) 102 $\pm$ 71 in the nominal group vs 127 $\pm$ 95 in the ECG-based optimization with a p-value of 0.05) (24). Similar findings were also described by Guo et al. in 2014. The QRS shortening was more expressive among the patients underwent BiV pacing fused with intrinsic AV conduction and ECG-based optimization (118.35 ± 21.59 ms) than in the conventional BiV pacing and echocardiographic optimization (146.35 ± 5.31 ms). A clinical and echocardiographic improvement were also seen when in favor of the fusion pacing method (25).

After all these promising results seen using manual adjustments of BiV with intrinsic fusion and the automatic algorithm of fusion between LV and intrinsic conduction, Varma et al. published the results of the first automatic algorithm allowing fusion between BiV pacing and intrinsic conduction in De novo CRT implants. In accordance with previously demonstrated, the new algorithm was able to achieve an expressive QRS narrowing (123 $\pm$ 12 ms of BiV with intrinsic vs 142 $\pm$ 17 ms of nominal BiV). The authors also demonstrated a further QRS narrowing comparing BiV + intrinsic with LV only + intrinsic conduction (136 $\pm$ 14 ms) (26).

CHAPTER 3:

Cardiac Resynchronization Therapy Reprogramming to Improve Electrical Synchrony in Patients with Existing Devices

3.1 Preface to the first manuscript

The following manuscript results of the idea to assess the effect of an ECG-based optimizations using the automatic algorithm for fusion pacing regarding QRS duration in chronically paced patients. The main objective was to assess the QRS narrowing using fusion pacing. We also aimed to validate the traditional 12-lead ECG as an easy and reproducible method for CRT optimization.

The manuscript has been published in the Journal of Electrocardiology, and should be referenced as follows:

A. AlTurki et al. / Journal of Electrocardiology 56 (2019) 94–99

3.2 Manuscript #1.

Cardiac Resynchronization Therapy Reprogramming to Improve Electrical Synchrony in Patients with Existing Devices

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Abstract

Background: Optimal programming of cardiac resynchronization therapy (CRT) has not yet been fully elucidated. A novel algorithm (SyncAV) has been developed to improve electrical synchrony by fusion of the triple wavefronts: intrinsic, right ventricular (RV)-paced, and left ventricular (LV)-paced.

Methods: Consecutive patients at a single tertiary care center with a previously implanted CRT device with SyncAV algorithm (programmable negative AV hysteresis) were evaluated. QRS duration (QRSd) was measured during 1) intrinsic conduction, 2) existing CRT pacing as chronically programmed by treating physician, 3) using the device-based QuickOpt™ algorithm for optimization of AV and VV delays, and 4) ECG-based optimized SyncAV programming. The paced QRSd was assessed and compared to intrinsic conduction and between the different modes of programming.

Results: Of 64 consecutive, potentially eligible patients who underwent assessment, 34 patients who were able to undergo SyncAV programming were included. Mean intrinsic conduction QRSd was 163 ± 24 ms. In comparison, the mean QRSd was 152 ± 25 ms (-11.1 ± 19.0) during existing CRT pacing, 160 ± 25 ms (-4.1 ± 25.2) using the QuickOpt™ algorithm and 138 ± 23 (-24.9 ± 17.2) using ECG-based optimized SyncAV programming. SyncAV optimization resulted in significant reductions in QRSd compared to existing CRT pacing ($P=0.02$) and QuickOpt™ ($P<0.001$). Of the 32% of patients who did not have QRS narrowing with existing CRT, 72% experienced QRS narrowing with SyncAV.

Conclusion: ECG-based atrio-ventricular delay optimization using SyncAV significantly improved electrical synchrony in patients with a previously implanted CRT. Further studies are needed to assess the impact on long-term outcomes.

Key words: biventricular pacing; cardiac resynchronization therapy; SyncAV

Background

Cardiac resynchronization therapy (CRT) improves cardiovascular outcomes in patients with heart failure (1). However, a significant proportion (around 30%) of patients who receive CRT do not improve and are deemed non-responders (2). While there have been significant efforts to identify predictors of response to CRT prior to device implantation such as left bundle branch block and a prolonged QRS duration (3), optimal programming of cardiac resynchronization therapy has not yet been fully elucidated. Given individual variations in ventricular activation sequences, a one-size fits all approach to CRT programming may be sub-optimal.

The goal of CRT is to improve electrical synchrony and in turn mechanical synchrony (4). A decrease in QRS duration (QRSd) after CRT is a predictor of clinical response (5, 6). A novel, device-based algorithm (SyncAV) included in certain Abbott CRT devices can be used to improve electrical synchrony by fusion of the triple wavefronts: intrinsic, right ventricular (RV)-paced, and left ventricular (LV)-paced. This algorithm automatically synchronizes ventricular pacing with intrinsic atrioventricular conduction by altering the atrioventricular delay. A shortening between 10 to 120 ms of the atrioventricular delay (relative to the measured intrinsic AV conduction interval) is programmed to allow fusion between intrinsic atrioventricular conduction and biventricular pacing. This would occur across various durations of intrinsic conduction (up to 350 ms) to allow a continuously adapting fusion pacing. Though the algorithm is programmed with a default SyncAV -50 millisecond offset, the offset is programmable to allow patient-specific optimization.

Whether electrical synchrony can be improved in patients with a chronically implanted CRT has not been proven. Therefore, we aimed to assess the difference in QRSd in patients with a previously implanted CRT who subsequently receive SyncAV pacing compared to existing chronic

CRT pacing as well as another proprietary device-based timing cycle optimization algorithm (QuickOpt™) (7).

Methods

Study patients

We performed a single center, retrospective study of patients with a CRT defibrillator (CRT-D) (St-Jude Unify Assura and Quadra Assura 3) or a CRT pacemaker (CRT-P) device (St-Jude Allure Quadra RF) with SyncAV algorithm™ (programmable negative AV hysteresis), implanted between January 2014 and November 2017 at the McGill University Health Center (MUHC), Montreal, Canada. Only patients able to be programmed to the SyncAV algorithm (i.e. in sinus rhythm with intrinsic AV conduction at implant) were included in this analysis. All patients included in the study fulfilled criteria for CRT implantation as per Canadian Cardiovascular Society guideline recommendations (3). This study was approved by the McGill University Health Center Institutional Review Board.

Device implantation and programming

CRT was programmed according to operator preference and SyncAV was not activated in any of the patients between January 2014 and November 2017; at the end of that year, patients with chronically implanted CRT devices underwent routine ECG-based SyncAV algorithm optimization during their next regular device clinic visit to assess the best QRS pattern. This method of optimization became the standard of care in our service since May 2018 for newly implanted devices and was extended to the previously implanted devices. Since then, all patients coming for regular clinical follow up had the device optimized according to our service's protocol including sequential ECGs.

Electrocardiographic measurements

Standard 12-lead electrocardiography was performed at a paper speed of 25 mm/s and a scale of 10 mm/mV. QRS duration, as recorded from the surface leads which have the greatest values, was measured automatically by the ECG machine (GE MACTM 5500 HD Resting ECG System). The ECG machine is programmed to measure the earliest onset of the QRS and the latest offset (8); in practical terms this would be from the time of the pacemaker spike until the end of the QRS. This was subsequently validated manually by a single investigator who was blinded to the clinical data and pacing programming. On the 12-lead ECG, the QRSd was defined as the duration from the earliest deflection from the isoelectric line to the latest return to the isoelectric line in any lead. The reasons for using automated QRS measurements were fourfold: 1) the lack of a standardized practice and the fact that CRT trials did not report the methods for QRSd measurement (9), which was likely automated; 2) the significant variability seen with manual QRSd measurements (10); 3) the reproducibility and precision of automated measurements (11); 4) the ease of use of automated measurements which would be readily translated to clinical practice.

QRSd was measured during 1) intrinsic conduction, 2) existing CRT pacing as chronically programmed by treating physician prior to SyncAV optimization, 3) using the device-based QuickOptTM algorithm for optimization of AV and VV delays and 4) manual ECG-based optimized SyncAV programming (with offsets of -10, -30, -50, -70, and -90ms evaluated). Change in QRSd was assessed and compared to intrinsic conduction and between the different modes of programming.

Statistical analysis

All data are presented as mean $\pm$ SD for continuous variables and as proportions for categorical variables. Mean QRSd was compared between the different CRT programming and intrinsic conduction by performing an analysis of variance (ANOVA) test. A P-value of <0.05 was considered statistically significant. Univariate and multivariate logistic regression analyses were performed to identify variables associated with a significant reduction in QRS duration (defined as ≥ 10 ms) compared to existing CRT pacing. All variables associated with a statistical significance of $P < 0.1$ were considered for multivariate analysis.

Results

A total of 64 patients who had a CRT device (with the SyncAV feature) implanted between January 2014 and November 2017 were considered for possible inclusion. Among these patients, 2 were not eligible due to prior system explant for device infection, 2 other patients had heart transplant prior to the appointment for the optimization, 2 patients had LV lead dysfunction/dislodgment and the lead was turned off, and 7 patients did not return for follow-up at our center's device clinic. Of the remaining 51 patients presenting to clinic for ECG-based optimization, 7 patients had intermittent AV block, or the PR interval was longer than 350 ms (making fusion pacing with the SyncAV feature not possible), 1 patient had normalization of the QRS width and was programmed to DDI 40 bpm, another 3 patients became exclusively palliative care and 6 patients refused to have the ECG-based optimization performed due to personal reasons. The remaining 34 patients had ECG-based optimization performed and were included in this analysis (Figure 1). The mean age was 74 ± 9 years, 41% were female and 59% had ischemic cardiomyopathy. Patient characteristics at time of SyncAV optimization are summarized in Table 1.

The mean intrinsic conduction QRSd was 163 ± 24 ms and the mean existing CRT pacing

QRSd was 152 ± 25 ms. Using the QuickOpt™ algorithm the mean QRSd was 160 ± 25 ms and using manual ECG-based optimized SyncAV programming the mean QRSd was 138 ± 23 . In comparison to intrinsic conduction, the change in QRSd was -11.1 ± 19.0 ($P=0.07$), -4.1 ± 25.2 ($P=0.53$) and -24.9 ± 17.2 ($P<0.001$) using existing CRT pacing, QuickOpt™ algorithm and manual ECG-based optimized SyncAV programming, respectively (Figure 2). Using SyncAV optimization resulted in significant reduction in QRSd compared to existing CRT pacing (-13.8 ± 12.4 , $P=0.02$) and the QuickOpt™ algorithm (-21.1 ± 17.8 , $P<0.001$). The distribution of the differences in QRSd between SyncAV and existing CRT pacing as well as the QuickOpt™ algorithm are shown in Figure 3A and 3B respectively. There was no difference in QRSd between existing CRT pacing and the QuickOpt™ algorithm.

There was no significant difference in QRSd between default SyncAV (offset -50) and manually adjusted SyncAV optimization ($P=0.17$). In 10 of the 34 included patients (29%), the default Sync AV setting (offset -50) achieved the optimal QRSd. In another 14 patients (41%), the difference in QRSd, between the default Sync AV setting and the manual SyncAV optimization, was ≤ 10 ms. However, in 6 of the 34 patients (18%), an alternative SyncAV setting (other than -50) reduced the QRSd by ≥ 10 ms; in 3 patients this was an offset of -30 ms and in the remaining 3 patients this was an offset of -70 or -90 ms.

In comparison to intrinsic conduction, there were 11 patients (32%) who did not have a decrease in QRSd with existing CRT pacing; 8 of these patients had a reduction in QRSd with SyncAV. In 79% of patients, SyncAV exclusively achieved the largest reduction in QRSd and in a further 9% SyncAV equaled the reduction achieved by existing CRT programming. Figure 4 illustrates the CRT setting that achieved the narrowest QRSd in each patient.

Univariate analysis showed an association between intrinsic QRSd, as well as existing CRT

pacing QRSd, and the reduction in QRSd with SyncAV (Table 2). After multivariate analysis, only QRSd with existing CRT pacing predicted a reduction in QRSd with SyncAV. Gender, age, time since implant, type of cardiomyopathy, NYHA class, intrinsic PR interval and LVEF did not predict a reduction in QRSd with SyncAV.

Discussion

The main finding of this analysis is that in patients with a previously implanted CRT device, further reduction in QRSd, and hence improvement in electrical synchrony, can be achieved using the SyncAV algorithm that leads to fusion of the triple wavefronts. The importance of these results is highlighted by recent evidence that a reduction in QRSd after CRT is well correlated with an increase in LVEF, currently the best indicator for clinical outcomes in heart failure patients. Coppola et al. examined the association between QRS narrowing and LV reverse remodelling and overall mortality in a cohort study of 311 patients. The authors found that a 12.5% narrowing of QRSd was associated with LV reverse remodelling at 6 months and a significant reduction in mortality (12). Furthermore, Karantzas et al. showed in a meta-analysis of 12 studies that CRT responders had narrower paced QRSd (post CRT) compared to CRT non-responders; both when defining response to CRT using clinical criteria (mean difference = -19.91 ms, 95% CI = -27.20 to -12.62 ms, $p < 0.00001$) as well as echocardiographic criteria (mean difference = -19.51 ms, 95% CI = -25.78 to -13.25 ms, $p < 0.00001$) (6).

QRS narrowing is a cheap and viable option for optimization of CRT that can be assessed easily during a clinic visit. Importantly, there was no significant difference between manually optimized SyncAV and the default SyncAV offset of -50 ms. This is especially relevant given the relatively time-consuming nature of manual ECG based optimization. However, in 18% of patients a manually optimized SyncAV offset achieved a significantly narrower QRS compared to the

default SyncAV setting and further work is required to identify these patients. Numerous options have been explored to optimize CRT. Several studies including randomized controlled trials have failed to show a benefit when echocardiography is used to guide CRT. In the echoCRT trial, patients with heart failure, dysynchrony on echocardiography and a QRS duration of less than 130 ms did not have benefit with CRT (13). In the PROSPECT trial, there was no echocardiographic measure that could predict response to CRT (14). In addition to the limited results, echocardiographic optimization is hampered by its time-consuming and operator-dependent nature as well as the technical difficulty in maintaining position and stability during the different pacing intervals (15).

Whether QRS reduction, beyond that seen after initial implantation, is associated with improved outcomes remains unclear. Yang et al. assessed a cohort of patients who were undergoing generator replacement. They found that super-responders and responders to CRT had further reductions in paced QRSd during follow-up. Patients who experienced further narrowing of the QRS complex, by ≥ 10 ms, after 6 months had a significant reduction in all-cause mortality. Therefore, it appears that QRS narrowing is a marker of reverse remodelling. Our finding of a significant reduction of QRSd achieved by activating SyncAV at a mean of 18 months post-implant indicates an opportunity for further reverse remodelling with simple device programming, though these finding need to be correlated with clinical and echocardiographic outcomes.

Non-response remains the greatest challenge to CRT with numerous efforts to improve patient selection. However, the proportion of non-responders is still high at around 30% (2). Our results are encouraging in that of the 32% of patients who did not experience a reduction of QRSd with existing CRT programming, 73% had significant reduction in QRSd with SyncAV. Non-responders to CRT are at high risk of major adverse cardiac events compared to responders and

the lack of response to CRT remains its greatest challenge (16). Our results showing the potential to produce a narrower QRS and possibly improve response to CRT in this patient population is encouraging.

Identifying patients who would potentially benefit from optimization of CRT programming remains problematic. While studies have shown that factors such as a wider QRS, female gender, left bundle branch block morphology and non-ischemic cardiomyopathy help predict response to CRT prior to device implantation and may therefore aid in patient selection, identifying those who may have further response is not clear (16). We demonstrate that a wide QRS at follow-up may identify a sub-group who may benefit from CRT optimization, specifically with SyncAV programming and potentially with other algorithms. Interestingly, we showed that optimization using SyncAV significantly reduced QRSd compared to another device-based algorithm that is currently used, QuickOpt™ (7).

This was a single-center retrospective study with its inherent limitations. While the sample size is relatively small, this is due to the limited number of patients with an existing CRT device with SyncAV algorithm at our centre, and the proportion of these patients for whom the algorithm is programmable (i.e., this algorithm is not useful in patients with AV block or atrial fibrillation). The current study was limited to electrocardiographic data and needs to be further corroborated with echocardiography and clinical outcomes in larger studies.

Conclusion

Manual ECG-based atrio-ventricular delay optimization using SyncAV significantly improved electrical synchrony in patients with a previously implanted CRT. Further studies are required to delineate the clinical and hemodynamic effects of using SyncAV in patients with

chronically implanted CRT devices.

Author contributions

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Figure legends

Figure 1. Flow diagram for patient selection

Figure 2. The change in QRS duration (milliseconds) using existing CRT, QuickOpt™ and SyncAV compared to intrinsic conduction

Figure 3. The differences in the change in QRS duration achieved by SyncAV compared to A) existing CRT and B) QuickOpt™

Figure 4. Proportion of patients who achieved the narrowest QRS stratified by CRT setting

Table 1. Patient characteristics

Characteristic	N=34
Male, n (%)	19 (56)
Age, year (range)	74 (60-93)
Time since implant in months, mean (range)	17.8±8.5
Ischemic cardiomyopathy, n (%)	21 (62)
Hypertension	28 (82)
Diabetes mellitus	8 (24)
Paroxysmal atrial fibrillation	10 (29)
Left bundle branch block	31 (91) *
Cardiac resynchronization therapy defibrillator	22 (65)
NYHA, n (%)	
I	4 (11.8)
II	24 (70.6)
III	6 (17.6)
QRS (ms)	163.5±24.3
Intrinsic PR interval (millisecond)	187.2±36.6
Left ventricular ejection fraction (%)	24.1±10.1
Medical therapy for heart failure	
ACEI/ARB	28 (82)
Beta blocker	28 (82)
MRA	5 (15)

*The remaining 3 were bi-fascicular block (right bundle branch block and left anterior fascicular block or left posterior fascicular block)

N= number; NYHA= New York Heart Association; ACEI= angiotensin converting enzyme inhibitor; ARB= angiotensin receptor blocker; MRA= mineralocorticoid receptor antagonist.

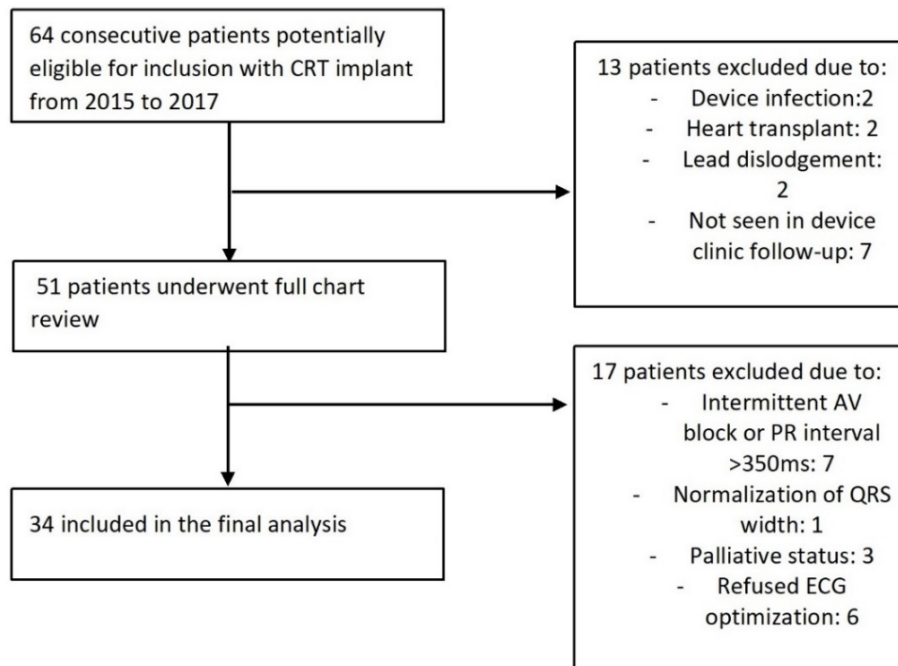


Figure 1.

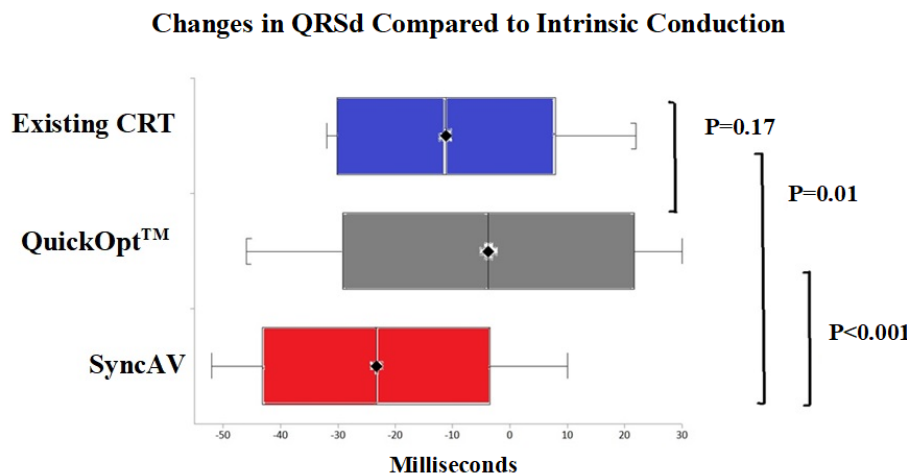
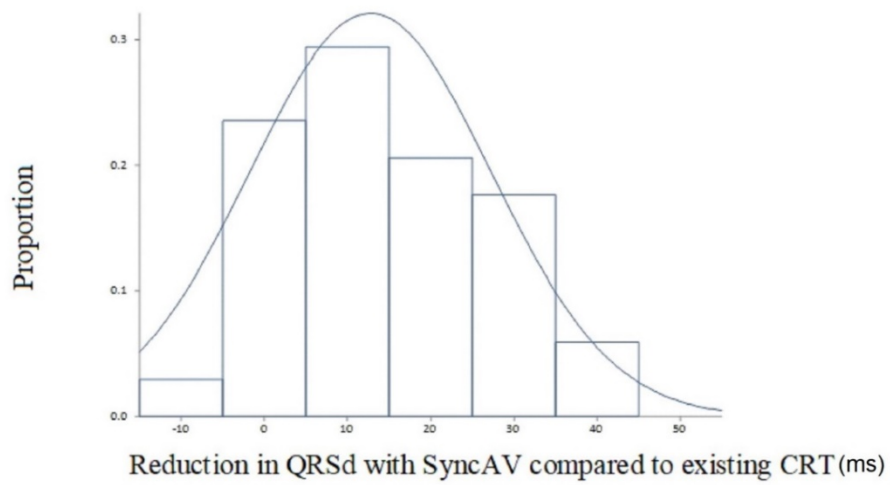


Figure 2.

A)



B)

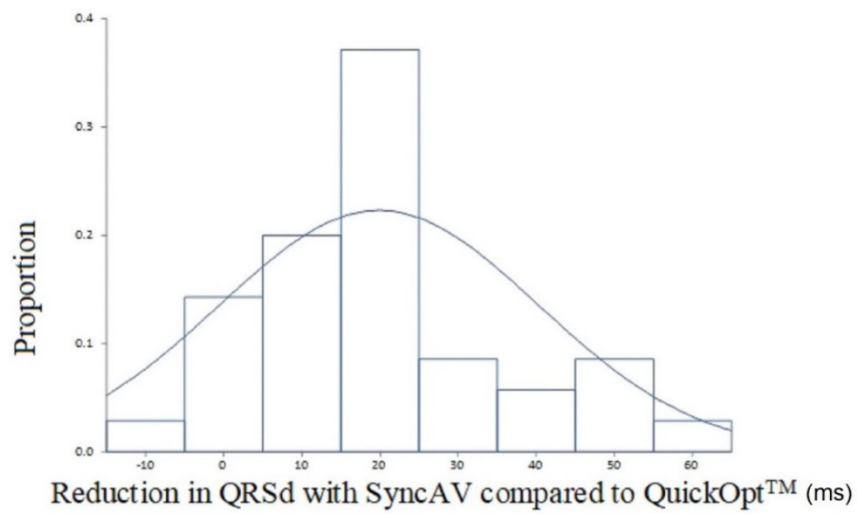
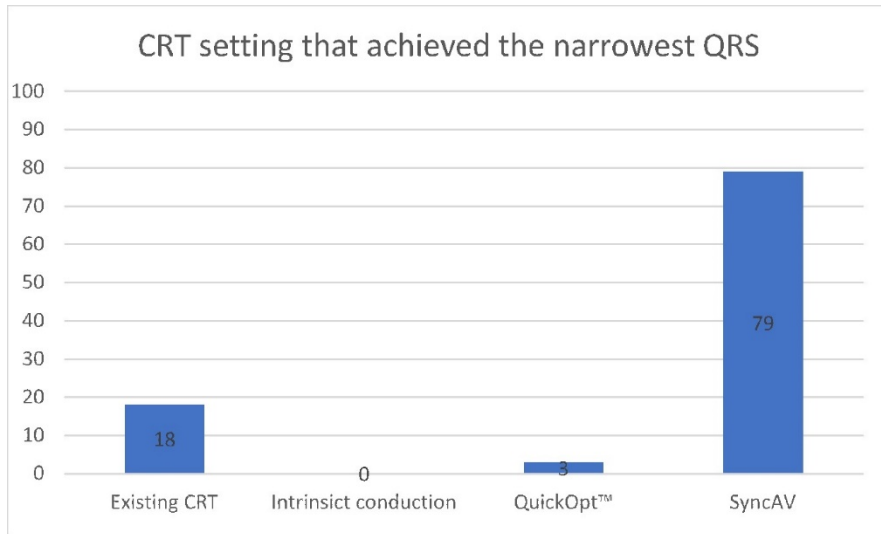


Figure 3.



Proportion of patients who achieved the narrowest QRS stratified by CRT setting. In 50% of the patients included above as achieving the narrowest QRS with existing CRT, SyncAV achieved the same QRS duration. CRT: cardiac resynchronization therapy

Figure 4.

CHAPTER 4:

Optimization of Chronic Cardiac Resynchronization Therapy using Fusion Pacing

Algorithm Improves Echocardiographic Response

4.1 Preface to the second manuscript

Considering the relevant QRS narrowing and the apparent feasibility of the automatic fusion pacing algorithm, we reassessed the patients at 6 months post optimization to evaluate clinical and echocardiographic improvement. With this information, we calculated the reduction on non-responders' rate.

The manuscript has been published in the Canadian Journal of Cardiology Open and should be referenced as follows:

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4.2 Manuscript #2

Optimization of Chronic Cardiac Resynchronization Therapy using Fusion Pacing Algorithm Improves Echocardiographic Response

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Abstract

Background: Whether reprogramming of cardiac resynchronization therapy (CRT) to increase electrical synchrony translates into echocardiographic improvement remains unclear. SyncAV is an algorithm that allows fusion of intrinsic conduction with biventricular pacing. We aimed to assess whether reprogramming chronically implanted CRT devices with SyncAV is associated with improved echocardiographic parameters.

Methods: Patients at a quaternary center with previously implanted CRT devices with programmable SyncAV algorithm underwent routine ECG-based SyncAV optimization during regular device clinic visits. This analysis included only patients who could be programmed to the SyncAV algorithm (i.e., in sinus rhythm with intrinsic AV conduction). Echocardiography was performed prior to and 6 months after CRT optimization.

Results: Of 64 consecutive, potentially eligible patients who underwent assessment, 34 patients who were able to undergo SyncAV programming were included. The mean age was 74 ± 9 years, 41% were female and 59% had ischemic cardiomyopathy. The mean time from CRT implant to SyncAV optimization was 17.8 ± 8.5 months. At 6-month follow-up, SyncAV optimization was associated with a significant increase in left ventricular ejection fraction (mean LVEF $36.5\% \pm 13.3\%$ versus $30.9\% \pm 13.3\%$; $P < 0.001$) as well as a reduction in left ventricular end-systolic volume (mean LVESV $110.5\text{ml} \pm 57.5\text{ml}$ versus $89.6\text{ml} \pm 52.4\text{ml}$; $P < 0.001$) compared to baseline existing CRT programming.

Conclusion: CRT reprogramming to maximize biventricular fusion pacing significantly increased LVEF and reduced LVESV in patients with chronic CRT devices. Further studies are needed to

assess if a continuous fusion pacing algorithm improves long-term clinical outcomes, and to identify which patients are most likely to derive benefit.

Key words: biventricular pacing; cardiac resynchronization therapy; fusion pacing; heart failure

Condensed abstract

We assessed whether reprogramming chronically implanted CRT to achieve fusion pacing is associated with an improvement in echocardiographic parameters. After SyncAV ECG optimization, an associated improvement in LVEF, LVESV, MR severity, LVEDV and PASP was noted including among previous CRT non-responders. There was no difference in NYHA functional class.

Introduction

Cardiac resynchronization therapy (CRT) decreases cardiovascular mortality and symptoms in heart failure patients (1). However, a lack of response to CRT remains its greatest challenge (2). The ideal method to optimize CRT post-implantation is controversial. Echocardiography has been used for CRT optimization (3). However, routine CRT settings are used for the majority of CRT implants due to the complex and time-consuming nature of echocardiographic optimization (4). In an international survey, 58% of electrophysiologists did not optimize atrioventricular (AV) and ventriculo-ventricular (VV) delays (5). Utilizing the electrocardiogram (ECG) would therefore be an inexpensive and practical process for CRT optimization (4). Narrowing of the QRS complex with biventricular pacing (the paced QRS duration, QRSd) has been shown to correlate with clinical and echocardiographic improvement (6, 7) as well as long-term mortality (8). One study has also reported that ECG-based optimization using the measurement of the narrowest QRS is comparable to echocardiography-based optimization with regards to LV reverse remodeling (9).

SyncAV is a device-based algorithm which is available in some Abbott manufactured CRT devices. The algorithm alters the AV delay to allow biventricular pacing synchronized with intrinsic AV conduction. (10). To achieve fusion between intrinsic conduction and biventricular pacing, the device continuously adjusts the AV delay by a set duration (programmable offset between 10 to 120 ms) relative to the measured intrinsic AV conduction interval. This process is dynamic and adjusts according to variations in device measured intrinsic conduction time, thereby resulting in continuously adapting fusion pacing. Fusion pacing can also be achieved by fusion of left ventricular pacing and intrinsic conduction (11). The concept of fusion optimized interval (FOI) was previously described by Arbelo *et al* who demonstrated a reduction in QRS duration and an

acute improvement in hemodynamics compared to nominal CRT programming (12). The same finding was also described by Varma *et al.* during a De novo implant prospective study using the specific SyncAV algorithm described above (10). Recently published data reported a significant QRS narrowing with programming of SyncAV in existing CRT devices as determined acutely by 12 lead ECG but did not report longer term outcomes (13, 14). The pacing configuration that achieved the narrowest QRS with SyncAV was biventricular pacing with SyncAV and an optimized offset (10, 14).

Whether reprogramming of CRT to increase electrical synchrony translates into echocardiographic and functional status improvement remains unclear. We aimed to assess whether reprogramming with SyncAV is associated with an increase in left ventricular ejection fraction (LVEF) and a decrease in left ventricular end-systolic volume (LVESV) compared to routine CRT programming in patients with chronic CRT devices.

Methods

Study population

Patients at a single quaternary cardiac center (McGill University Health Center, Montreal, Canada) with a CRT defibrillator (CRT-D) or a CRT pacemaker (CRT-P) with programmable SyncAV algorithm (St-Jude Unify Assura™ and Quadra Assura™, or St-Jude Allure Quadra™ RF) implanted between January 2014 and November 2017 were evaluated for SyncAV optimization starting May 2018. The flow diagram for patient selection is shown in Figure 1. Of the 64 potentially eligible consecutive CRT implants, we excluded patients with device explant, lead dislodgement, loss to follow-up, loss of required AV conduction (preventing use of SyncAV algorithm), transition to palliation or refusal of optimization. The remaining 34 patients had ECG-

based optimization performed and were included in this analysis. This study was approved by the McGill University Health Center Institutional Review Board and patients included in the study fulfilled criteria for CRT implantation as per Canadian Cardiovascular Society guideline recommendations (15).

Device programming

Details for ECG-based SyncAV optimization were as previously described (14). In brief, all patients at our center were programmed according to operator preference (without use of SyncAV) until December 2017 when ECG-based CRT optimization became the standard of care for newly implanted devices. Routine in-clinic CRT optimization was performed starting May 2018 for patients with chronically implanted devices according to our protocol including sequential ECGs (14). When programming with SyncAV, the optimal offset achieving the narrowest QRS was used.

Standard programming prior to the SyncAV optimization involved programming as set by the treating physician according to their standard clinical practice; there was no mandated programming protocol. This programming may have been nominal settings or settings selected by the treating physician (considering baseline ECG and post-op paced ECG to guide programming). None of the patients were previously programmed using the SyncAV algorithm.

The SyncAV algorithm has been described previously (13, 14). In brief, the SyncAV algorithm periodically extends the atrio-ventricular delay. When intrinsic ventricular events are sensed, the device reprograms the atrio-ventricular delay to a programmed shorter offset (default offset -50ms) than the measured intrinsic AV interval. The offset can be programmed over a range of values to find the ideal offset that achieves electrical synchrony for each patient. The device

was then programmed at that “ideal” offset for each patient.

Electrocardiographic measurements

Standard 12-lead electrocardiography was performed at a paper speed of 25 mm/s and a scale of 10 mm/mV and QRS duration was measured automatically by the ECG machine (GE MACTM 5500 HD Resting ECG System) as previously described (14). The ECG machine is programmed to measure the earliest onset of the QRS and the latest offset; this translates into the duration from the pacemaker spike until the end of the QRS. QRS duration was subsequently validated manually by a single investigator who was blinded to the clinical data and pacing programming.

Echocardiographic and clinical outcomes

At the baseline visit in which SyncAV programming was activated, all patients had a clinical assessment including determination of NYHA functional class as well as a transthoracic echocardiogram. All patients were scheduled for a clinical follow-up and a transthoracic echocardiogram 6 months post-optimization. NYHA functional class, LVEF, LVESV and mitral regurgitation (MR) severity as assessed on a grade scale (0= none or trivial, 1= mild, 2= moderate, 3= moderate to severe and 4 =severe) (16) were recorded. Other echocardiographic measurements included left ventricular end diastolic volume (LVEDV) and pulmonary artery systolic pressure (PASP). LVESV and LVEDV were measured in the apical four chamber and apical two chamber views and then averaged; LVEF was calculated using Simpson’s biplane method. The echocardiograms were read by level III trained echocardiographers who were unaware of device programming.

We defined a positive LVEF response to CRT as an absolute increase in LVEF $\geq 10\%$; we

find this value to be of clinical relevance. Previous studies have used cut-offs ranging from 5-15% (17). LVEF response was assessed ≥ 6 months after initial implant procedure (compared to LVEF prior to CRT implant), and LVEF response was subsequently reassessed 6 months after SyncAV ECG optimization (compared to LVEF immediately prior to SyncAV ECG optimization). In addition, response as measured by a $\geq 15\%$ decrease in LVESV was also assessed 6 months after SyncAV ECG optimization compared to LVESV prior to SyncAV ECG optimization; the LVESV response after initial CRT could not be assessed due to the absence of data regarding LVESV prior to initial CRT.

Statistical analysis

All data are presented as mean $\pm$ SD for continuous variables and as proportions for categorical variables. A paired t-test was used to compare outcomes prior to and 6 months after SyncAV optimization. A P-value of <0.05 was considered statistically significant. Statistical analysis was performed using StatsDirect 3 (England: StatsDirect Ltd. 2013).

Results

Patient characteristics

Patient characteristics at time of SyncAV optimization are summarized in Table 1. At 6 months of follow-up, 94% of patients had complete clinical and echocardiographic data. The mean age was 74 ± 9 years, 41% were female and 59% had ischemic cardiomyopathy. The mean time from CRT implant to SyncAV optimization was 17.8 ± 8.5 months. At the time of SyncAV optimization, the mean intrinsic conduction QRSd was 163 ± 24 ms, the mean existing CRT pacing QRSd was 152 ± 25 ms, and the SyncAV optimized mean QRSd was 138 ± 23 ms.

In terms of response to CRT, the mean LVEF was 24.1 ± 10.1 prior to initial CRT

implantation, and with standard CRT programming, 44% of patients had had a significant improvement in LVEF (LVEF responders $\geq 10\%$) while the remaining 56% had not improved their LVEF $\geq 10\%$ and were deemed CRT LVEF non-responders.

Left ventricular ejection fraction

The mean LVEF prior to SyncAV optimization was $30.9\% \pm 13.3\%$ (median 27.5%, interquartile range 20% to 40%) and after 6 months increased to $36.5\% \pm 13.3\%$ (median 40%, interquartile range 25% to 50%); The mean difference in LVEF was 6.3%, 95% confidence interval (CI)= 3.1%-9.5%, $P < 0.001$ (Figure 2A). Of the 32 patients with follow up LVEF, 40% had an increase $\geq 10\%$, including 9% who had an increase $> 15\%$. In addition, a further 19% of patients had an increase of $\geq 5\%$ but not reaching 10%, and the remaining (41%) had no significant change in LVEF (Figure 3). Of those who had not responded to initial CRT (19, 56%), 9 patients (47%) had a significant improvement in LVEF (LVEF responders, $\geq 10\%$) while 10 patients (53%) remained non-responders after SyncAV optimization (Figure 4); this increased the proportion of total LVEF responders to 71%. In contrast, 33% of those who had already responded to initial CRT had a significant further improvement in LVEF ($\geq 10\%$). No patient had a significant reduction in LVEF ($> 5\%$).

In patients who responded to initial CRT, mean LVEF increased from $41.1\% \pm 9.6\%$ to $45.4\% \pm 8.2\%$ ($P = 0.01$) after SyncAV ECG optimization. In patients who did not respond to initial CRT, mean LVEF increased from $23.4\% \pm 10.6\%$ to $31.4\% \pm 13.3\%$ ($P < 0.001$) after SyncAV ECG optimization (Supplementary Figure S1). There was no difference in change in LVEF after SyncAV optimization between those who had initially responded and those who had not ($P = 0.24$).

Left ventricular end systolic volume

Mean LVESV prior to SyncAV optimization was 110.5ml±57.5ml and after 6 months decreased to 89.6ml±52.4ml; the mean difference in LVESV was -19.0ml, 95% CI= -8.3 to -29.6, P<0.001 (Figure 2B). After SyncAV ECG optimization, 17 patients (53%) had a significant decrease ≥15% in LVESV. Of these patients, 7 (41%) were already LVEF responders after initial CRT and 10 (59%) did not have an LVEF response after initial CRT.

Mitral regurgitation

After optimization with SyncAV, there was a significant reduction in the severity of MR (mean MR grade 0.9±1.0 prior to SyncAV versus 0.5±1.0 post SyncAv optimization; P<0.001) (Figure 5). Prior to SyncAV optimization 41% of patients had no or trivial MR, 41% had mild MR, 16% had moderate to severe MR and 3% had severe MR. At 6 months of follow-up post SyncAV optimization, 68% had no or trivial MR, 16% had mild MR, 16% had moderate to severe MR and none had severe MR. The distribution of MR severity is shown in Figure 6.

Other echocardiographic measurements

Mean LVEDV prior to SyncAV optimization was 157.5 ml±56.6ml and after 6 months decreased to 141.3 ml±55.7 ml; the mean difference in LVEDV was -14.1.ml, 95% CI= -3.1. to -25.2, P=0.007. PASP also decreased after SyncAV ECG optimization. Mean PASP was 37.5 mmHg ± 14.7mmHg prior to SyncAV optimization and decreased to 32.9 mmHg ± 10.3 at 6 months after optimization (mean difference -4.2 mmHg, 95% CI -0.3 to -8.1, P=0.04)

NYHA and medication use

No significant difference in NYHA functional class was observed after SyncAV optimization (mean NYHA 2.1±0.5 prior to SyncAV versus 2.0±0.5 post SyncAV optimization; P=0.16). The distribution of NYHA functional class is summarized in Supplementary Figure S2.

There was no significant difference in the use of heart failure medication (Supplementary Table S1).

Discussion

The main finding of this analysis is that in patients with chronically implanted CRT devices, optimization using a biventricular fusion-pacing algorithm to achieve further reduction in QRSd was associated with a significant increase in LVEF at 6 months following optimization. To the best of our knowledge, this is the first study to demonstrate that an increase in electrical synchrony is associated with echocardiographic improvement in chronically implanted CRT patients, irrespective of previous responder status, using an easy, quick, and reproducible ECG-based optimization that can be performed during a regular device clinic follow up visit. Echocardiographic response to CRT has been assessed using cut-offs of an increase in LVEF $\geq 5\%$ and a decrease in LVESV $\geq 10\%$ (18, 19). A combination of an LVEF improvement $\geq 5\%$ and LVESV reduction $\geq 10\%$ were shown to be the best predictor for improved survival (20). In this analysis, stricter cut-offs of an increase in LVEF $\geq 10\%$ and a decrease in LVESV $\geq 15\%$ were used to provide a more specific indicator of CRT response.

Another important finding is the high proportion of patients (44%) classified as non-responders following initial CRT therapy who subsequently had a significant improvement in LVEF (at least 10% absolute LVEF increase) after optimization using SyncAV. In addition to conversion of non-responders to responders, QRS narrowing and a further increase in LVEF (at least 10%) were also seen in 1 in every 3 patients who already responded to initial CRT therapy, demonstrating a further improvement in electrical and mechanical synchrony. Importantly, none of the patients has QRS widening or worsening in the LVEF or MR at 6 months following continuous CRT optimization using the SyncAV algorithm. Trucco et al. showed that baseline

manual optimization of the AV and VV delays, to achieve biventricular fusion pacing, immediately post-implantation leads to a greater proportion of patients achieving both electrical synchrony and LV reverse remodelling at 12 months (21). Our study validates the long-term effect of an automated continuously optimized biventricular fusion-pacing algorithm.

Unfortunately, CRT device optimization is not routinely performed as revealed in the international survey by Gras et al. Around 58% of electrophysiologists do not optimize CRT post-implantation and just used the nominal settings (4). Part of this issue is probably related to the time consuming and complex nature of echocardiographic and intrinsic electrogram based optimization (4). In addition, multiple studies have shown a lack of benefit of these approaches compared to routine out-of-the-box settings (22). Even in studies that used an ECG-based optimization, the ECG analyses were performed with a paper speed between 50 mm/s to 300 mm/s, utilized computerized recording systems and required experienced observers for QRS width measurement (12, 21). In contrast, we used the standard 12-lead surface ECG at a regular speed of 25 mm/s with automated measurements, which are faster, accurate and easily reproducible.

Our study was unable to demonstrate a significant improvement in NYHA functional class status, though no patient had a worsening of functional status. The QRS narrowing observed during our analysis (152 ± 25 ms during the baseline evaluation to 138 ± 23 ms after optimization) was similar to that observed in other studies that assessed fusion pacing (4, 7). Reassuringly, such a reduction in QRSd has been shown to correlate with clinical outcomes. In a meta-analysis, Korantzopoulos et al. showed that QRS narrowing is a strong predictor of clinical and echocardiographic response (or super response) to CRT (7). Left ventricular fusion pacing has been tested using the AdaptiveCRT algorithm which periodically assesses intrinsic conduction; during normal AV conduction only LV-pacing is provided while biventricular pacing with adjustments of

the ventriculoventricular timing occurs during prolonged AV conduction (23, 24). AdaptiveCRT has been shown to be non-inferior to nominal CRT with suggestion of improvements in clinical status, echocardiographic parameters and clinical outcomes as well as a reduction in the incidence of atrial fibrillation particularly in patients with normal AV conduction (23-26). A large prospective, randomized, controlled, multicentre, clinical trial is underway to assess the impact of AdaptiveCRT on cardiovascular outcomes (27).

Identifying predictors of non-response to CRT remains a great challenge. Despite important advances to improve patient selection based on clinical characteristics, QRS duration and QRS morphology, the frequency of non-response to CRT continues to be a major issue (2, 28). Our results suggest that in a considerable proportion of these patients, if sinus rhythm with intrinsic AV conduction is present, a fusion pacing algorithm can improve electrical and mechanical synchrony.

Limitations

This is a single-center study with a limited sample size and 6 months of follow-up following SyncAV optimization. However, significant improvements in LVEF were demonstrable and correlated with QRS narrowing. It is noteworthy that clinical improvement after CRT usually coincides with electrical synchrony as well as LV reverse remodelling and an increase in LVEF (7, 29, 30). Furthermore, previous data indicate that patients who respond to CRT in the first 6 months are likely to have further improvement in LVEF at the 1- and 2-year marks (31). While the trajectory for LVEF after initial CRT cannot be definitively ascertained, most studies assess CRT response at 6 months or 12 months, and the vast majority of responders usually show improvement at 6 months (18, 19, 32). In this study, the mean time from implantation of CRT to initial programming of SyncAV was 17.8 ± 8.5 months and the results of this study assess echocardiographic parameters prior to and 6 months after SyncAV optimization. In addition, we

used stricter cut-offs for LVEF and LVESV to increase the robustness of our results. The study is well powered for the detection of changes in QRSd and LVEF but not for clinical outcomes. Whether the improvement in LVEF translates into better clinical outcomes will require larger randomized studies with longer term follow-up. A randomized trial of around 200 patients is currently underway and will provide such much-needed insight (NCT03961399). In addition, larger studies will be needed to identify predictors of response to SyncAV optimized pacing. Finally, the determination of response to CRT was based on LVEF and not LVESV due to lack of LVESV data prior to initial CRT. However, while LVESV is a sensitive marker for LV reverse remodelling, an LVEF increase $\geq 10\%$ is likely to reflect a more clinically meaningful echocardiographic improvement and if anything may underestimate the response to SyncAV. In addition, we have provided the LVESV data prior to and after SyncAV optimization. The time from initial CRT implant to pre-SyncAV echo varied in each patient but the time pre and post SyncAV was very similar at around 6 months.

Conclusion

ECG-based CRT optimization using an algorithm to achieve biventricular pacing fused with intrinsic conduction significantly improved electrical synchrony and LVEF in chronically CRT-paced patients. Improved ventricular function at 6 months following CRT optimization was independent of prior response to conventional CRT. This clinic-based method was a simple, safe and effective means to optimize previously implanted CRT devices. Larger randomized studies are required to compare long-term clinical outcomes between dynamically optimized biventricular fusion pacing and traditional biventricular CRT pacing to inform whether patients with chronic CRT devices with this algorithm should be reprogrammed.

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Disclosures

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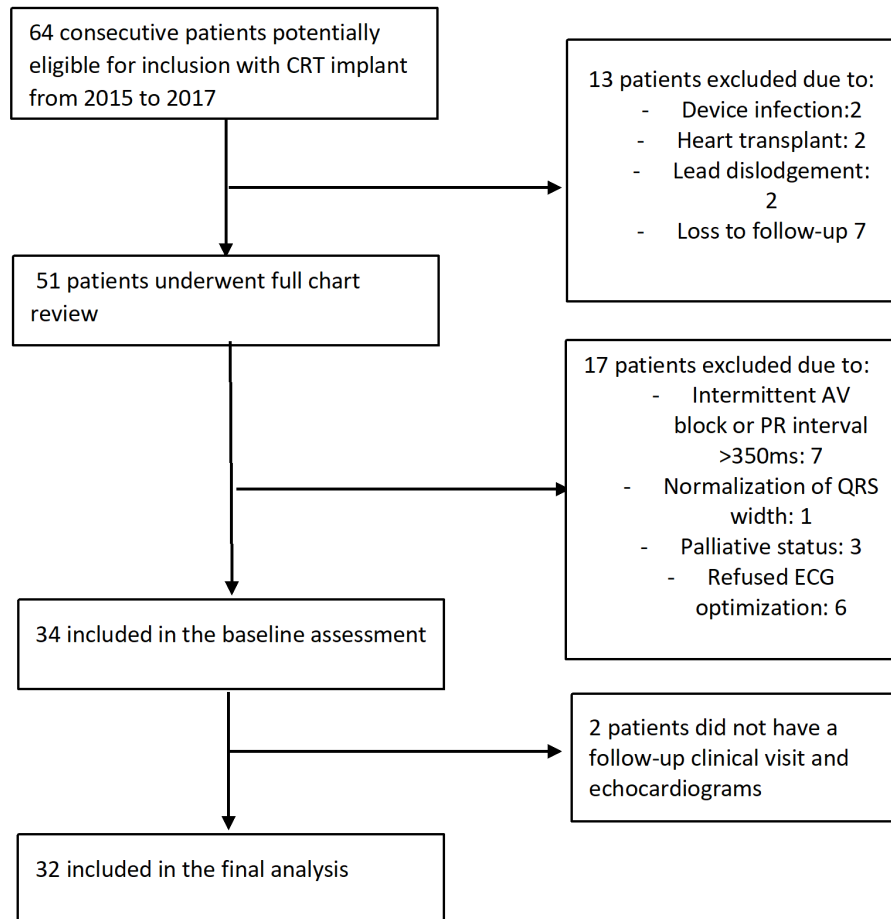
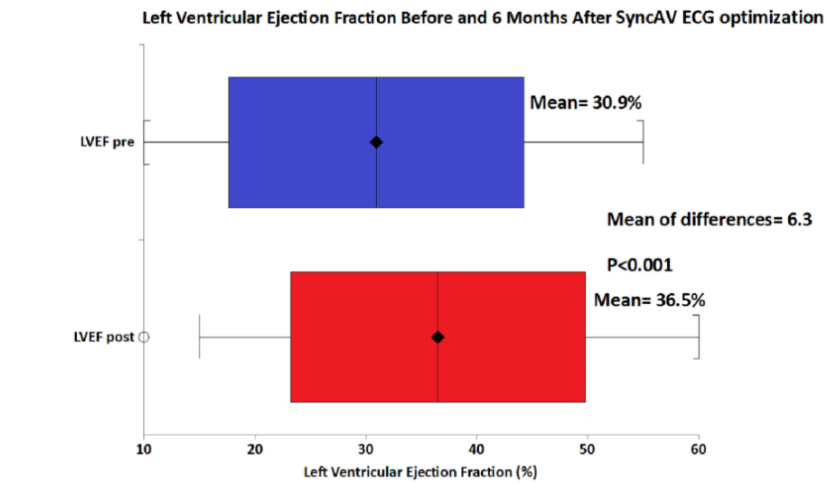
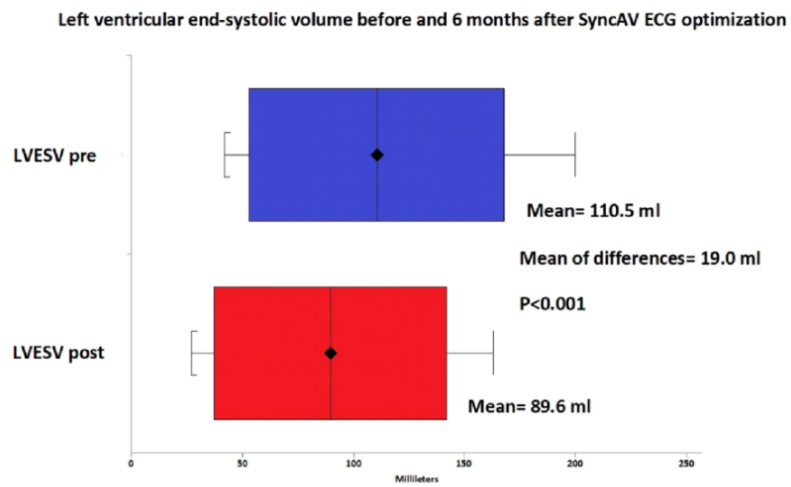


Figure 1.



A)



B)

Figure 2.

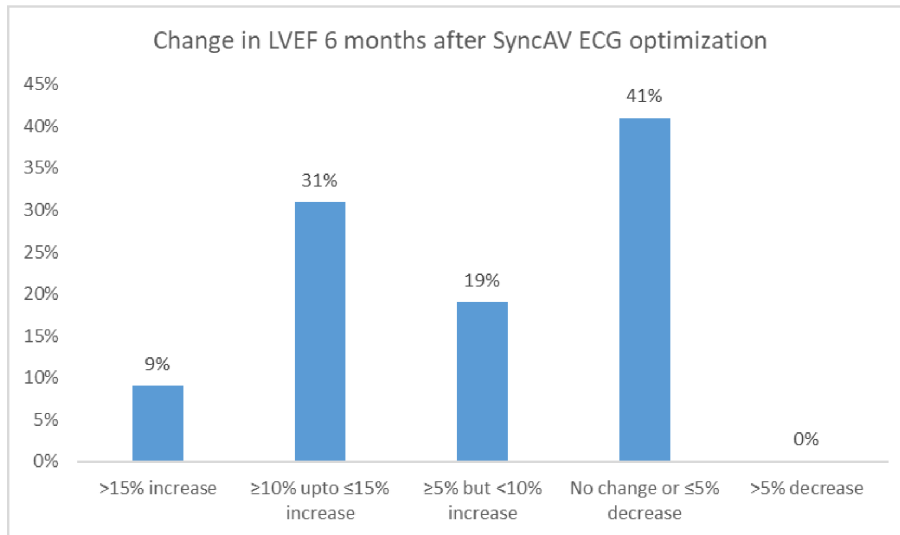
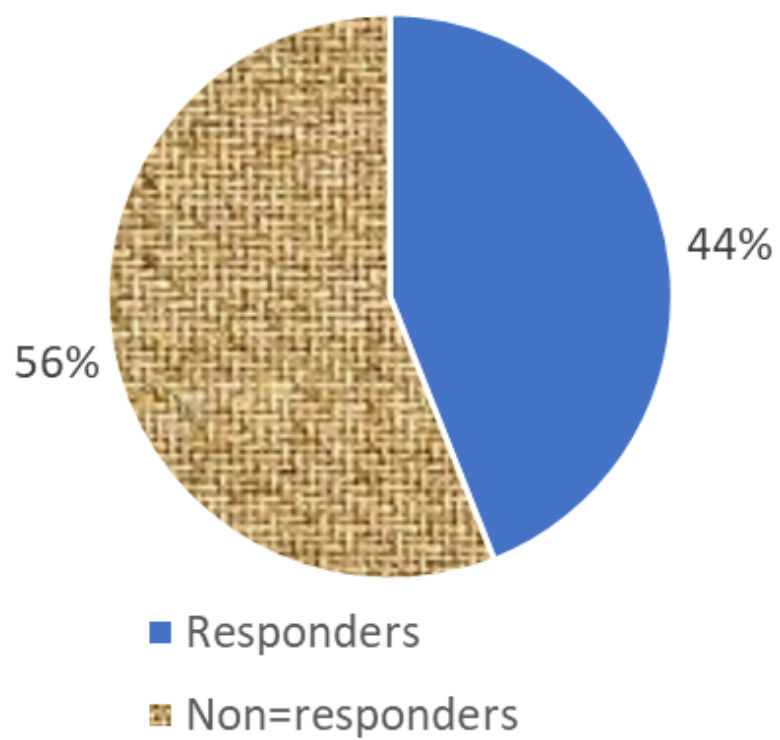


Figure 3.

A)



B)

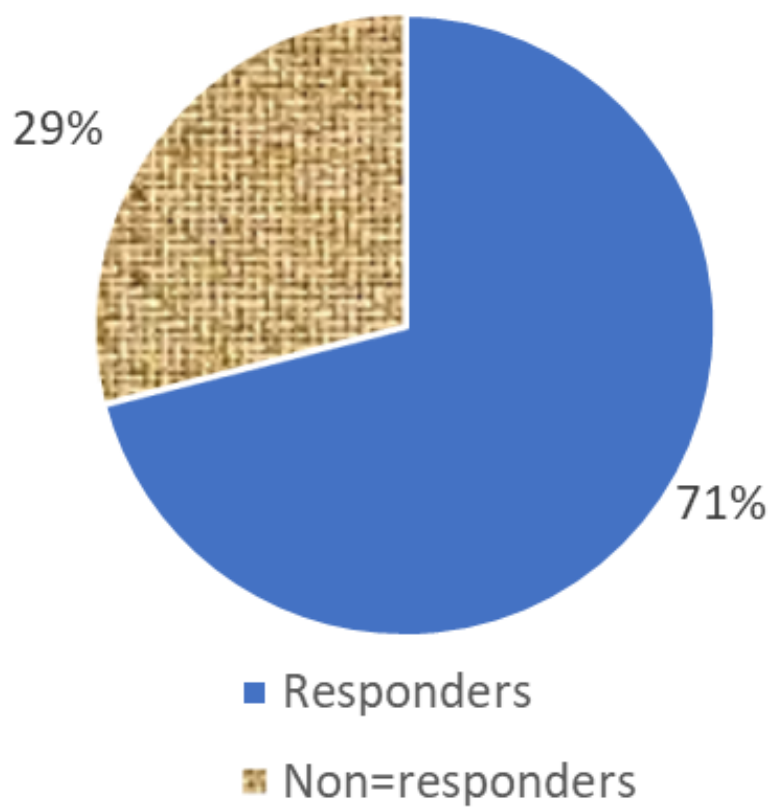


Figure 4.

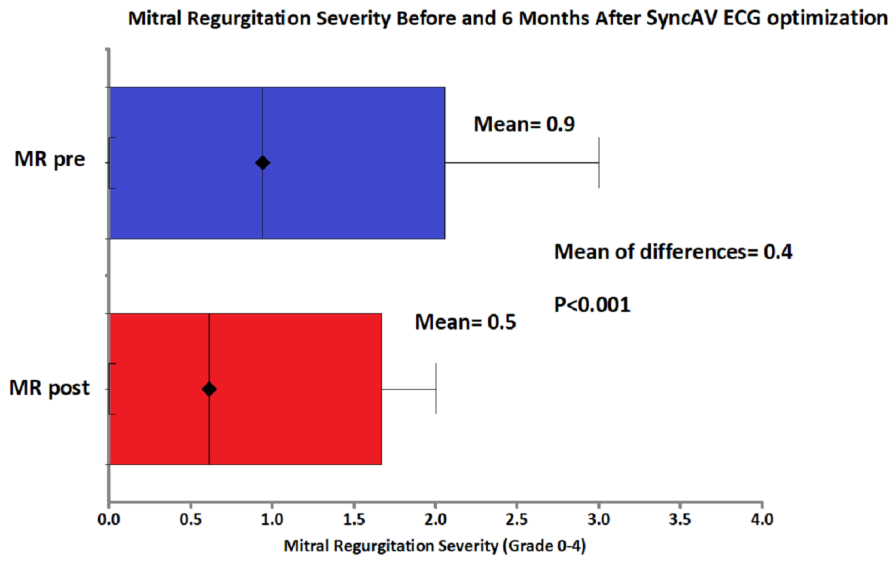


Figure 5.

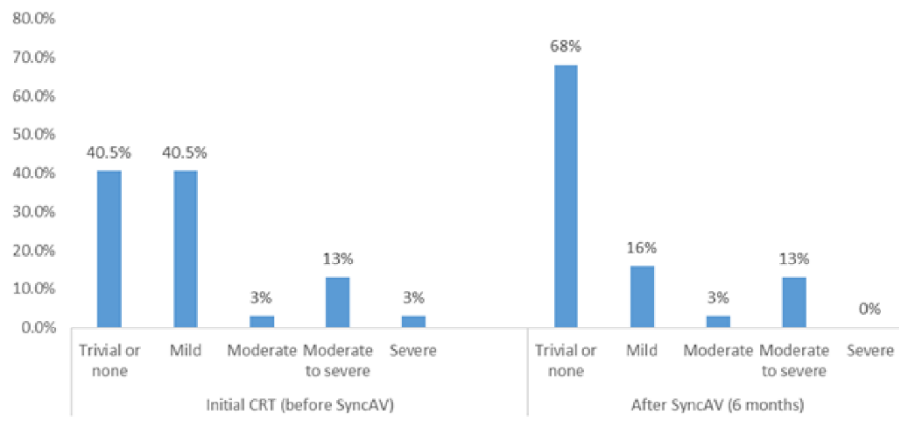


Figure 6.

CHAPTER 5:

Fusion Pacing in Patients with Right Bundle Branch Block who Undergo Cardiac

Resynchronization Therapy

5.1 Preface to the third manuscript

After the initial data analysis and the reasonable evidence that the fusion pacing is related to QRS narrowing and echocardiographic improvement, reducing the rate of non-responders, we decided to apply the new algorithm to RBBB patients, which is a population with traditional lower rate of CRT response.

The manuscript has been published in the Journal of Electrocardiology, and should be referenced as follows:

A. AlTurki, P.Y. Lima, A. Vidal et al. Journal of Electrocardiology 64 (2021) 66–71

5.2 Manuscript #3

Fusion Pacing in Patients with Right Bundle Branch Block who Undergo Cardiac Resynchronization Therapy

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Running title: Fusion pacing in RBBB

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Abstract

Purpose: Patients with right bundle branch block (RBBB) are less likely to respond to cardiac resynchronization therapy (CRT). We aimed to assess whether patients with RBBB respond to CRT with biventricular fusion pacing.

Methods: Consecutive patients with RBBB at a single tertiary care center, who were implanted with a CRT device capable of biventricular fusion pacing using SyncAV programming, were assessed and compared to a historical cohort of CRT patients with RBBB. QRSd was measured and compared during intrinsic conduction, nominal CRT pacing and manual electrocardiogram-based optimized SyncAV programming. Left ventricular ejection fraction (LVEF) was also compared before and 6 months after CRT.

Results: We included 8 consecutive patients with RBBB (group 1) who were able to undergo SyncAV programming and 16 patients with RBBB (group 2) from a historical cohort. In group 1, compared to mean intrinsic conduction QRSd (155 ± 13 ms), mean nominally-paced QRSd was 156 ± 15 ms (Δ QRSd 1.3 ± 11.6 ; $p=0.77$) and SyncAV-optimized paced QRSd was 135 ± 14 ms (Δ QRSd -20.0 ± 20.4 ; $p=0.03$ and Δ QRSd -21.3 ± 16.3 ; $p=0.008$; compared to intrinsic conduction and nominal pacing respectively). In group 2, mean QRSd with nominal pacing was 160 ± 24 ms (Δ QRSd 3.8 ± 33.4 ; $p=0.66$ compared to intrinsic conduction). In group 1, baseline LVEF was 22.1 ± 11.5 and after 6 months of follow-up was 27.8 ± 8.6 ($p=0.047$). In group 2, the baseline LVEF was 27.2 ± 10.6 and after 6 months of follow-up was 25.0 ± 10.0 ($p=0.45$).

Conclusions: CRT programed to allow biventricular fusion pacing significantly improved electrical synchrony and LVEF in patients with RBBB. Larger studies are required to confirm these findings.

Key words: cardiac resynchronization therapy; fusion pacing

Introduction

Cardiac resynchronization therapy (CRT) is an important therapeutic modality in patients with heart failure and reduced ejection fraction, who have left bundle branch block (LBBB) (1). CRT, in this population, reduces cardiovascular death and heart failure hospitalization (2). It is well known that in those with non-LBBB morphology, the response to CRT is significantly lower (3, 4). In particular, those with right bundle branch block (RBBB) are less likely to respond to CRT. In 2016, a sub-analysis of the MADIT-CRT trial found no overall clinical benefit with CRT in those with non-LBBB, including the sub-group with RBBB (5). One possible mechanism is that biventricular pacing does not lead to improved electrical synchrony. In an analysis of electrical synchrony after CRT, Hadjis et al. showed that those with non-LBBB were unlikely to achieve improved electrical synchrony and consequently reverse remodelling after CRT (6). Another study targeting the site of latest electrical activation when implanting the left ventricular lead in patients with non-LBBB did not result in improved outcomes (7).

SyncAV is a closed-loop algorithm that dynamically adjusts the atrioventricular (AV) delay to continuously synchronize biventricular pacing with intrinsic AV conduction. By periodically extending the AV delay, the device examines intrinsic ventricular events that are sensed (8-11). A shortening between 10 to 120 ms (default 50ms) of the AV delay, relative to the measured intrinsic AV conduction interval, is programmed to allow fusion between intrinsic AV conduction and biventricular pacing. This allows the paced ventricular wavefronts to fuse with intrinsic wavefronts propagating down the interventricular septum.

Recently, several studies have demonstrated greater electrical synchrony, based on the narrowing of the QRS complex, using a SyncAV fusion stimulation strategy (8, 9, 11). The improvement in electrical synchrony was also confirmed using vectorcardiography (12). SyncAV

fusion pacing provided the greatest improvement in electrical synchrony compared to conventional CRT and multi-point pacing as well as having a synergistic effect when superimposed with the latter (13). Furthermore, fusion pacing using the SyncAV algorithm was associated with improvements in acute hemodynamic measures as well as reverse remodelling on echocardiography (10, 14). However, these studies were almost exclusively in patients with LBBB.

Efforts are required to improve electrical synchrony after CRT in patients with RBBB. Whether biventricular fusion pacing using SyncAV can increase electrical synchrony has not been elucidated. We aimed to assess whether patients with RBBB have a significant reduction in QRS complex duration (QRSd), as a metric of electrical resynchronization, with SyncAV fusion pacing compared to both CRT pacing with nominal AV delays and intrinsic rhythm without pacing.

Methods

Study design and population

This was a single center, retrospective study conducted at the McGill University Health Center, Montreal, Canada. This study was approved by the McGill University Health Center Institutional Review Board. All patients included in the study fulfilled criteria for CRT implantation as per Canadian Cardiovascular Society guideline recommendations (15). The main cohort in this study (group 1) had a CRT defibrillator (CRT-D) (St-Jude Unify Assura and Quadra Assura 3) or CRT pacemaker (CRT-P) (St-Jude Allure Quadra RF) with programmable SyncAV algorithm, implanted between April 2015 and November 2019. To be eligible for inclusion in this analysis, patients had to be programmable to the SyncAV algorithm, i.e. be in sinus rhythm with intrinsic AV conduction. This analysis was limited to patients with RBBB, which was defined in accordance with standard electrocardiogram (ECG) interpretation recommendations (16).

Comparison was provided by a historical cohort of consecutive patients with RBBB and implanted between January 2012 and March 2015 (group 2), before negative AV hysteresis (SyncAV) was used at our site (6). Of 231 CRT devices implanted during that time period in patients with intrinsic conduction and QRS >120ms, 197 were excluded on the basis of LBBB morphology. Of the remaining 34 patients with non-LBBB morphology, only patients with RBBB as well as in sinus rhythm with intrinsic conduction (PR <350ms) were included in the current analysis (Figure 1).

Device programming

ECG-based optimization to identify the best QRS width to adjust the resynchronization has become the standard of care in our center starting in 2018. All patients in the main cohort of this study (group 1 with SyncAV capable devices) coming for regular clinical follow up had the device optimized according to our service's protocol including sequential ECGs. This included those who received new CRT implants in 2018 as well as those with devices implanted prior to 2018 coming for regular device clinic follow-up. At the first clinical follow-up for each patient in 2018 and immediately post-implantation for new devices implanted since 2018, the device was programmed at the following pacing configurations to allow comparative measurements by 12-lead continuous ECG recordings: 1) intrinsic conduction, 2) CRT pacing as programmed by the treating physician prior to SyncAV optimization (nominal biventricular CRT), 3) manual ECG-based optimized SyncAV programming. In order to identify the most optimized SyncAV programming, various SyncAV offsets of -10, -30, -50, -70, -90 and -120ms were evaluated. After completion of the above ECG data collection, devices were programmed to the SyncAV setting with the narrowest QRS. In the historical cohort, ECG recordings were obtained prior to and immediately after device implantation. Biventricular pacing was compared to intrinsic conduction. The setting for biventricular pacing was the discretion of the operator: either nominal settings or optimized

ventriculo-ventricular delays based on perception of optimal QRS width and vector. This was performed immediately after implantation.

Electrocardiographic measurements

Standard 12-lead electrocardiography was performed at a paper speed of 25 mm/s and a scale of 10 mm/mV. QRS duration, as recorded from the surface leads with the greatest values, was automatically measured by the ECG machine (GE MACTM 5500 HD Resting ECG System). The ECG machine is programmed to measure the earliest onset of the QRS and the latest offset, which would be from the time of the pacemaker spike until the end of the QRS. Validation was then manually performed by a single investigator, blinded to the clinical data and pacing programming: the QRSd was defined as the duration from the earliest deflection from the isoelectric line to the latest return to the isoelectric line in any lead ignoring any pre-QRS deflections attributed to pacing artifacts. Change in QRSd was assessed and compared to intrinsic conduction and between the different modes of programming. These measurements were similarly obtained in both cohorts.

Echocardiographic assessment

In patients receiving a new device implant, all patients underwent a transthoracic echocardiogram which included the determination of left ventricular ejection fraction (LVEF) using Simpson's biplane method, prior to device implantation. The interpretation was performed by a level III echocardiographer. At 6 to 9 months post-implantation, a repeat echocardiogram was performed to reassess LVEF. In patients with a previously implanted device in whom SyncAV programming was activated, an echocardiogram was performed prior to SyncAV programming and 6 to 9 months after. The echocardiographer was unaware of changes in device programming.

In the historical cohort, echocardiography was performed at baseline prior to implantation and follow-up echocardiography was performed between 6 and 12 months post implantation.

Statistical analysis

All data are presented as mean $\pm$ SD for continuous variables and as proportions for categorical variables. Differences in QRSd and Δ QRSd among settings were assessed using one-way ANOVA, followed by Tukey-Kramer multiple-comparison tests. A paired t-test was used to compare outcomes prior to and 6 months after CRT or SyncAV optimization. An unpaired t-test was used to compare between groups 1 and 2. A P-value of <0.05 was considered statistically significant.

Results

Patient characteristics

We included 8 consecutive patients (group 1) with RBBB who were able to undergo SyncAV programming (5 new device implants and 3 previously implanted patients, time from implant ranging from 15 to 29 months). The mean age was 70 ± 12 years, 88% were male, 63% had ischemic cardiomyopathy, 75% received a CRT-D and the mean NYHA score was 2.1 ± 0.6 . Baseline characteristics are summarized in Table 1. All patients were receiving angiotensin converting enzyme inhibitors/angiotensin receptor blockers and beta blockers and 50% were receiving mineralocorticoid receptor antagonists. The mean intrinsic conduction QRSd was 155 ± 13 ms.

In comparison, there were 16 patients (group 2) with RBBB who received a CRT device in the historical cohort. The mean age was 71 ± 16 years, 88% were male, 63% had ischemic cardiomyopathy, and the mean NYHA score was 2.3 ± 0.8 . The mean intrinsic conduction QRSd

was 164 ± 22 ms.

Change in QRSd

In the first group of patients with SyncAV capable devices, mean QRSd with nominal pacing was 156 ± 15 ms (Δ QRSd 1.3 ± 11.6 ; $p=0.77$ compared to intrinsic conduction) (Figure 2) and 135 ± 14 ms (Δ QRSd -20.0 ± 20.4 ; $p=0.03$) with optimized SyncAV pacing. Optimized SyncAV was also associated with a reduction in QRSd compared to nominal CRT pacing (Δ QRSd -21.3 ± 16.3 ; $p=0.008$). In the group 2, mean QRSd with nominal pacing was 160 ± 24 ms (Δ QRSd 3.8 ± 33.4 ; $p=0.66$ compared to intrinsic conduction).

Change in LVEF

In group 1 with SyncAV programmable devices, the baseline LVEF was 22.1 ± 11.5 and after 6 months of SyncAV CRT pacing was 27.8 ± 8.6 (Δ LVEF 5.7 ± 6.1 , $p=0.047$) (Figure 3). In group 2, the baseline LVEF was 27.2 ± 10.6 and after 6 months of nominal CRT pacing post implant was 25.0 ± 10.0 (Δ LVEF -2.2 ± 11.4 , $p=0.45$). Compared to nominal CRT pacing in group 2, optimized SyncAV CRT pacing in group 1 was associated with an increase in LVEF ($p=0.04$).

Responder status

In the first group with SyncAV capable devices, only 13 % of patients had a significant reduction in QRSd (≥ 10 ms) with nominal CRT pacing compared to 63% with optimized SyncAV pacing ($p=0.06$) (Figure 4). Interestingly, in those who had a significant reduction in QRSd with optimized SyncAV pacing, the SyncAV offset was ≥ 90 ms in 80% of patients. Of the 8 patients, 4 (50%) had a significant improvement in LVEF ($\geq 10\%$), all of whom had a significant reduction in QRSd. In the second group, 31% had a significant reduction in QRSd with nominal pacing and 13% had a significant increase in LVEF ($\geq 10\%$). All those who had a significant increase in LVEF

also had a significant reduction in QRSd. There was a statistically significant, moderate negative correlation between change in QRS duration and change in LVEF (Spearman correlation coefficient = -0.42, $p=0.02$) (Figure 5)

Discussion

Fusion pacing using the SyncAV algorithm was associated with a significant reduction in QRSd compared to intrinsic and nominal biventricular pacing in patients with RBBB. Furthermore, fusion pacing using the SyncAV algorithm was associated with a significant improvement in LVEF. Importantly, these findings of a reduction in QRSd and increase in LVEF are in contrast to a similar cohort of patients who did not receive SyncAV fusion pacing. To our knowledge, our study is the first to assess the effect of fusion pacing on electrical and echocardiographic parameters in patients with RBBB morphology. The results of our analysis also reinforce the need for tailored programming to achieve the narrowest QRS.

An increase in electrical synchrony as manifested by a reduction in QRSd after CRT is an important therapeutic target and has been shown to correlate with echocardiographic and clinical outcomes, including reverse remodelling (17). This was described by Korantzopoulos and colleagues in a meta-analysis of 27 studies; in this analysis a mean difference of -19 ms (95%CI -15 to -24) predicted both a clinically and echocardiographic response to CRT (18). In the current study, we observed a mean decrease of -20 ms in QRSd using SyncAV compared to both intrinsic rhythm as well as nominal CRT pacing. Furthermore, in the historical cohort, there was no reduction in QRSd with CRT. Our results indicate that in patients with RBBB, electrical synchrony was achieved using SyncAV but not nominal CRT. In another analysis of electrical synchrony after CRT, Hadjis et al. examined the effect of QRS morphology on QRSd reduction for patients divided into three groups: those that met strict LBBB criteria (19) who are more likely to have a true LBBB,

those who only met conventional LBBB criteria but not strict LBBB and those with non-LBBB morphology (6). Only those who met strict LBBB had a mean reduction in QRSd (-20.9 ± 12.4 ms). Interestingly, this magnitude of QRSd reduction was similar to that observed in the current study for patients with RBBB and SyncAV optimized CRT pacing. In the current study, we also found a similar moderate negative correlation between change in QRSd and change in LVEF.

A fusion pacing strategy has been shown to achieve the narrowest QRS duration and improve electrical synchrony in patients with preserved AV conduction in both De novo and chronically biventricular paced situations as compared to intrinsic rhythm, nominal CRT pacing and an algorithm designed to achieve electrical synchrony (8, 9, 11, 12). However, none of these studies were designed or had been able to make a dedicated analysis of fusion pacing in RBBB patients. Varma and colleagues analyzed a cohort of 75 patients who had LBBB at the time of CRT implantation with optimized LV position. The mean QRSd was 162 ± 16 ms and was reduced by a mean of 20 ms to 30 ms depending on SyncAV optimization (fixed offset up to tailored offset) (11). AlTurki et al. analyzed a cohort of 32 patients who were chronically paced by CRT (mean time since implant of 18 months) with a mean intrinsic conduction QRSd of 163 ± 24 ms. Mean QRSd was reduced by a mean of 11 ms with nominal pacing and 24 ms with optimized SyncAV programming (8). The reduction in QRSd with optimized SyncAV observed in those with RBBB in our study approaches that seen with LBBB in the aforementioned studies. The results highlight the benefit of the triple-front waveform to achieve a proper activation among these patients with different activation pattern, which has been shown to achieve the best acute hemodynamic benefit with CRT (14, 20).

Given the different activation patterns in RBBB and LBBB patients, it would be unlikely that the same nominal programming would lead to optimal electrical synchrony in both RBBB and

LBBB patients. In those with LBBB, the optimal SyncAV offset was 30-50 ms in around 66% to 80% of patients and the majority of the remaining patients had an optimal offset of less than 30 ms (8, 9). In contrast, we found that in patients with RBBB, the optimal offset was around 90 ms in the vast majority. This finding is key in considering the optimal negative AV hysteresis offset required to achieve fusion; given that the AV delay is measured by the device using the right ventricular lead, the presence of RBBB results in delayed detection of ventricular activation (relative to surface ECG) and the need to program a more negative AV offset to achieve fusion. The present study supports the concept that fusion pacing using programmable negative AV hysteresis offset tailored using surface ECG for optimization should be performed in patients with preserved AV conduction and correlates with an increased number of responders even in patients with RBBB. Interestingly, PR interval prolongation is a predictor of poor outcomes after CRT in those LBBB but not RBBB (21).

Compared to LBBB patients, the CRT response among those with RBBB morphology remains uncertain and often discouraging (22, 23). Rickard et al. assessed the effect of baseline QRS morphology on clinical outcomes and echocardiographic parameters in 335 patients, 10% of them with RBBB morphology, after CRT implant (4). Similar to findings in other cohorts, patients with heart failure and RBBB had a higher mortality rate (26%) compared to those with LBBB (16%) and were less likely to derive benefit from CRT (4). Those with RBBB did not have a significant improvement in LVEF post CRT, which is similar to what we observed in our historical cohort of patients that did not receive SyncAV fusion pacing. The improvement in LVEF in our cohort of patients with RBBB who received SyncAV fusion pacing approaches the improvement seen in those with LBBB in the cohort described by Rickard et al. as well and Zhang et al (4, 24). Importantly, the degree of LVEF improvement was similar to that seen in patients with LBBB who

received SyncAV fusion pacing (10). Larger studies are now needed to confirm these findings in patients with RBBB.

This was a single center, retrospective analysis with a limited number of patients. The small number of patients with RBBB probably reflects the discouraging results from the available data regarding CRT in patients with non-LBBB morphology QRS prolongation and the limited indications for CRT in this specific population. The current study should serve as a proof-of-concept for fusion pacing as a potentially effective alternative for this group of patients and raise questions about the particularities of CRT programming and optimization in patients with RBBB. The degree to which fusion can be achieved with fixed AV delay adjustment in RBBB patients without a dynamic fusion pacing algorithm was not evaluated. Echocardiographic follow-up is performed at 6 months as per the current protocol for all CRTs at our institution. Longer-term follow-up with echocardiography as well as clinical heart failure outcomes are needed.

Conclusion

Biventricular fusion pacing is associated with improved electrical synchrony and increased LVEF when compared with traditional biventricular pacing in patients with underlying RBBB. This study demonstrated that a simple, ECG-based algorithm to optimize AV delays can significantly improve electrical synchrony in patients with RBBB. Larger studies are required to confirm these findings.

Declarations

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Conflicts of interest: Dr Essebag has received honoraria from Abbott, Biosense Medical, Boston Scientific and Medtronic. All other authors have no relevant disclosures.

Ethics approval: This study was approved by the McGill University Health Center Institutional Review Board

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Figure legends

Figure 1. Flow diagram for inclusion or exclusion of patients. CRT= cardiac resynchronization therapy; LBBB= left bundle branch block; RBBB= right bundle branch block; IVCD= interventricular conduction delay.

Figure 2. QRS duration after nominal CRT and SyncAV programming compared to intrinsic QRS duration in patients A) with SyncAV capable devices (group 1) and B) without SyncAV capable devices (group 2). BiV= biventricular.

Figure 3. Left ventricular ejection fraction after nominal CRT and SyncAV programming compared to baseline left ventricular ejection fraction in patients A) with SyncAV capable devices (group 1) and B) without SyncAV capable devices (group 2). LVEF= left ventricular ejection fraction; CRT= cardiac resynchronization therapy.

Figure 4. Responder status. A) Improved electrical synchrony as defined by reduction in QRSd ≥ 10 ms after SyncAV CRT in group 1 and nominal CRT in group 2 and B) Echocardiographic response as defined by an absolute increase in LVEF of $\geq 10\%$ after SyncAV CRT in group 1 and nominal CRT in group 2. LVEF= left ventricular ejection fraction; CRT= cardiac resynchronization therapy.

Figure 5. Correlation between Δ QRS and Δ LVEF after cardiac resynchronization therapy in patients with RBBB (groups 1 and 2 included). LVEF= left ventricular ejection fraction.

Table 1. Baseline patient characteristics.

Characteristic	RBBB with SyncAV device (Group 1)	RBBB with non-SyncAV device (Group 2)
N	8	16
Male, n (%)	7 (88)	14 (88)
Mean age, year	70±12	71±16
Ischemic cardiomyopathy, n (%)	5 (63)	10 (63)
Hypertension	7 (88)	12 (75)
Diabetes mellitus	4 (50)	7 (44)
Paroxysmal atrial fibrillation	4 (50)	9 (56)
Cardiac resynchronization therapy defibrillator	6 (75)	13 (81)
Mean NYHA, (SD)	2.1±0.6	2.3±0.8
Intrinsic QRSd (ms)	155±13	164±22
Conduction abnormalities		
RBBB only	1 (13)	4 (25)
RBBB+ LAFB	6 (75)	11 (69)
RBBB+LPFB	1 (13)	1 (6)
Left ventricular ejection fraction (%) prior to initial CRT	22.1±11.5	27.2±10.6
Medical therapy for heart failure		
ACEI/ARB	8 (100)	16 (100)
Beta blocker	8 (100)	16 (100)
MRA	4 (50)	7 (44)

N= number; NYHA= New York Heart Association; ACEI= angiotensin converting enzyme inhibitor; ARB= angiotensin receptor blocker; SD= standard deviation. RBBB= right bundle branch block; LAFB= left anterior fascicular block; LPFB= left posterior fascicular block; CRT= cardiac resynchronization therapy; MRA= mineralocorticoid receptor antagonist.

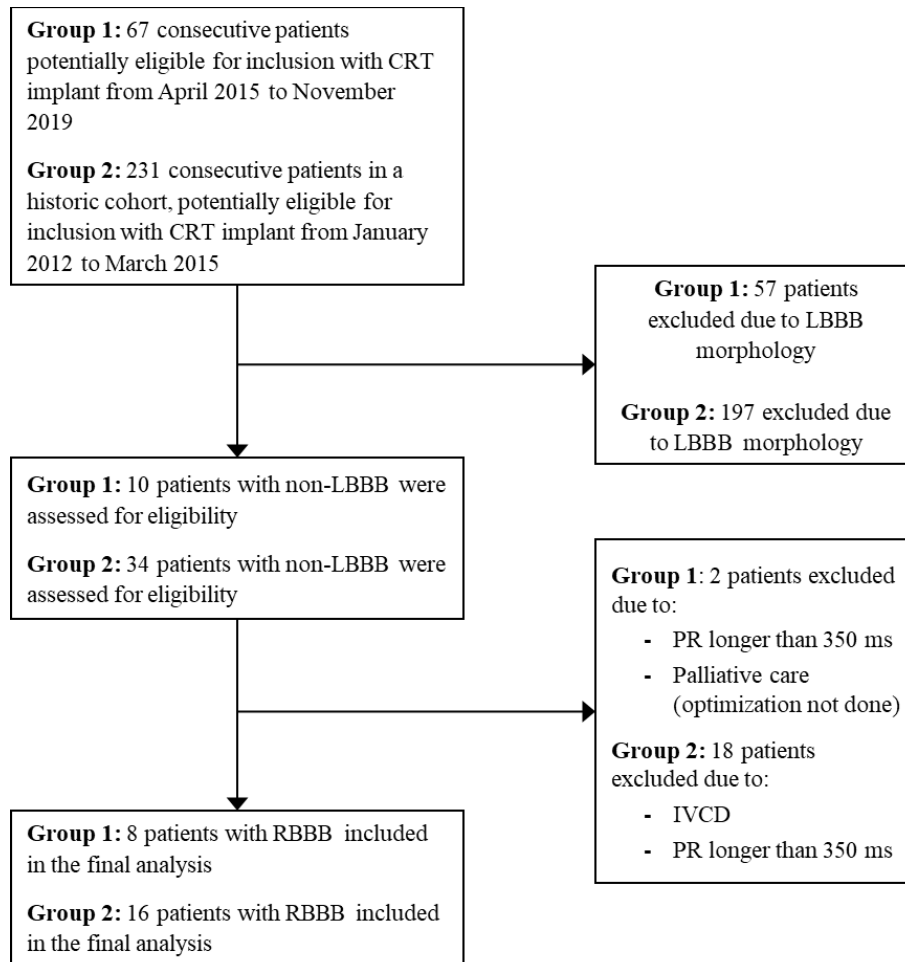
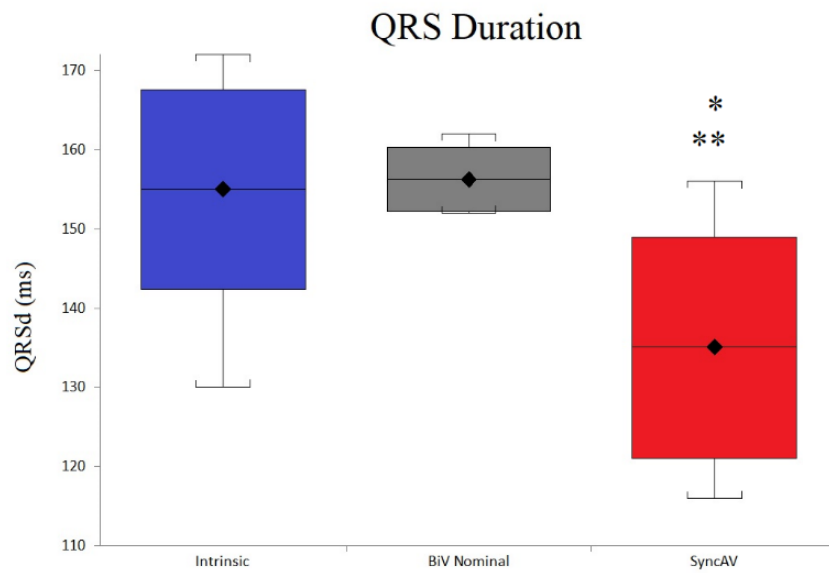
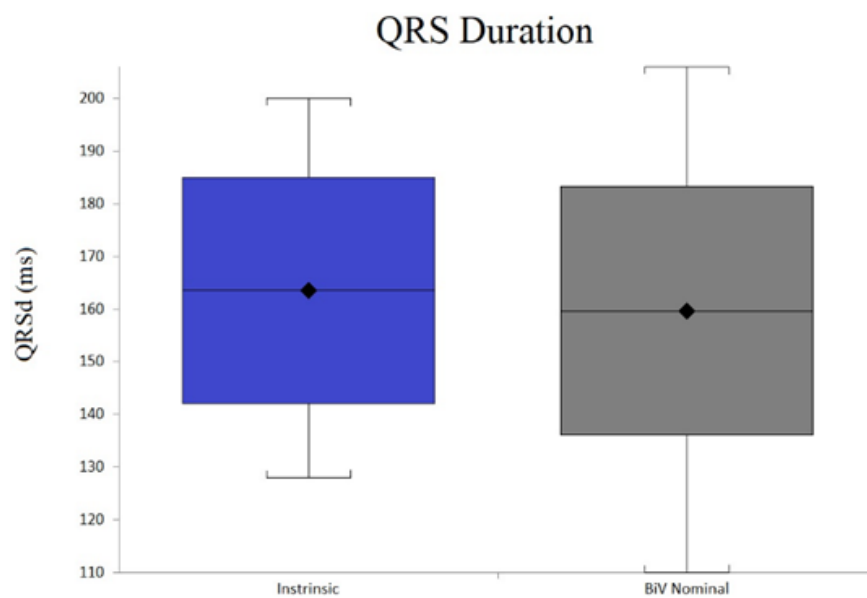


Figure 1.

A)



B)

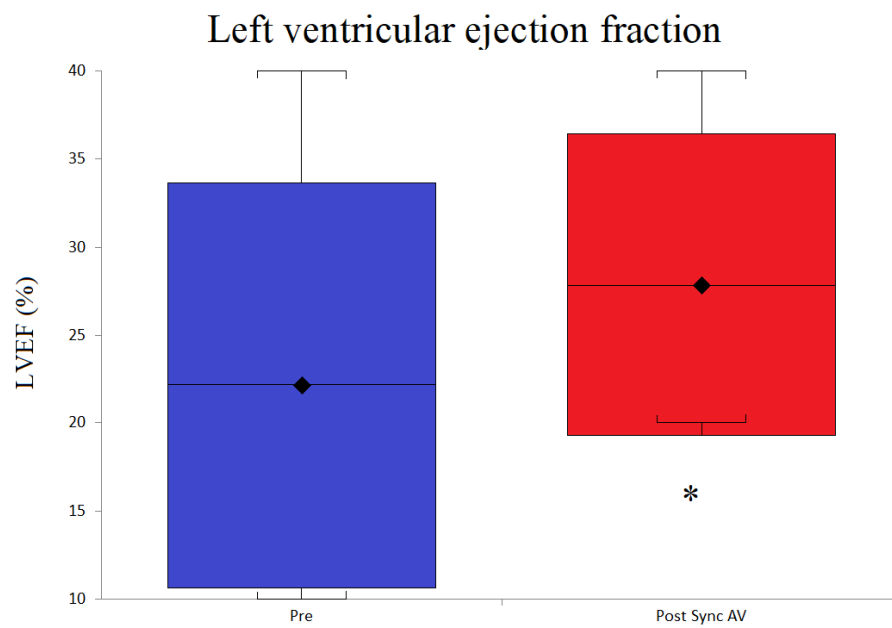


* P=0.03 compared to intrinsic rhythm

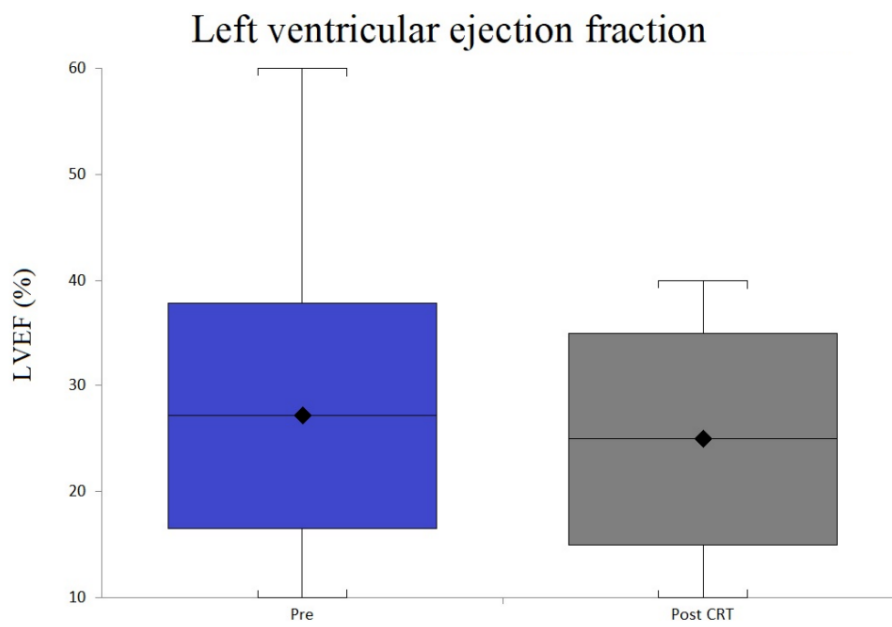
** P=0.008 compared to nominal CRT pacing

Figure 2.

A)



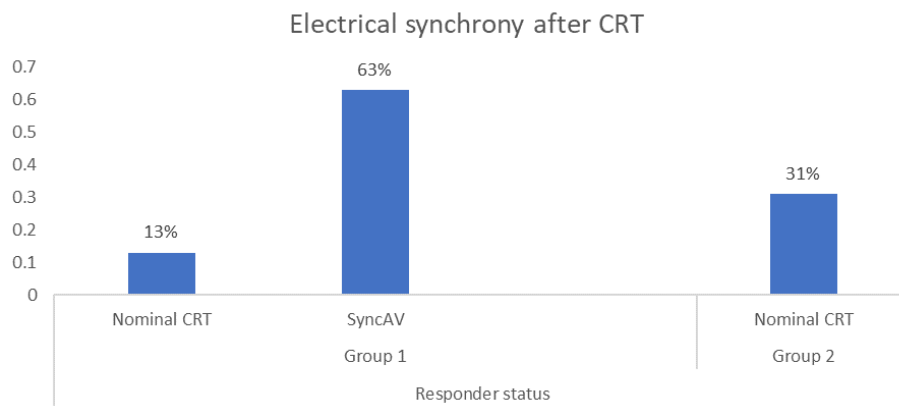
B)



* P= 0.047

Figure 3.

A)



B)

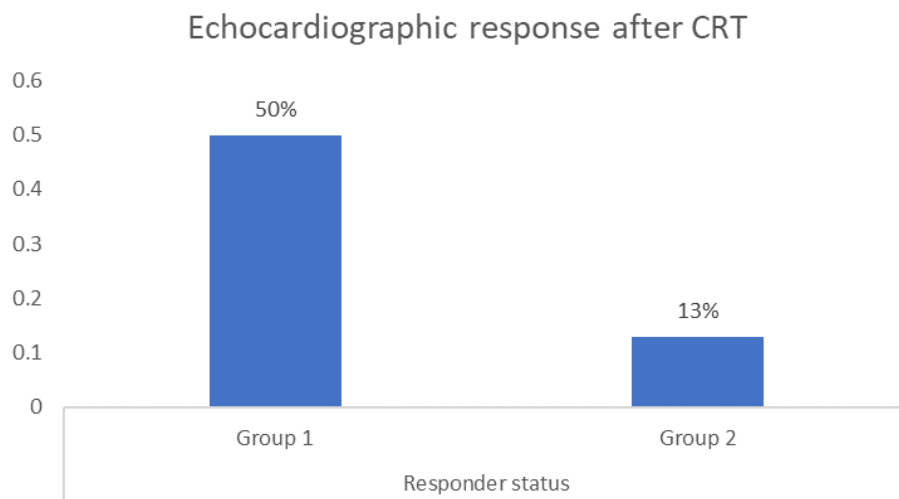


Figure 4.

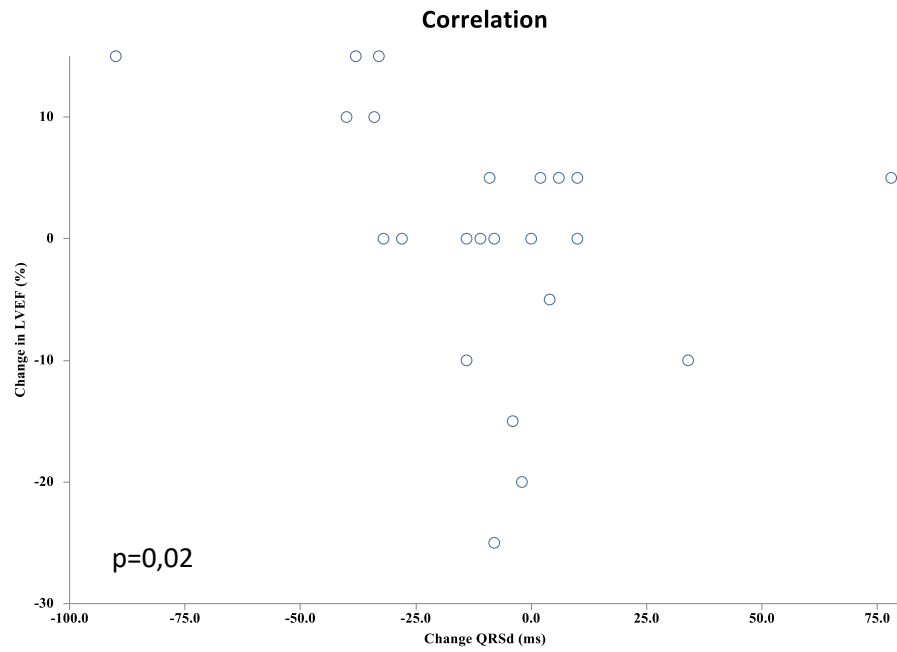


Figure 5.

CHAPTER 6: DISCUSSION AND CONCLUSIONS

6.1 Discussion

This research demonstrated that the fusion pacing can be an effective alternative for patients with preserved intrinsic conduction, regardless of the underlying conduction disturbance (LBBB or RBBB) and for how long the patient had been paced. We also described the use of an ECG-based optimization as a feasible, reliable, reproducible, and quick method to optimize the CRT devices allowing fusion pacing. The QRS narrowing found was similar to previous studies that evaluated patients using fusion pacing with BiV and intrinsic conduction (12, 20-23). There is a lack of information about QRS narrowing in studies with LV pacing and intrinsic conduction (9, 10). None of these previous studies in this matter assessed chronically paced patients. The amount of QRS reduction was similar among RBBB and LBBB patients optimized using the fusion pacing algorithm. The only difference between the two groups was the offset of AV delay shortening need to achieve the best fusion. In the RBBB, the shortening was at least 90 ms, while in the LBBB group the best values were between 30 to 50 ms.

The echocardiographic data measured at 6 months post optimization revealed improvements as published in LV pacing and intrinsic conduction (10). These parameters were not evaluated in other studies that performed triple wavefront fusion strategies. The LVEF improvement and the LVESV reduction led to a greater proportion of responders in patients that experienced fusion pacing optimization. Even among the RBBB patients, which are known as poor CRT responders, we achieved satisfactory rate of response.

Limitations of our study include the small number of patients and the fact that it is a single center study derived from a retrospective analysis of the new standard optimization protocol. The aim was to prove that fusion pacing performed after an ECG-based optimization could be an easy,

reproducible, cheap, and effective method for CRT adjustment. Further larger, multicentric, randomized clinical trials are needed to confirm and validate the findings described.

6.2 Conclusion

Fusion pacing using an automatic algorithm after ECG-based optimization resulted in a narrowing of QRS duration, echocardiographic improvements, and higher rates of responders among patients with underlying LBBB or RBBB. The use of the new automatic algorithm for fusion pacing associated with the ECG-based optimization is an effective method to achieve QRS narrowing and increase the rate of CRT responders and can routinely be performed during the patients follow up.

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CHAPTER 8: APPENDIX

Reprint of manuscript 1



Cardiac resynchronization therapy reprogramming to improve electrical synchrony in patients with existing devices

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ABSTRACT

Background: Optimal programming of cardiac resynchronization therapy (CRT) has not yet been fully elucidated. A novel algorithm (SyncAV) has been developed to improve electrical synchrony by fusion of the triple wavefronts: intrinsic, right ventricular (RV)-paced, and left ventricular (LV)-paced.

Methods: Consecutive patients at a single tertiary care center with a previously implanted CRT device with SyncAV algorithm (programmable negative AV hysteresis) were evaluated. QRS duration (QRSd) was measured during 1) intrinsic conduction, 2) existing CRT pacing as chronically programmed by treating physician, 3) using the device-based QuickOpt™ algorithm for optimization of AV and VV delays, and 4) ECG-based optimized SyncAV programming. The paced QRSd was assessed and compared to intrinsic conduction and between the different modes of programming.

Results: Of 64 consecutive, potentially eligible patients who underwent assessment, 34 patients who were able to undergo SyncAV programming were included. Mean intrinsic conduction QRSd was 163 ± 24 ms. In comparison, the mean QRSd was 152 ± 25 ms (-11.1 ± 19.0) during existing CRT pacing, 160 ± 25 ms (-4.1 ± 25.2) using the QuickOpt™ algorithm and 138 ± 23 (-24.9 ± 17.2) using ECG-based optimized SyncAV programming. SyncAV optimization resulted in significant reductions in QRSd compared to existing CRT pacing ($P = 0.02$) and QuickOpt™ ($P < 0.001$). Of the 32% of patients who did not have QRS narrowing with existing CRT, 72% experienced QRS narrowing with SyncAV.

Conclusion: ECG-based atrio-ventricular delay optimization using SyncAV significantly improved electrical synchrony in patients with a previously implanted CRT. Further studies are needed to assess the impact on long-term outcomes.

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Background

Cardiac resynchronization therapy (CRT) improves cardiovascular outcomes in patients with heart failure [1]. However, a significant proportion (around 30%) of patients who receive CRT do not improve and are deemed non-responders [2]. While there have been significant efforts to identify predictors of response to CRT prior to device implantation such as left bundle branch block and a prolonged QRS duration [3], optimal programming of cardiac resynchronization therapy has not yet been fully elucidated. Given individual variations in ventricular activation sequences, a one-size fits all approach to CRT programming may be sub-optimal.

The goal of CRT is to improve electrical synchrony and in turn mechanical synchrony [4]. A decrease in QRS duration (QRSd) after CRT is a predictor of clinical response [5,6]. A novel, device-based algorithm (SyncAV) included in certain Abbott CRT devices can be used to improve electrical synchrony by fusion of the triple wavefronts: intrinsic, right ventricular (RV)-paced, and left ventricular (LV)-paced [7]. This algorithm automatically synchronizes ventricular pacing with intrinsic atrioventricular conduction by altering the atrioventricular delay. A shortening between 10 and 120 ms of the atrioventricular delay (relative to the measured intrinsic AV conduction interval) is programmed to allow fusion between intrinsic atrioventricular conduction and biventricular pacing. This would occur across various durations of intrinsic conduction (up to 350 ms) to allow a continuously adapting fusion pacing. Though the algorithm is programmed with a default SyncAV -50 millisecond offset, the offset is programmable to allow patient-specific optimization.

Whether electrical synchrony can be improved in patients with a chronically implanted CRT has not been proven. Therefore, we aimed

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to assess the difference in QRSd in patients with a previously implanted CRT who subsequently receive SyncAV pacing compared to existing chronic CRT pacing as well as another proprietary device-based timing cycle optimization algorithm (QuickOpt™) [8].

Methods

Study patients

We performed a single center, retrospective study of patients with a CRT defibrillator (CRT-D) (St-Jude Unify Assura and Quadra Assura 3) or a CRT pacemaker (CRT-P) device (St-Jude Allure Quadra RF) with SyncAV algorithm TM (programmable negative AV hysteresis), implanted between January 2014 and November 2017 at the McGill University Health Center (MUHC), Montreal, Canada. Only patients able to be programmed to the SyncAV algorithm (i.e. in sinus rhythm with intrinsic AV conduction at implant) were included in this analysis. All patients included in the study fulfilled criteria for CRT implantation as per Canadian Cardiovascular Society guideline recommendations [9]. This study was approved by the McGill University Health Center Institutional Review Board.

Device implantation and programming

CRT was programmed according to operator preference and SyncAV was not activated in any of the patients between January 2014 and November 2017; at the end of that year, patients with chronically implanted CRT devices underwent routine ECG-based SyncAV algorithm optimization during their next regular device clinic visit to assess the best QRS pattern. This method of optimization became the standard of care in our service since May 2018 for newly implanted devices and was extended to the previously implanted devices. Since then, all patients coming for regular clinical follow up had the device optimized according to our service's protocol including sequential ECGs.

Electrocardiographic measurements

Standard 12-lead electrocardiography was performed at a paper speed of 25 mm/s and a scale of 10 mm/mV. QRS duration, as

recorded from the surface leads which have the greatest values, was measured automatically by the ECG machine (GE MACTM 5500 HD Resting ECG System). The ECG machine is programmed to measure the earliest onset of the QRS and the latest offset [10]; in practical terms this would be from the time of the pacemaker spike until the end of the QRS. This was subsequently validated manually by a single investigator who was blinded to the clinical data and pacing programming. On the 12 lead ECG, the QRSd was defined as the duration from the earliest deflection from the isoelectric line to the latest return to the isoelectric line in any lead. The reasons for using automated QRS measurements were fourfold: 1) the lack of a standardized practice and the fact that CRT trials did not report the methods for QRSd measurement [11], which was likely automated; 2) the significant variability seen with manual QRSd measurements [12]; 3) the reproducibility and precision of automated measurements [13]; 4) the ease of use of automated measurements which would be readily translated to clinical practice.

QRSd was measured during 1) intrinsic conduction, 2) existing CRT pacing as chronically programmed by treating physician prior to SyncAV optimization, 3) using the device-based QuickOpt™ algorithm for optimization of AV and VV delays and 4) manual ECG-based optimized SyncAV programming (with offsets of −10, −30, −50, −70, and −90 ms evaluated). Change in QRSd was assessed and compared to intrinsic conduction and between the different modes of programming.

Statistical analysis

All data are presented as mean $\pm$ SD for continuous variables and as proportions for categorical variables. Mean QRSd was compared between the different CRT programming and intrinsic conduction by performing an analysis of variance (ANOVA) test. A P-value of <0.05 was considered statistically significant. Univariate and multivariate logistic regression analyses were performed to identify variables associated with a significant reduction in QRS duration (defined as ≥ 10 ms) compared to existing CRT pacing. All variables associated with a statistical significance of $P < 0.1$ were considered for multivariate analysis.

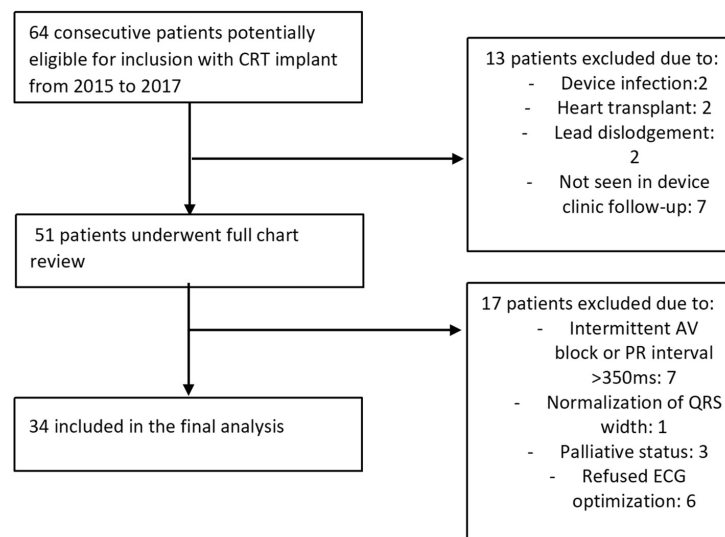


Fig. 1. Flow diagram for patient selection.

Table 1
Patient characteristics.

Characteristic	N = 34
Male, n (%)	19 (56)
Age, year (range)	74 (60–93)
Time since implant in months, mean (range)	17.8 ± 8.5
Ischemic cardiomyopathy, n (%)	21 (62)
Hypertension	28 (82)
Diabetes mellitus	8 (24)
Paroxysmal atrial fibrillation	10 (29)
Left bundle branch block	31 (91) ^a
Cardiac resynchronization therapy defibrillator	22 (65)
NYHA, n (%)	
I	4 (11.8)
II	24 (70.6)
III	6 (17.6)
QRS (ms)	163.5 ± 24.3
Intrinsic PR interval (millisecond)	187.2 ± 36.6
Left ventricular ejection fraction (%)	24.1 ± 10.1
Medical therapy for heart failure	
ACEI/ARB	28 (82)
Beta blocker	28 (82)
MRA	5 (15)

N = number; NYHA = New York Heart Association; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; MRA = mineralocorticoid receptor antagonist.

^a The remaining 3 were bi-fascicular block (right bundle branch block and left anterior fascicular block or left posterior fascicular block).

Results

A total of 64 patients who had a CRT device (with the SyncAV feature) implanted between January 2014 and November 2017 were considered for possible inclusion. Among these patients, 2 were not eligible due to prior system explant for device infection, 2 other patients had heart transplant prior to the appointment for the optimization, 2 patients had LV lead dysfunction/dislodgment and the lead was turned off, and 7 patients did not return for follow-up at our center's device clinic. Of the remaining 51 patients presenting to clinic for ECG-based optimization, 7 patients had intermittent AV block or the PR interval was longer than 350 ms (making fusion pacing with the SyncAV feature not possible), 1 patient had normalization of the QRS width and was programmed to DDI 40 bpm, another 3 patients became exclusively palliative care and 6 patients refused to have the ECG-based optimization performed due to personal reasons. The remaining 34 patients had ECG-based optimization performed and were included in this analysis (Fig. 1). The mean age was 74 ± 9 years, 41% were female and 59% had ischemic cardiomyopathy. Patient characteristics at time of SyncAV optimization are summarized in Table 1.

The mean intrinsic conduction QRSD was 163 ± 24 ms and the mean existing CRT pacing QRSD was 152 ± 25 ms. Using the QuickOpt™ algorithm the mean QRSD was 160 ± 25 ms and using manual ECG-based optimized SyncAV programming the mean QRSD was 138 ± 23 . In comparison to intrinsic conduction, the change in QRSD was -11.1 ± 19.0 ($P = 0.07$), -4.1 ± 25.2 ($P = 0.53$) and -24.9 ± 17.2 ($P < 0.001$) using existing CRT pacing, QuickOpt™ algorithm and manual ECG-based optimized SyncAV programming, respectively (Fig. 2). Using SyncAV optimization resulted in significant reduction in QRSD compared to existing CRT pacing (-13.8 ± 12.4 , $P = 0.02$) and the QuickOpt™ algorithm (-21.1 ± 17.8 , $P < 0.001$). The distribution of the differences in QRSD between SyncAV and existing CRT pacing as well as the QuickOpt™ algorithm are shown in Fig. 3A and B respectively. There was no difference in QRSD between existing CRT pacing and the QuickOpt™ algorithm.

There was no significant difference in QRSD between default SyncAV (offset -50) and manually adjusted SyncAV optimization ($P = 0.17$). In 10 of the 34 included patients (29%), the default Sync AV setting (offset -50) achieved the optimal QRSD. In another 14 patients (41%), the difference in QRSD, between the default Sync AV setting and the manual SyncAV optimization, was ≤ 10 ms. However, in 6 of the 34 patients (18%), an alternative SyncAV setting (other than -50) reduced the QRSD by ≥ 10 ms; in 3 patients this was an offset of -30 ms and in the remaining 3 patients this was an offset of -70 or -90 ms.

In comparison to intrinsic conduction, there were 11 patients (32%) who did not have a decrease in QRSD with existing CRT pacing; 8 of these patients had a reduction in QRSD with SyncAV. In 79% of patients, SyncAV exclusively achieved the largest reduction in QRSD and in a further 9% SyncAV equaled the reduction achieved by existing CRT programming. Fig. 4 illustrates the CRT setting that achieved the narrowest QRSD in each patient.

Univariate analysis showed an association between intrinsic QRSD, as well as existing CRT pacing QRSD, and the reduction in QRSD with SyncAV (Table 2). After multivariate analysis, only QRSD with existing CRT pacing predicted a reduction in QRSD with SyncAV. Gender, age, time since implant, type of cardiomyopathy, NYHA class, intrinsic PR interval and LVEF did not predict a reduction in QRSD with SyncAV.

Discussion

The main finding of this analysis is that in patients with a previously implanted CRT device, further reduction in QRSD, and hence improvement in electrical synchrony, can be achieved using the SyncAV algorithm that leads to fusion of the triple wavefronts. The importance of these results is highlighted by recent evidence that a reduction in

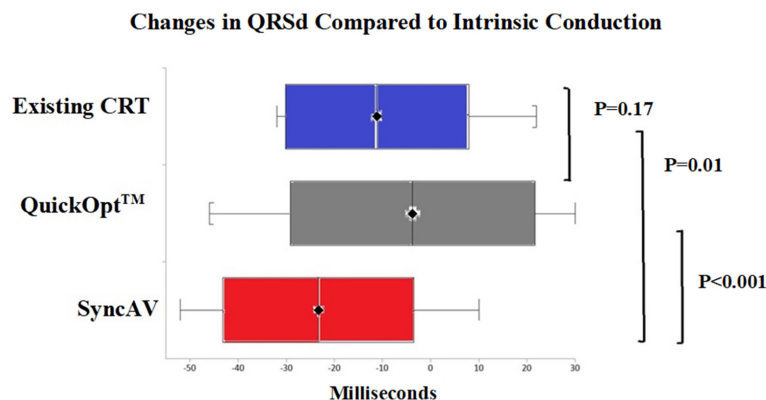


Fig. 2. The change in QRS duration (milliseconds) using existing CRT, QuickOpt™ and SyncAV compared to intrinsic conduction.

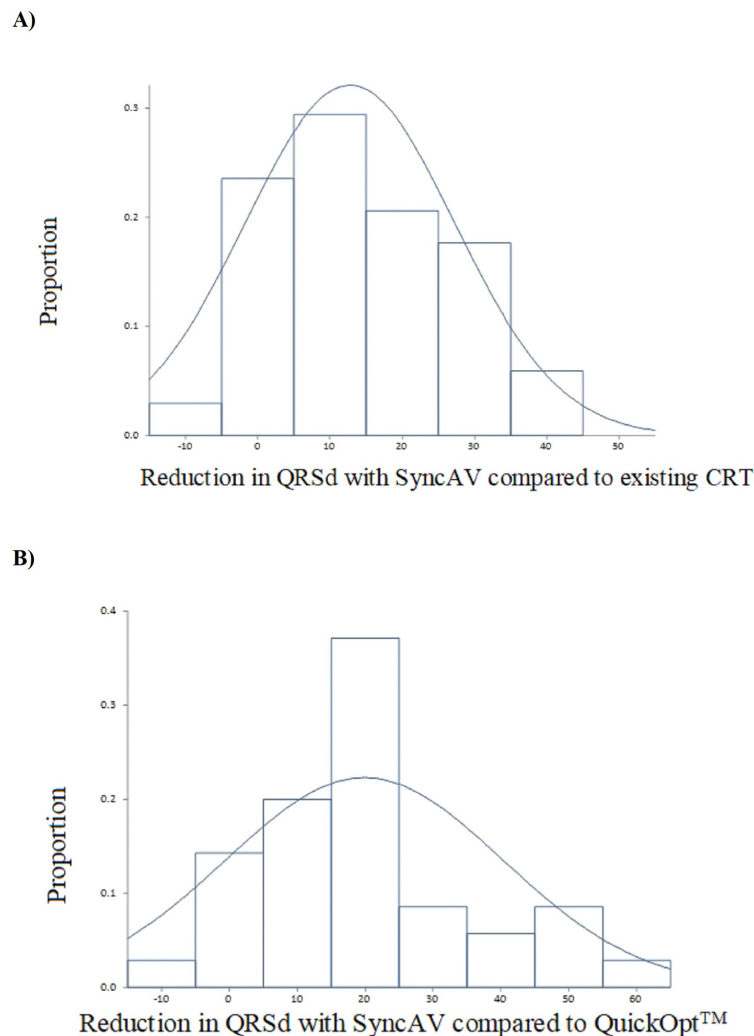


Fig. 3. The differences in the change in QRS duration achieved by SyncAV compared to A) existing CRT and B) QuickOpt™.

QRSd after CRT is well correlated with an increase in LVEF, currently the best indicator for clinical outcomes in heart failure patients [14]. Coppola et al. examined the association between QRS narrowing and LV reverse remodelling and overall mortality in a cohort study of 311 patients. The authors found that a 12.5% narrowing of QRSd was associated with LV reverse remodelling at 6 months and a significant reduction in mortality [15]. Furthermore, Karantzopoulos et al. showed in a meta-analysis of 12 studies that CRT responders had narrower paced QRSd (post CRT) compared to CRT non-responders; both when defining response to CRT using clinical criteria (mean difference = -19.91 ms, 95% CI = -27.20 to -12.62 ms, $P < 0.00001$) as well as echocardiographic criteria (mean difference = -19.51 ms, 95% CI = -25.78 to -13.25 ms, $p < 0.00001$) [6].

QRS narrowing is a cheap and viable option for optimization of CRT that can be assessed easily during a clinic visit. Importantly, there was no significant difference between manually optimized SyncAV and the default SyncAV offset of -50 ms. This is especially relevant given the

relatively time-consuming nature of manual ECG based optimization. However, in 18% of patients a manually optimized SyncAV offset achieved a significantly narrower QRS compared to the default SyncAV setting and further work is required to identify these patients. Numerous options have been explored to optimize CRT. Several studies including randomized controlled trials have failed to show a benefit when echocardiography is used to guide CRT. In the echoCRT trial, patients with heart failure, synchrony on echocardiography and a QRS duration of <130 ms did not have benefit with CRT [16]. In the PROSPECT trial, there was no echocardiographic measure that could predict response to CRT [17]. In addition to the limited results, echocardiographic optimization is hampered by its time-consuming and operator-dependent nature as well as the technical difficulty in maintaining position and stability during the different pacing intervals [18].

Whether QRS reduction, beyond that seen after initial implantation, is associated with improved outcomes remains unclear. Yang et al. assessed a cohort of patients who were undergoing generator

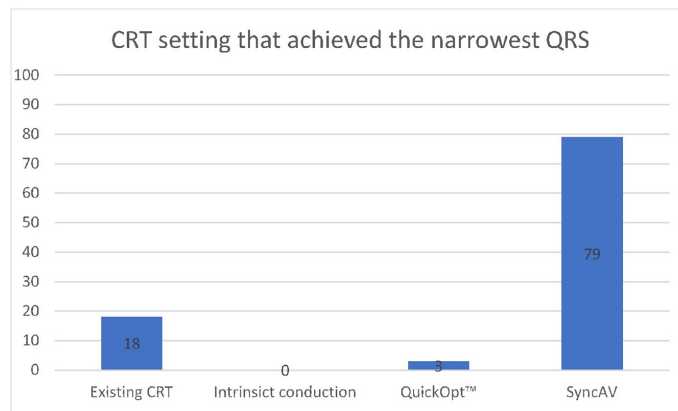


Fig. 4. Proportion of patients who achieved the narrowest QRS stratified by CRT setting.

replacement. They found that super-responders and responders to CRT had further reductions in paced QRSD during follow-up. Patients who experienced further narrowing of the QRS complex, by ≥ 10 ms, after 6 months had a significant reduction in all-cause mortality [19]. Therefore, it appears that QRS narrowing is a marker of reverse remodelling. Our finding of a significant reduction of QRSD achieved by activating SyncAV at a mean of 18 months post-implant indicates an opportunity for further reverse remodelling with simple device programming, though these findings need to be correlated with clinical and echocardiographic outcomes.

Non-response remains the greatest challenge to CRT with numerous efforts to improve patient selection. However, the proportion of non-responders is still high at around 30% [2]. Our results are encouraging in that of the 32% of patients who did not experience a reduction of QRSD with existing CRT programming, 73% had significant reduction in QRSD with SyncAV. Non-responders to CRT are at high risk of major adverse cardiac events compared to responders and the lack of response to CRT remains its greatest challenge [20]. Our results showing the potential to produce a narrower QRS and possibly improve response to CRT in this patient population is encouraging.

Identifying patients who would potentially benefit from optimization of CRT programming remains problematic. While studies have shown that factors such as a wider QRS, female gender, left bundle branch block morphology and non-ischemic cardiomyopathy help predict response to CRT prior to device implantation and may therefore aid in patient selection, identifying those who may have further response is

not clear [20]. We demonstrate that a wide QRS at follow-up may identify a sub-group who may benefit from CRT optimization, specifically with SyncAV programming and potentially with other algorithms. Interestingly, we showed that optimization using SyncAV significantly reduced QRSD compared to another device-based algorithm that is currently used, QuickOpt™ [8].

This was a single-center retrospective study with its inherent limitations. While the sample size is relatively small, this is due to the limited number of patients with an existing CRT device with SyncAV algorithm at our centre, and the proportion of these patients for whom the algorithm is programmable (i.e. this algorithm is not useful in patients with AV block or atrial fibrillation). The current study was limited to electrocardiographic data and needs to be further corroborated with echocardiography and clinical outcomes in larger studies.

Conclusion

Manual ECG-based atrio-ventricular delay optimization using SyncAV significantly improved electrical synchrony in patients with a previously implanted CRT. Further studies are required to delineate the clinical and hemodynamic effects of using SyncAV in patients with chronically implanted CRT devices.

Disclosures

Dr. Essebag has received honoraria from Abbott, Biosense Medical, Boston Scientific and Medtronic. Dr. Essebag is the recipient of a Clinical Research Scholar Award from the Fonds de recherche du Québec-Santé (FRQS).

Author contributions

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Data analysis/interpretation: Ahmed Alturki; Pedro Yuri; Vidal Essebag.

Drafting article: Ahmed Alturki; Pedro Yuri; Vidal Essebag.

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Table 2

Univariate and multivariate predictors of significant reduction in QRSD compared to existing CRT pacing.

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Age	1.09	0.97–1.23	0.16	–	–	–
Gender (female)	4.26	0.47–38.53	0.20	–	–	–
CMP (non-ischemic)	2.44	0.25–23.67	0.44	–	–	–
Hypertension	0.54	0.01–27.46	0.75	–	–	–
Diabetes mellitus	3.70	0.33–41.63	0.29	–	–	–
Atrial fibrillation	1.89	0.16–23.03	0.62	–	–	–
LVEF	1.11	0.97–1.27	0.13	–	–	–
Intrinsic QRSD	0.94	0.88–1.01	0.08	0.94	0.89–1.00	0.05
Existing CRT QRSD	1.08	1.01–1.17	0.03	1.08	1.02–1.14	0.01

OR = odds ratio; CI = confidence interval; CMP = cardiomyopathy; LVEF = left ventricular ejection fraction; CRT = cardiac resynchronization therapy.

Approval of article: Ahmed Alturki; Pedro Yuri; Daniel Garcia, Mauricio Montemezzo, Alaa Al-Dosari, Alejandro Vidal, Bruno Toscani, Sergio Diaz, Martin Bernier, Tomy Hadjis, Jacqueline Joza; Vidal Essebag.

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Reprint of manuscript 2

Original Article

Optimization of Chronic Cardiac Resynchronization Therapy Using Fusion Pacing Algorithm Improves Echocardiographic Response

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ABSTRACT

Background: Whether reprogramming of cardiac resynchronization therapy (CRT) to increase electrical synchrony translates into echocardiographic improvement remains unclear. SyncAV is an algorithm that allows fusion of intrinsic conduction with biventricular pacing. We aimed to assess whether reprogramming chronically implanted CRT devices with SyncAV is associated with improved echocardiographic parameters.

Methods: Patients at a quaternary center with previously implanted CRT devices with a programmable SyncAV algorithm underwent routine electrocardiography-based SyncAV optimization during regular

RÉSUMÉ

Contexte : On ignore si la reprogrammation du dispositif de resynchronisation cardiaque (DRC) afin d'améliorer la synchronisation électrique se traduit réellement par une amélioration échocardiographique. L'algorithme SyncAV permet de fusionner la conduction intrinsèque et la stimulation biventriculaire. Nous avons tenté de déterminer si la reprogrammation à l'aide de l'algorithme SyncAV d'un DRC implanté de façon permanente permet d'améliorer les paramètres échocardiographiques.

Méthodologie : Les patients d'un centre de soins quaternaires porteurs d'un DRC doté d'un algorithme SyncAV programmable ont subi

Cardiac resynchronization therapy (CRT) decreases cardiovascular mortality and symptoms in patients with heart failure.¹ However, a lack of response to CRT remains its greatest challenge.² The ideal method to optimize CRT post-implantation is controversial. Echocardiography has been used for CRT optimization.³ However, routine CRT settings are used for the majority of CRT implants because of the complex and time-consuming nature of echocardiographic optimization.⁴ In an international survey, 58% of electrophysiologists did not optimize atrioventricular (AV) and ventriculo-ventricular delays.⁵ Therefore, using the electrocardiogram (ECG) would be an inexpensive and practical process for CRT optimization.⁴ Narrowing of the QRS complex with

biventricular pacing (the paced QRS duration [QRSd]) has been shown to correlate with clinical and echocardiographic improvement,^{6,7} as well as long-term mortality.⁸ One study has also reported that ECG-based optimization using the measurement of the narrowest QRS is comparable to echocardiography-based optimization with regard to left ventricle (LV) reverse remodeling.⁹

SyncAV is a device-based algorithm that is available in some CRT devices manufactured by Abbott (Chicago, IL). The algorithm alters the AV delay to allow biventricular pacing synchronized with intrinsic AV conduction.¹⁰ To achieve fusion between intrinsic conduction and biventricular pacing, the device continuously adjusts the AV delay by a set duration (programmable offset between 10 and 120 ms) relative to the measured intrinsic AV conduction interval. This process is dynamic and adjusts according to variations in device-measured intrinsic conduction time, thereby resulting in continuously adapting fusion pacing. Fusion pacing can also be achieved by fusion of LV pacing and intrinsic conduction.¹¹ The concept of fusion optimized interval was previously described by Arbelo et al.,¹² who demonstrated a reduction in QRS duration and an acute improvement in hemodynamics compared with nominal CRT programming. The same finding was also described by Varma et al.¹⁰ during

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Ethics Statement: This study was approved by the McGill University Health Center Institutional Review Board.

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device clinic visits. This analysis included only patients who could be programmed to the SyncAV algorithm (i.e., in sinus rhythm with intrinsic atrioventricular conduction). Echocardiography was performed before and 6 months after CRT optimization.

Results: Of 64 consecutive, potentially eligible patients who underwent assessment, 34 who were able to undergo SyncAV programming were included. Their mean age was 74 ± 9 years, 41% were female, and 59% had ischemic cardiomyopathy. The mean time from CRT implant to SyncAV optimization was 17.8 ± 8.5 months. At 6-month follow-up, SyncAV optimization was associated with a significant increase in left ventricular ejection fraction (LVEF) (mean LVEF $36.5\% \pm 13.3\%$ vs $30.9\% \pm 13.3\%$; $P < 0.001$) and a reduction in left ventricular end-systolic volume (LVESV) (mean LVESV 110.5 ± 57.5 mL vs 89.6 ± 52.4 mL; $P < 0.001$) compared with baseline existing CRT programming.

Conclusion: CRT reprogramming to maximize biventricular fusion pacing significantly increased LVEF and reduced LVESV in patients with chronic CRT devices. Further studies are needed to assess if a continuous fusion pacing algorithm improves long-term clinical outcomes and to identify which patients are most likely to derive benefit.

a de novo implant prospective study using the specific SyncAV algorithm described earlier. Recent published data reported a significant QRS narrowing with programming of SyncAV in existing CRT devices as determined acutely by 12-lead ECG, but did not report longer-term outcomes.^{13,14} The pacing configuration that achieved the narrowest QRS with SyncAV was biventricular pacing with SyncAV and an optimized offset.^{10,14}

Whether reprogramming of CRT to increase electrical synchrony translates into echocardiographic and functional status improvement remains unclear. We aimed to assess whether reprogramming with SyncAV is associated with an increase in left ventricular ejection fraction (LVEF) and a decrease in left ventricular end-systolic volume (LVESV) compared with routine CRT programming in patients with chronic CRT devices.

Methods

Study population

Patients at a single quaternary cardiac center (McGill University Health Center, Montreal, Canada) with a CRT defibrillator or a CRT pacemaker with a programmable SyncAV algorithm (St. Jude Unify Assura and Quadra Assura, or St. Jude Allure Quadra RF; St. Jude Medical, Saint Paul, MN) implanted between January 2014 and November 2017 were evaluated for SyncAV optimization starting in May 2018. The flow diagram for patient selection is shown in Figure 1. Of the 64 potentially eligible consecutive CRT implants, we excluded patients with device explant, lead dislodgement, loss to follow-up, loss of required AV conduction (preventing use of SyncAV

une optimisation électrocardiographique de routine de cet algorithme à l'occasion d'une consultation de suivi. L'analyse ne portait que sur les patients dont le dispositif pouvait être programmé au moyen de l'algorithme SyncAV (c.-à-d. en rythme sinusal avec conduction auriculoventriculaire intrinsèque). Une échocardiographie a été réalisée avant l'optimisation du DRC, puis 6 mois après.

Résultats : Sur les 64 patients consécutifs potentiellement admissibles qui ont fait l'objet d'une évaluation, 34 sujets dont le DRC pouvait être programmé à l'aide de l'algorithme SyncAV ont été retenus. Les sujets avaient en moyenne 74 ± 9 ans; 41 % d'entre eux étaient des femmes, et 59 % présentaient une cardiomyopathie ischémique. Le temps écoulé entre l'implantation du DRC et l'optimisation au moyen de l'algorithme SyncAV était en moyenne de $17,8 \pm 8,5$ mois. Au moment du suivi à 6 mois, l'optimisation au moyen de l'algorithme SyncAV a été associée à une augmentation significative de la fraction d'éjection ventriculaire gauche (FEVG) (FEVG moyenne de $36,5\% \pm 13,3\%$ vs $30,9\% \pm 13,3\%$; $p < 0,001$) et à une réduction du volume télesystolique ventriculaire gauche (VTSVG) (VTSVG moyen de $110,5 \pm 57,5$ mL vs $89,6 \pm 52,4$ mL; $p < 0,001$) comparativement à la programmation initiale du DRC.

Conclusion : La reprogrammation du DRC afin de maximiser la stimulation biventriculaire par fusion a considérablement augmenté la FEVG et réduit le VTSVG chez les patients porteurs d'un DRC permanent. D'autres études sont nécessaires pour déterminer si un algorithme de stimulation par fusion en continu permet d'améliorer les résultats cliniques à long terme et pour établir le profil des patients les plus susceptibles de bénéficier d'une telle intervention.

algorithm), transition to palliation, or refusal of optimization. The remaining 34 patients had ECG-based optimization performed and were included in this analysis. This study was approved by the McGill University Health Center Institutional Review Board, and patients included in the study fulfilled criteria for CRT implantation as per Canadian Cardiovascular Society guideline recommendations.¹⁵

Device programming

Details for ECG-based SyncAV optimization were as previously described.¹⁴ In brief, devices in all patients at our center were programmed according to operator preference (without use of SyncAV) until December 2017 when ECG-based CRT optimization became the standard of care for newly implanted devices. Routine in-clinic CRT optimization was performed starting May 2018 for patients with chronically implanted devices according to our protocol, including sequential ECGs.¹⁴ When programming with SyncAV, the optimal offset achieving the narrowest QRS was used.

Standard programming before the SyncAV optimization involved programming as set by the treating physician according to his/her standard clinical practice; there was no mandated programming protocol. This programming may have been nominal settings or settings selected by the treating physician (considering baseline ECG and postoperative paced ECG to guide programming). None of the devices in the patients were previously programmed using the SyncAV algorithm.

The SyncAV algorithm has been described.^{13,14} In brief, the SyncAV algorithm periodically extends the AV delay. When intrinsic ventricular events are sensed, the device

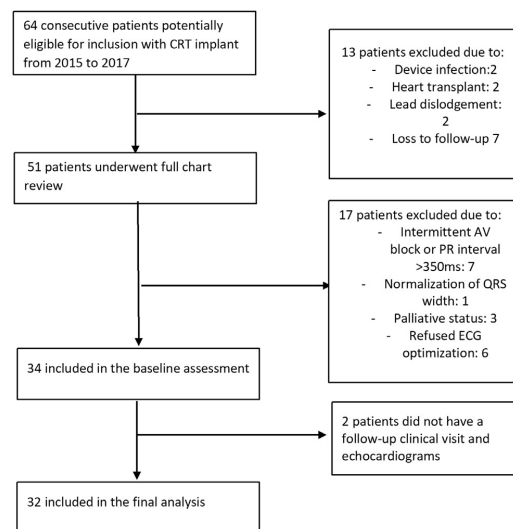


Figure 1. Flow diagram for patient selection. Modified from Aiturki et al.¹⁴ with permission from Elsevier.

reprograms the AV delay to a programmed shorter offset (default offset –50 ms) than the measured intrinsic AV interval. The offset can be programmed over a range of values to find the ideal offset that achieves electrical synchrony for each patient. The device was then programmed at that “ideal” offset for each patient.

Electrocardiographic measurements

Standard 12-lead electrocardiography was performed at a paper speed of 25 mm/s and a scale of 10 mm/mV, and QRS duration was measured automatically by the ECG machine (GE MAC 5500 HD Resting ECG System, Boston, MA) as previously described.¹⁴ The ECG machine is programmed to measure the earliest onset of the QRS and the latest offset; this translates into the duration from the pacemaker spike until the end of the QRS. QRS duration was subsequently validated manually by a single investigator who was blinded to the clinical data and pacing programming.

Echocardiographic and clinical outcomes

At the baseline visit during which SyncAV programming was activated, all patients had a clinical assessment, including determination of New York Heart Association (NYHA) functional class and a transthoracic echocardiogram. All patients were scheduled for a clinical follow-up and a transthoracic echocardiogram 6 months postoptimization. NYHA functional class, LVEF, LVESV, and mitral regurgitation (MR) severity as assessed on a grade scale (0 = none or trivial, 1 = mild, 2 = moderate, 3 = moderate to severe, and 4 = severe)¹⁶ were recorded. Other echocardiographic measurements included left ventricular end-diastolic volume (LVEDV) and pulmonary artery systolic pressure (PASP). LVESV and LVEDV were measured in the apical 4-chamber and apical 2-chamber views and then averaged; LVEF was calculated using Simpson’s biplane

method. The echocardiograms were read by level III trained echocardiographers who were unaware of device programming.

We defined a positive LVEF response to CRT as an absolute increase in LVEF $\geq 10\%$; we find this value to be of clinical relevance. Previous studies have used cutoffs ranging from 5% to 15%.¹⁷ LVEF response was assessed ≥ 6 months after the initial implant procedure (compared with LVEF before CRT implant), and LVEF response was subsequently reassessed 6 months after SyncAV ECG optimization (compared with LVEF immediately before SyncAV ECG optimization). In addition, response as measured by a $\geq 15\%$ decrease in LVESV was also assessed 6 months after SyncAV ECG optimization compared with LVESV before SyncAV ECG optimization; the LVESV response after initial CRT could not be assessed because of the absence of data regarding LVESV before initial CRT.

Statistical analysis

All data are presented as mean $\pm$ standard deviation for continuous variables and as proportions for categorical variables. A paired *t* test was used to compare outcomes before and 6 months after SyncAV optimization. A *P* value of < 0.05 was considered statistically significant. Statistical analysis was performed using StatsDirect 3 (StatsDirect Ltd., 2013, Birkenhead, England).

Results

Patient characteristics

Patient characteristics at the time of SyncAV optimization are summarized in Table 1. At 6 months of follow-up, 94% of patients had complete clinical and echocardiographic data. Their mean age was 74 ± 9 years, 41% were female, and 59% had ischemic cardiomyopathy. The mean time from CRT implant to SyncAV optimization was 17.8 ± 8.5 months. At the time of SyncAV optimization, the mean intrinsic conduction QRSD was 163 ± 24 ms, the mean existing CRT pacing QRSD was 152 ± 25 ms, and the SyncAV optimized mean QRSD was 138 ± 23 ms.

In terms of response to CRT, the mean LVEF was 24.1 ± 10.1 before initial CRT implantation, and with standard CRT programming, 44% of patients had had a significant improvement in LVEF (LVEF responders $\geq 10\%$), whereas the remaining 56% had not improved their LVEF $\geq 10\%$ and were deemed CRT LVEF nonresponders.

Left ventricular ejection fraction

The mean LVEF before SyncAV optimization was $30.9\% \pm 13.3\%$ (median, 27.5%; interquartile range, 20%–40%) and after 6 months increased to $36.5\% \pm 13.3\%$ (median, 40%; interquartile range, 25%–50%). The mean difference in LVEF was 6.3%, 95% confidence interval (CI), 3.1%–9.5%, $P < 0.001$ (Fig. 2A). Of the 32 patients with follow-up LVEF, 40% had an increase $\geq 10\%$, including 9% who had an increase $> 15\%$. In addition, a further 19% of patients had an increase of $\geq 5\%$ but not reaching 10%, and the remaining (41%) had no significant change in LVEF (Fig. 3). Of those who had not responded to initial CRT (19, 56%), 9 patients (47%) had a significant improvement in LVEF (LVEF responders, $\geq 10\%$),

Table 1. Baseline patient characteristics

Characteristic	All patients N = 34	Initial CRT responders N = 15	Initial CRT nonresponders N = 19
Male, n (%)	19 (56)	7 (50)	12 (63)
Age, y (range)	74 (60-93)	74 (60-89)	75 (63-93)
Time since implant in mo, mean (range)	17.8 ± 8.5	16.5 ± 9.3	17.8 ± 7.2
Ischemic cardiomyopathy, n (%)	21 (62)	6 (40)	15 (79)
Hypertension	28 (82)	14 (93)	14 (78)
Diabetes mellitus	8 (24)	4 (27)	4 (21)
Paroxysmal atrial fibrillation	10 (29)	3 (20)	7 (37)
Left bundle branch block	31 (91)*	15 (100)	16 (84)
CRT defibrillator	22 (65)	10 (67)	12 (63)
NYHA, n (%) [†]			
I	4 (11.8)	1 (7)	3 (16)
II	24 (70.6)	14 (93)	10 (53)
III	6 (17.6)	0 (0)	6 (31)
QRSd (ms)	163.5 ± 24.3	168.1 ± 17.3	158.9 ± 29.1
Intrinsic PR interval (ms)	187.2 ± 36.6	184.9 ± 21.1	187.3 ± 46.5
LVEF (%) before initial CRT	24.1 ± 10.1	24.9 ± 9.4	23.7 ± 10.5
LVEF (%) before SyncAV	30.9 ± 13.3	41.1 ± 9.6	23.4 ± 10.6
LVEDV (mL) [‡]	157.5 ± 56.6	133.4 ± 43.5	174.1 ± 59.7
LVESV (mL) [‡]	110.5 ± 57.5	75.6 ± 31.8	134.5 ± 59.7
Left atrial diameter (cm)	43.3 ± 7.0	42.5 ± 6.6	43.9 ± 7.5
Medical therapy for heart failure			
ACEI/ARB	28 (82)	12 (80)	16 (84)
β-Blocker	28 (82)	12 (80)	16 (84)
MRA	5 (15)	2 (13)	3 (16)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT, cardiac resynchronization therapy; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MRA, magnetic resonance angiography; NYHA, New York Heart Association; QRSd, QRS duration.

Modified from Alturki et al.¹⁴ with permission from Elsevier.

* The remaining 3 were bifascicular block (right bundle branch block and left anterior fascicular block or left posterior fascicular block).

[†] Before SyncAV ECG optimization.

and 10 patients (53%) remained nonresponders after SyncAV optimization (Fig. 4). This increased the proportion of total LVEF responders to 71%. In contrast, 33% of those who had already responded to initial CRT had a significant further improvement in LVEF ($\geq 10\%$). No patient had a significant reduction in LVEF ($>5\%$).

In patients who responded to initial CRT, mean LVEF increased from $41.1\% \pm 9.6\%$ to $45.4\% \pm 8.2\%$ ($P = 0.01$) after SyncAV ECG optimization. In patients who did not respond to initial CRT, mean LVEF increased from $23.4\% \pm 10.6\%$ to $31.4\% \pm 13.3\%$ ($P < 0.001$) after SyncAV ECG optimization (Supplemental Fig. S1). There was no difference in change in LVEF after SyncAV optimization between those who had initially responded and those who had not ($P = 0.24$).

Left ventricular end-systolic volume

Mean LVESV before SyncAV optimization was 110.5 ± 57.5 mL and after 6 months decreased to 89.6 ± 52.4 mL; the mean difference in LVESV was -19.0 mL, 95% CI, -8.3 to -29.6 , $P < 0.001$ (Fig. 2B). After SyncAV ECG optimization, 17 patients (53%) had a significant decrease $\geq 15\%$ in LVESV. Of these patients, 7 (41%) were already LVEF responders after initial CRT and 10 (59%) did not have an LVEF response after initial CRT.

Mitral regurgitation

After optimization with SyncAV, there was a significant reduction in the severity of MR (mean MR grade 0.9 ± 1.0 before SyncAV vs 0.5 ± 1.0 after SyncAV optimization;

$P < 0.001$) (Fig. 5). Before SyncAV optimization, 41% of patients had no or trivial MR, 41% had mild MR, 16% had moderate to severe MR, and 3% had severe MR. At 6 months of follow-up after SyncAV optimization, 68% had no or trivial MR, 16% had mild MR, 16% had moderate to severe MR, and none had severe MR. The distribution of MR severity is shown in Figure 6.

Other echocardiographic measurements

Mean LVEDV before SyncAV optimization was 157.5 ± 56.6 mL and after 6 months decreased to 141.3 ± 55.7 mL; the mean difference in LVEDV was -14.1 mL, 95% CI, -3.1 to -25.2 , $P = 0.007$. PASP also decreased after SyncAV ECG optimization. Mean PASP was 37.5 ± 14.7 mm Hg before SyncAV optimization and decreased to 32.9 mm Hg ± 10.3 at 6 months after optimization (mean difference -4.2 mm Hg, 95% CI, -0.3 to -8.1 , $P = 0.04$).

NYHA and medication use

No significant difference in NYHA functional class was observed after SyncAV optimization (mean NYHA 2.1 ± 0.5 before SyncAV vs 2.0 ± 0.5 after SyncAV optimization; $P = 0.16$). The distribution of NYHA functional class is summarized in Supplemental Figure S2. There was no significant difference in the use of heart failure medication (Supplemental Table S1).

Discussion

The main finding of this analysis is that in patients with chronically implanted CRT devices, optimization using a

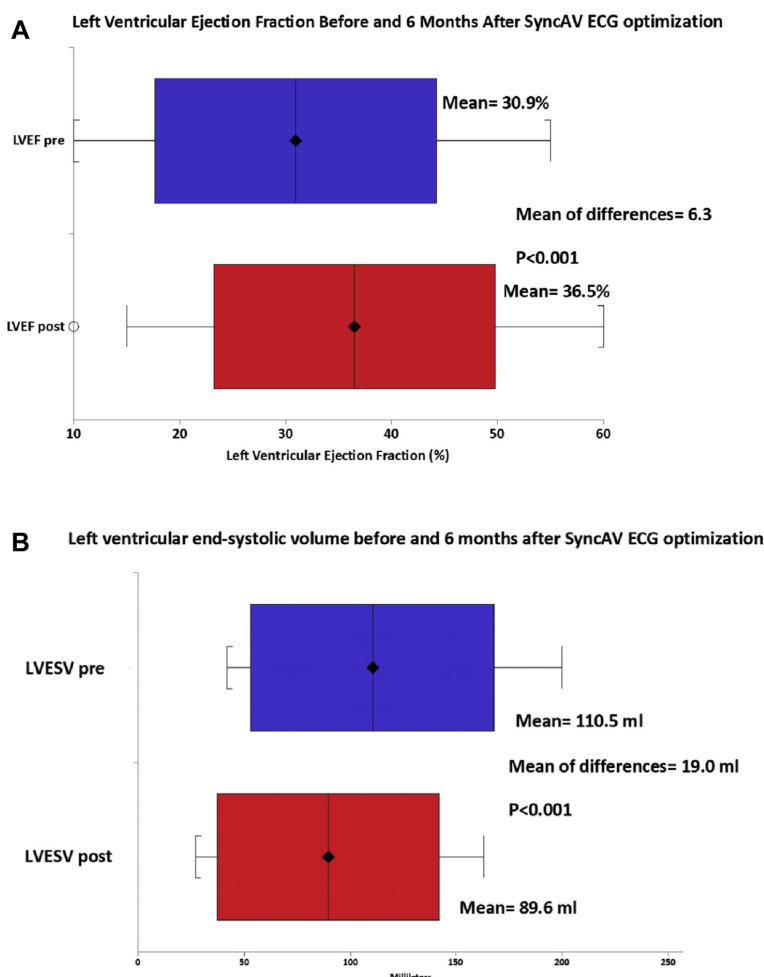


Figure 2. Change in (A) left ventricular ejection fraction (LVEF) and (B) left ventricular end-systolic volume (LVESV) before and 6 months after SyncAV electrocardiogram (ECG) optimization.

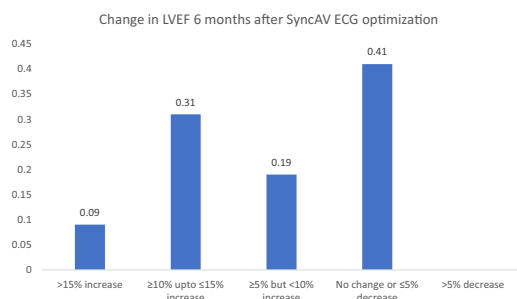


Figure 3. Patients stratified by the change in LVEF at 6-month follow-up compared with baseline.

biventricular fusion-pacing algorithm to achieve further reduction in QRSd was associated with a significant increase in LVEF at 6 months after optimization. To the best of our knowledge, this is the first study to demonstrate that an increase in electrical synchrony is associated with echocardiographic improvement in patients chronically implanted with CRTs, irrespective of previous responder status, using an easy, quick, and reproducible ECG-based optimization that can be performed during a regular device clinic follow-up visit. Echocardiographic response to CRT has been assessed using cutoffs of an increase in LVEF $\geq 5\%$ and a decrease in LVESV $\geq 10\%$.^{18,19} A combination of an LVEF improvement $\geq 5\%$ and LVESV reduction $\geq 10\%$ was shown to be the best predictor for improved survival.²⁰ In this analysis, stricter cutoffs of an

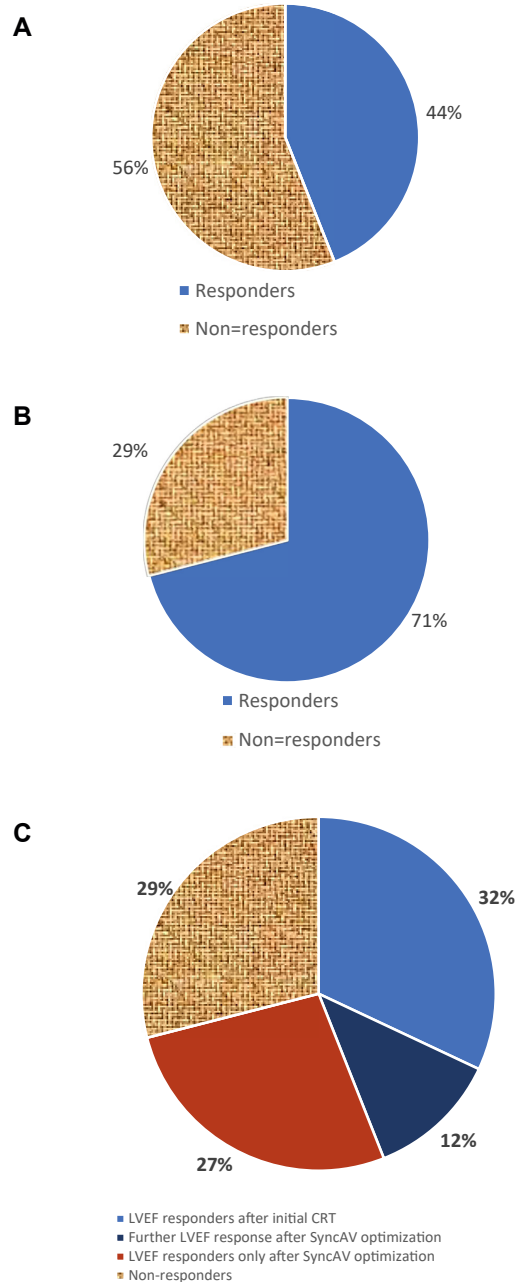


Figure 4. Proportion of patients who responded to cardiac resynchronization therapy (CRT) as defined by an LVEF increase of ≥ 10 . **(A)** After initial CRT. **(B)** After SyncAV. **(C)** After SyncAV stratified by initial response to CRT.

increase in LVEF $\geq 10\%$ and a decrease in LVESV $\geq 15\%$ were used to provide a more specific indicator of CRT response.

Another important finding is the high proportion of patients (44%) classified as nonresponders after initial CRT therapy who subsequently had a significant improvement in LVEF (at least 10% absolute LVEF increase) after optimization using SyncAV. In addition to conversion of non-responders to responders, QRS narrowing and a further increase in LVEF (at least 10%) were also seen in 1 in every 3 patients who already responded to initial CRT therapy, demonstrating a further improvement in electrical and mechanical synchrony. None of the patients had QRS widening or worsening in the LVEF or MR at 6 months after continuous CRT optimization using the SyncAV algorithm. Trucco et al.²¹ showed that baseline manual optimization of the AV and ventriculo-ventricular delays, to achieve biventricular fusion pacing, immediately postimplantation leads to a greater proportion of patients achieving both electrical synchrony and LV reverse remodelling at 12 months. Our study validates the long-term effect of an automated continuously optimized biventricular fusion-pacing algorithm.

Unfortunately, CRT device optimization is not routinely performed as revealed in the international survey by Gras et al.⁵ Approximately 58% of electrophysiologists do not optimize CRT postimplantation and just used the nominal settings.⁴ Part of this issue is probably related to the time-consuming and complex nature of echocardiographic and intrinsic electrogram-based optimization.⁴ In addition, multiple studies have shown a lack of benefit of these approaches compared with routine out-of-the-box settings.²² Even in studies that used an ECG-based optimization, the ECG analyses were performed with a paper speed between 50 and 300 mm/s, used computerized recording systems, and required experienced observers for QRS width measurement.^{12,21} In contrast, we used the standard 12-lead surface ECG at a regular speed of 25 mm/s with automated measurements, which are faster, accurate, and easily reproducible.

Our study was unable to demonstrate a significant improvement in NYHA functional class status, although no patient had a worsening of functional status. The QRS narrowing observed during our analysis (152 ± 25 ms during the baseline evaluation to 138 ± 23 ms after optimization) was similar to that observed in other studies that assessed fusion pacing.^{4,7} Such a reduction in QRSd has been shown to correlate with clinical outcomes. In a meta-analysis, Korantzopoulos et al.⁷ showed that QRS narrowing is a strong predictor of clinical and echocardiographic response (or super response) to CRT. LV fusion pacing has been tested using the AdaptiveCRT algorithm, which periodically assesses intrinsic conduction; during normal AV conduction, only LV pacing is provided while biventricular pacing with adjustments of the ventriculo-ventricular timing occurs during prolonged AV conduction.^{23,24} Adaptive CRT has been shown to be non-inferior to nominal CRT with suggestion of improvements in clinical status, echocardiographic parameters, and clinical outcomes, and a reduction in the incidence of atrial fibrillation particularly in patients with normal AV conduction.^{23–26} A large prospective, randomized, controlled, multicentre,

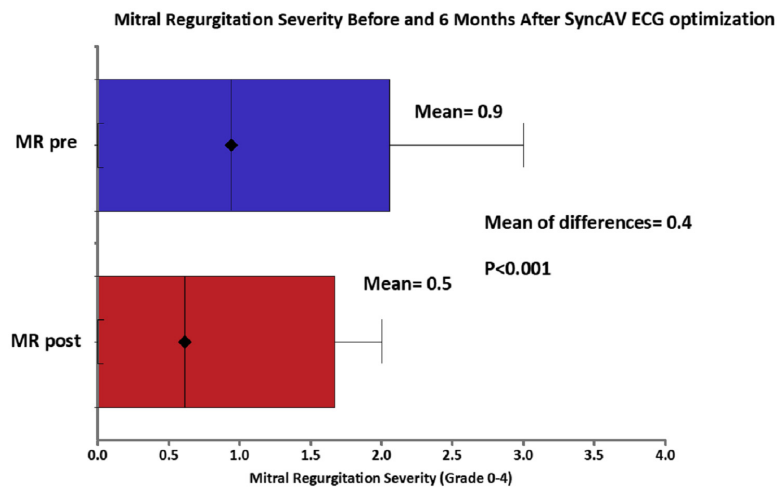


Figure 5. Change in mitral regurgitation (MR) severity before and 6 months after SyncAV ECG optimization.

clinical trial is under way to assess the impact of AdaptiveCRT on cardiovascular outcomes.²⁷

Identifying predictors of nonresponse to CRT remains a great challenge. Despite important advances to improve patient selection based on clinical characteristics, QRS duration, and QRS morphology, the frequency of nonresponse to CRT continues to be a major issue.^{2,28} Our results suggest that in a considerable proportion of these patients, if sinus rhythm with intrinsic AV conduction is present, a fusion pacing algorithm can improve electrical and mechanical synchrony.

Limitations

This is a single-center study with a limited sample size and 6 months of follow-up after SyncAV optimization. However, significant improvements in LVEF were demonstrable and correlated with QRS narrowing. It is noteworthy that clinical improvement after CRT usually

coincides with electrical synchrony and LV reverse remodelling and an increase in LVEF.^{7,29,30} Furthermore, previous data indicate that patients who respond to CRT in the first 6 months are likely to have further improvement in LVEF at the 1- and 2-year marks.³¹ Although the trajectory for LVEF after initial CRT cannot be definitively ascertained, most studies assess CRT response at 6 months or 12 months, and the majority of responders usually show improvement at 6 months.^{18,19,32} In this study, the mean time from implantation of CRT to initial programming of SyncAV was 17.8 ± 8.5 months, and the results of this study assess echocardiographic parameters before and 6 months after SyncAV optimization. In addition, we used stricter cutoffs for LVEF and LVESV to increase the robustness of our results. The study is well powered for the detection of changes in QRSd and LVEF but not for clinical outcomes. Whether the improvement in LVEF translates into better clinical outcomes will require larger

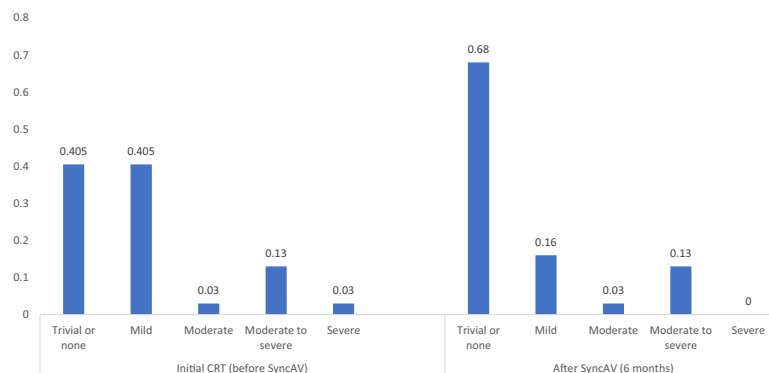


Figure 6. Proportion of patients with various MR severity grades after initial CRT (before SyncAV optimization) and after SyncAV optimization.

randomized studies with longer-term follow-up. A randomized trial of approximately 200 patients is currently under way and will provide the needed insight (NCT03961399). In addition, larger studies will be needed to identify predictors of response to SyncAV optimized pacing. Finally, the determination of response to CRT was based on LVEF and not LVESV because of lack of LVESV data before initial CRT. However, although LVESV is a sensitive marker for LV reverse remodelling, an LVEF increase $\geq 10\%$ is likely to reflect a more clinically meaningful echocardiographic improvement and if anything may underestimate the response to SyncAV. In addition, we have provided the LVESV data before and after SyncAV optimization. The time from initial CRT implant to pre-SyncAV echo varied in each patient, but the time before and after SyncAV was similar at approximately 6 months.

Conclusion

ECG-based CRT optimization using an algorithm to achieve biventricular pacing fused with intrinsic conduction significantly improved electrical synchrony and LVEF in chronically CRT-paced patients. Improved ventricular function at 6 months after CRT optimization was independent of prior response to conventional CRT. This clinic-based method was a simple, safe, and effective means to optimize previously implanted CRT devices. Larger randomized studies are required to compare long-term clinical outcomes between dynamically optimized biventricular fusion pacing and traditional biventricular CRT pacing to inform whether chronic CRT devices with this algorithm in these patients should be reprogrammed.

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Disclosures

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at <https://www.cjcopen.ca/> and at <https://doi.org/10.1016/j.cjco.2019.12.005>.

Reprint of manuscript 3



Fusion pacing in patients with right bundle branch block who undergo cardiac resynchronization therapy

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ABSTRACT

Purpose: Patients with right bundle branch block (RBBB) are less likely to respond to cardiac resynchronization therapy (CRT). We aimed to assess whether patients with RBBB respond to CRT with biventricular fusion pacing. **Methods:** Consecutive patients with RBBB at a single tertiary care center, who were implanted with a CRT device capable of biventricular fusion pacing using SyncAV programming, were assessed and compared to a historical cohort of CRT patients with RBBB. QRSd was measured and compared during intrinsic conduction, nominal CRT pacing and manual electrocardiogram-based optimized SyncAV programming. Left ventricular ejection fraction (LVEF) was also compared before and 6 months after CRT.

Results: We included 8 consecutive patients with RBBB (group 1) who were able to undergo SyncAV programming and 16 patients with RBBB (group 2) from a historical cohort. In group 1, compared to mean intrinsic conduction QRSd (155 ± 13 ms), mean nominally-paced QRSd was 156 ± 15 ms (Δ QRSd 1.3 ± 11.6 ; $p = 0.77$) and SyncAV-optimized paced QRSd was 135 ± 14 ms (Δ QRSd -20.0 ± 20.4 ; $p = 0.03$ and Δ QRSd -21.3 ± 16.3 ; $p = 0.008$; compared to intrinsic conduction and nominal pacing respectively). In group 2, mean QRSd with nominal pacing was 160 ± 24 ms (Δ QRSd 3.8 ± 33.4 ; $p = 0.66$ compared to intrinsic conduction). In group 1, baseline LVEF was 22.1 ± 11.5 and after 6 months of follow-up was 27.8 ± 8.6 ($p = 0.047$). In group 2, the baseline LVEF was 27.2 ± 10.6 and after 6 months of follow-up was 25.0 ± 10.0 ($p = 0.45$).

Conclusions: CRT programed to allow biventricular fusion pacing significantly improved electrical synchrony and LVEF in patients with RBBB. Larger studies are required to confirm these findings.

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Introduction

Cardiac resynchronization therapy (CRT) is an important therapeutic modality in patients with heart failure and reduced ejection fraction, who have left bundle branch block (LBBB) [1]. CRT, in this population, reduces cardiovascular death and heart failure hospitalization [2]. It is well known that in those with non-LBBB morphology, the response to CRT is significantly lower [3,4]. In particular, those with right bundle branch block (RBBB) are less likely to respond to CRT. In 2016, a sub-analysis of the MADIT-CRT trial found no overall clinical benefit with CRT in those with non-LBBB, including the sub-group with RBBB [5]. One possible mechanism is that biventricular pacing does not lead to improved electrical synchrony. In an analysis of electrical synchrony after CRT, Hadjis et al. showed that those with non-LBBB were unlikely to achieve improved electrical synchrony and consequently reverse

remodelling after CRT [6]. Another study targeting the site of latest electrical activation when implanting the left ventricular lead in patients with non-LBBB did not result in improved outcomes [7].

SyncAV is a closed-loop algorithm that dynamically adjusts the atrioventricular (AV) delay to continuously synchronize biventricular pacing with intrinsic AV conduction. By periodically extending the AV delay, the device examines intrinsic ventricular events that are sensed [8–11]. A shortening between 10 and 120 ms (default 50 ms) of the AV delay, relative to the measured intrinsic AV conduction interval, is programmed to allow fusion between intrinsic AV conduction and biventricular pacing. This allows the paced ventricular wavefronts to fuse with intrinsic wavefronts propagating down the interventricular septum.

Recently, several studies have demonstrated greater electrical synchrony, based on the narrowing of the QRS complex, using a SyncAV fusion stimulation strategy [8,9,11]. The improvement in electrical synchrony was also confirmed using vectorcardiography [12]. SyncAV fusion pacing provided the greatest improvement in electrical synchrony compared to conventional CRT and multi-point pacing as well as having a synergistic effect when superimposed with the latter [13].

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Furthermore, fusion pacing using the SyncAV algorithm was associated with improvements in acute hemodynamic measures as well as reverse remodelling on echocardiography [10,14]. However, these studies were almost exclusively in patients with LBBB.

Efforts are required to improve electrical synchrony after CRT in patients with RBBB. Whether biventricular fusion pacing using SyncAV can increase electrical synchrony has not been elucidated. We aimed to assess whether patients with RBBB have a significant reduction in QRS complex duration (QRSd), as a metric of electrical resynchronization, with SyncAV fusion pacing compared to both CRT pacing with nominal AV delays and intrinsic rhythm without pacing.

Methods

Study design and population

This was a single center, retrospective study conducted at the McGill University Health Center, Montreal, Canada. This study was approved by the McGill University Health Center Institutional Review Board. All patients included in the study fulfilled criteria for CRT implantation as per Canadian Cardiovascular Society guideline recommendations [15]. The main cohort in this study (group 1) had a CRT defibrillator (CRT-D) (St-Jude Unify Assura and Quadra Assura 3) or CRT pacemaker (CRT-P) (St-Jude Allure Quadra RF) with programmable SyncAV algorithm, implanted between April 2015 and November 2019. To be eligible for inclusion in this analysis, patients had to be programmable to the SyncAV algorithm, i.e. be in sinus rhythm with intrinsic AV conduction. This analysis was limited to patients with RBBB, which was defined in accordance with standard electrocardiogram (ECG) interpretation recommendations [16]. Comparison was provided by a historical cohort of consecutive patients with RBBB and implanted between January 2012 and March 2015 (group 2), before negative AV hysteresis (SyncAV) was used at our site [6]. Of 231 CRT devices implanted during that time period in patients with intrinsic conduction and QRS >120 ms, 197 were excluded on the basis of LBBB morphology. Of the remaining 34 patients with non-LBBB morphology, only patients with RBBB as well as in sinus rhythm with intrinsic conduction (PR <350 ms) were included in the current analysis (Fig. 1).

Device programming

ECG-based optimization to identify the best QRS width to adjust the resynchronization has become the standard of care in our center starting in 2018. All patients in the main cohort of this study (group 1 with SyncAV capable devices) coming for regular clinical follow up had the device optimized according to our service's protocol including sequential ECGs. This included those who received new CRT implants in 2018 as well as those with devices implanted prior to 2018 coming for regular device clinic follow-up. At the first clinical follow-up for each patient in 2018 and immediately post-implantation for new devices implanted since 2018, the device was programed at the following pacing configurations to allow comparative measurements by 12-lead continuous ECG recordings: 1) intrinsic conduction, 2) CRT pacing as programmed by the treating physician prior to SyncAV optimization (nominal biventricular CRT), 3) manual ECG-based optimized SyncAV programming. In order to identify the most optimized SyncAV programming, various SyncAV offsets of −10, −30, −50, −70, −90 and −120 ms were evaluated. After completion of the above ECG data collection, devices were programmed to the SyncAV setting with the narrowest QRS. In the historical cohort, ECG recordings were obtained prior to and immediately after device implantation. Biventricular pacing was compared to intrinsic conduction. The setting for biventricular pacing was the discretion of the operator: either nominal settings or optimized ventriculo-ventricular delays based on perception of optimal QRS width and vector. This was performed immediately after implantation.

Electrocardiographic measurements

Standard 12-lead electrocardiography was performed at a paper speed of 25 mm/s and a scale of 10 mm/mV. QRS duration, as recorded from the surface leads with the greatest values, was automatically measured by the ECG machine (GE MACTM 5500 HD Resting ECG System). The ECG machine is programmed to measure the earliest onset of the QRS and the latest offset, which would be from the time of the pace-maker spike until the end of the QRS. Validation was then manually performed by a single investigator, blinded to the clinical data and pacing programming: the QRSd was defined as the duration from the earliest deflection from the isoelectric line to the latest return to the isoelectric line in any lead ignoring any pre-QRS deflections attributed to pacing artifacts. Change in QRSd was assessed and compared to intrinsic conduction and between the different modes of programming. These measurements were similarly obtained in both cohorts.

Echocardiographic assessment

In patients receiving a new device implant, all patients underwent a transthoracic echocardiogram which included the determination of left ventricular ejection fraction (LVEF) using Simpson's biplane method, prior to device implantation. The interpretation was performed by a level III echocardiographer. At 6 to 9 months post-implantation, a repeat echocardiogram was performed to reassess LVEF. In patients with a previously implanted device in whom SyncAV programming was activated, an echocardiogram was performed prior to SyncAV programming and 6 to 9 months after. The echocardiographer was unaware of changes in device programming. In the historical cohort, echocardiography was performed at baseline prior to implantation and follow-up echocardiography was performed between 6 and 12 months post implantation.

Statistical analysis

All data are presented as mean $\pm$ SD for continuous variables and as proportions for categorical variables. Differences in QRSd and Δ QRSd among settings were assessed using one-way ANOVA, followed by Tukey-Kramer multiple-comparison tests. A paired *t*-test was used to compare outcomes prior to and 6 months after CRT or SyncAV optimization. An unpaired *t*-test was used to compare between groups 1 and 2. A *P*-value of <0.05 was considered statistically significant.

Results

Patient characteristics

We included 8 consecutive patients (group 1) with RBBB who were able to undergo SyncAV programming (5 new device implants and 3 previously implanted patients, time from implant ranging from 15 to 29 months). The mean age was 70 ± 12 years, 88% were male, 63% had ischemic cardiomyopathy, 75% received a CRT-D and the mean NYHA score was 2.1 ± 0.6 . Baseline characteristics are summarized in Table 1. All patients were receiving angiotensin converting enzyme inhibitors/angiotensin receptor blockers and beta blockers and 50% were receiving mineralocorticoid receptor antagonists. The mean intrinsic conduction QRSd was 155 ± 13 ms.

In comparison, there were 16 patients (group 2) with RBBB who received a CRT device in the historical cohort. The mean age was 71 ± 16 years, 88% were male, 63% had ischemic cardiomyopathy, and the mean NYHA score was 2.3 ± 0.8 . The mean intrinsic conduction QRSd was 164 ± 22 ms.

Change in QRSd

In the first group of patients with SyncAV capable devices, mean QRSd with nominal pacing was 156 ± 15 ms (Δ QRSd 1.3 ± 11.6 ; *p* =

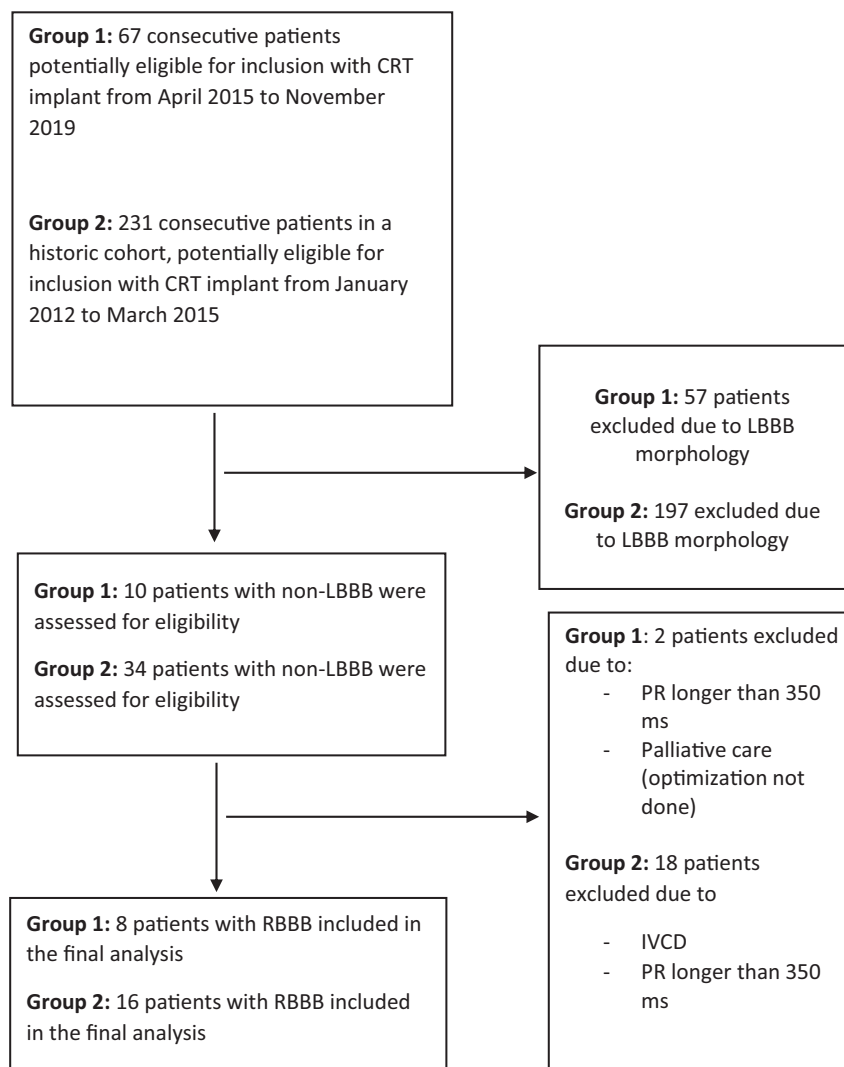


Fig. 1. Flow diagram for inclusion or exclusion of patients. CRT = cardiac resynchronization therapy; LBBB = left bundle branch block; RBBB = right bundle branch block; IVCD = interventricular conduction delay.

0.77 compared to intrinsic conduction) (Fig. 2) and 135 ± 14 ms ($\Delta\text{QRSd} -20.0 \pm 20.4$; $p = 0.03$) with optimized SyncAV pacing. Optimized SyncAV was also associated with a reduction in QRSd compared to nominal CRT pacing ($\Delta\text{QRSd} -21.3 \pm 16.3$; $p = 0.008$). In the group 2, mean QRSd with nominal pacing was 160 ± 24 ms ($\Delta\text{QRSd} 3.8 \pm 33.4$; $p = 0.66$ compared to intrinsic conduction).

Change in LVEF

In group 1 with SyncAV programmable devices, the baseline LVEF was 22.1 ± 11.5 and after 6 months of SyncAV CRT pacing was 27.8 ± 8.6 ($\Delta\text{LVEF} 5.7 \pm 6.1$, $p = 0.047$) (Fig. 3). In group 2, the baseline LVEF was 27.2 ± 10.6 and after 6 months of nominal CRT pacing post

implant was 25.0 ± 10.0 ($\Delta\text{LVEF} -2.2 \pm 11.4$, $p = 0.45$). Compared to nominal CRT pacing in group 2, optimized SyncAV CRT pacing in group 1 was associated with an increase in LVEF ($p = 0.04$).

Responder status

In the first group with SyncAV capable devices, only 13% of patients had a significant reduction in QRSd (≥ 10 ms) with nominal CRT pacing compared to 63% with optimized SyncAV pacing ($p = 0.06$) (Fig. 4). Interestingly, in those who had a significant reduction in QRSd with optimized SyncAV pacing, the SyncAV offset was ≥ 90 ms in 80% of patients. Of the 8 patients, 4 (50%) had a significant improvement in LVEF ($\geq 10\%$), all of whom had a significant reduction in QRSd. In the second group,

Table 1
Baseline patient characteristics.

Characteristic	RBBB with SyncAV device (Group 1)	RBBB with non-SyncAV device (Group 2)
N	8	16
Male, n (%)	7 (88)	14 (88)
Mean age, year	70 ± 12	71 ± 16
Ischemic cardiomyopathy, n (%)	5 (63)	10 (63)
Hypertension	7 (88)	12 (75)
Diabetes mellitus	4 (50)	7 (44)
Paroxysmal atrial fibrillation	4 (50)	9 (56)
Cardiac resynchronization therapy defibrillator	6 (75)	13 (81)
Mean NYHA, (SD)	2.1 ± 0.6	2.3 ± 0.8
Intrinsic QRSD (ms)	155 ± 13	164 ± 22
Conduction abnormalities		
RBBB only	1 (13)	4 (25)
RBBB + LAFB	6 (75)	11 (69)
RBBB + LPFB	1 (13)	1 (6)
Left ventricular ejection fraction (%) prior to initial CRT	22.1 ± 11.5	27.2 ± 10.6
Medical therapy for heart failure		
ACEI/ARB	8 (100)	16 (100)
Beta blocker	8 (100)	16 (100)
MRA	4 (50)	7 (44)

N = number; NYHA = New York Heart Association; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; SD = standard deviation. RBBB = right bundle branch block; LAFB = left anterior fascicular block; LPFB = left posterior fascicular block; CRT = cardiac resynchronization therapy; MRA = mineralocorticoid receptor antagonist.

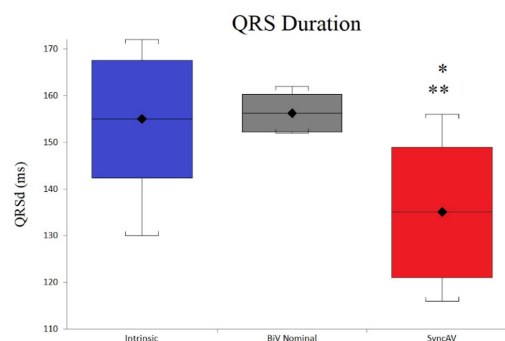
31% had a significant reduction in QRSD with nominal pacing and 13% had a significant increase in LVEF ($\geq 10\%$). All those who had a significant increase in LVEF also had a significant reduction in QRSD. There was a statistically significant, moderate negative correlation between change in QRS duration and change in LVEF (Spearman correlation coefficient = -0.42 , $p = 0.02$) (Fig. 5).

Discussion

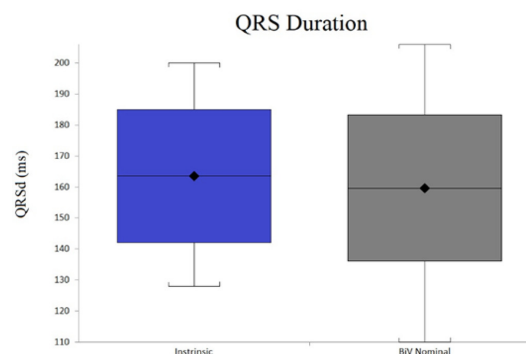
Fusion pacing using the SyncAV algorithm was associated with a significant reduction in QRSD compared to intrinsic and nominal biventricular pacing in patients with RBBB. Furthermore, fusion pacing using the SyncAV algorithm was associated with a significant improvement in LVEF. Importantly, these findings of a reduction in QRSD and increase in LVEF are in contrast to a similar cohort of patients who did not receive SyncAV fusion pacing. To our knowledge, our study is the first to assess the effect of fusion pacing on electrical and echocardiographic parameters in patients with RBBB morphology. The results of our analysis also reinforce the need for tailored programming to achieve the narrowest QRS.

An increase in electrical synchrony as manifested by a reduction in QRSD after CRT is an important therapeutic target and has been shown to correlate with echocardiographic and clinical outcomes, including reverse remodelling [17]. This was described by Korantzopoulos and colleagues in a meta-analysis of 27 studies; in this analysis a mean difference of -19 ms (95% CI -15 to -24) predicted both a clinically and echocardiographic response to CRT [18]. In the current study, we observed a mean decrease of -20 ms in QRSD using SyncAV compared to both intrinsic rhythm as well as nominal CRT pacing. Furthermore, in the historical cohort, there was no reduction in QRSD with CRT. Our results indicate that in patients with RBBB, electrical synchrony was achieved using SyncAV but not nominal CRT. In another analysis of electrical synchrony after CRT, Hadjis et al. examined the effect of QRS morphology on QRSD reduction for patients divided into three groups: those that met strict LBBB criteria [19] who are more likely to have a true LBBB, those who only met conventional LBBB criteria but not strict

A)



B)



* $P=0.03$ compared to intrinsic rhythm

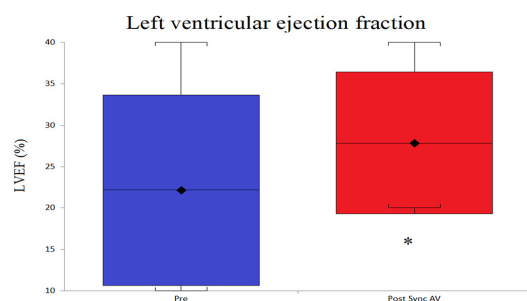
** $P=0.008$ compared to nominal CRT pacing

Fig. 2. QRS duration after nominal CRT and SyncAV programming compared to intrinsic QRS duration in patients A) with SyncAV capable devices (group 1) and B) without SyncAV capable devices (group 2). Biv = biventricular.

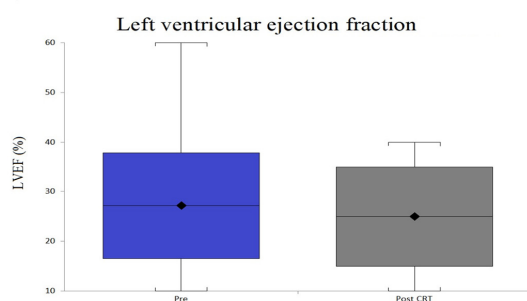
LBBB and those with non-LBBB morphology [6]. Only those who met strict LBBB had a mean reduction in QRSD (-20.9 ± 12.4 ms). Interestingly, this magnitude of QRSD reduction was similar to that observed in the current study for patients with RBBB and SyncAV optimized CRT pacing. In the current study, we also found a similar moderate negative correlation between change in QRSD and change in LVEF.

A fusion pacing strategy has been shown to achieve the narrowest QRS duration and improve electrical synchrony in patients with preserved AV conduction in both de novo and chronically biventricular paced situations as compared to intrinsic rhythm, nominal CRT pacing and an algorithm designed to achieve electrical synchrony [8,9,11,12]. However, none of these studies were designed or had been able to make a dedicated analysis of fusion pacing in RBBB patients. Varma and colleagues analyzed a cohort of 75 patients who had LBBB at the time of CRT implantation with optimized LV position. The mean QRSD was 162 ± 16 ms and was reduced by a mean of 20 ms to 30 ms depending on SyncAV optimization (fixed offset up to tailored

A)



B)



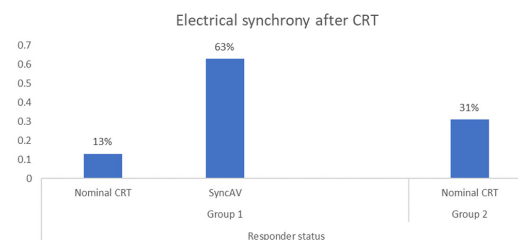
* P= 0.047

Fig. 3. Left ventricular ejection fraction after nominal CRT and SyncAV programming compared to baseline left ventricular ejection fraction in patients A) with SyncAV capable devices (group 1) and B) without SyncAV capable devices (group 2). LVEF = left ventricular ejection fraction; CRT = cardiac resynchronization therapy.

offset) [11]. Alturki et al. analyzed a cohort of 32 patients who were chronically paced by CRT (mean time since implant of 18 months) with a mean intrinsic conduction QRSD of 163 ± 24 ms. Mean QRSD was reduced by a mean of 11 ms with nominal pacing and 24 ms with optimized SyncAV programming [8]. The reduction in QRSD with optimized SyncAV observed in those with RBBB in our study approaches that seen with LBBB in the aforementioned studies. The results highlight the benefit of the triple-front waveform to achieve a proper activation among these patients with different activation pattern, which has been shown to achieve the best acute hemodynamic benefit with CRT [14,20].

Given the different activation patterns in RBBB and LBBB patients, it would be unlikely that the same nominal programming would lead to optimal electrical synchrony in both RBBB and LBBB patients. In those with LBBB, the optimal SyncAV offset was 30–50 ms in around 66% to 80% of patients and the majority of the remaining patients had an optimal offset of less than 30 ms [8,9]. In contrast, we found that in patients with RBBB, the optimal offset was around 90 ms in the vast majority. This finding is key in considering the optimal negative AV hysteresis offset required to achieve fusion; given that the AV delay is measured by the device using the right ventricular lead, the presence of RBBB results in delayed detection of ventricular activation (relative to surface ECG) and the need to program a more negative AV offset to achieve fusion. The present study supports the concept that fusion pacing using programmable negative AV hysteresis offset tailored using surface ECG for optimization should be performed in patients with preserved AV conduction and correlates with an increased number of responders

A)



B)

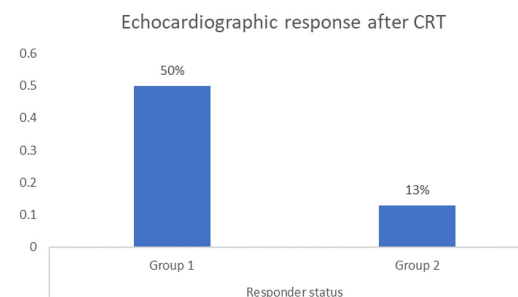


Fig. 4. Responder status. A) Improved electrical synchrony as defined by reduction in QRSD ≥ 10 ms after SyncAV CRT in group 1 and nominal CRT in group 2 and B) Echocardiographic response as defined by an absolute increase in LVEF of $\geq 10\%$ after SyncAV CRT in group 1 and nominal CRT in group 2. LVEF = left ventricular ejection fraction; CRT = cardiac resynchronization therapy.

even in patients with RBBB. Interestingly, PR interval prolongation is a predictor of poor outcomes after CRT in those LBBB but not RBBB [21].

Compared to LBBB patients, the CRT response among those with RBBB morphology remains uncertain and often discouraging [22,23]. Rickard et al. assessed the effect of baseline QRS morphology on clinical outcomes and echocardiographic parameters in 335 patients, 10% of them with RBBB morphology, after CRT implant [4]. Similar to findings in other cohorts, patients with heart failure and RBBB had a higher

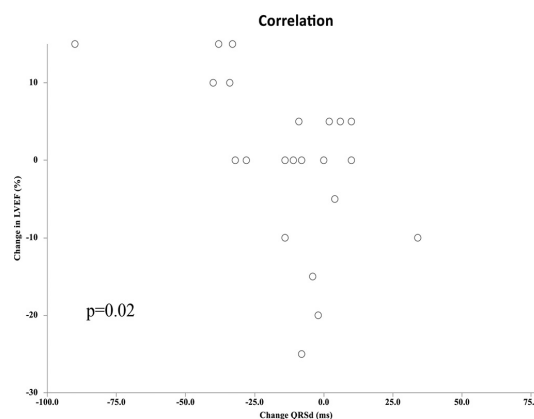


Fig. 5. Correlation between Δ QRS and Δ LVEF after cardiac resynchronization therapy in patients with RBBB (groups 1 and 2 included). LVEF = left ventricular ejection fraction.

mortality rate (26%) compared to those with LBBB (16%) and were less likely to derive benefit from CRT [4]. Those with RBBB did not have a significant improvement in LVEF post CRT, which is similar to what we observed in our historical cohort of patients that did not receive SyncAV fusion pacing. The improvement in LVEF in our cohort of patients with RBBB who received SyncAV fusion pacing approaches the improvement seen in those with LBBB in the cohort described by Rickard et al. as well and Zhang et al. [4,24]. Importantly, the degree of LVEF improvement was similar to that seen in patients with LBBB who received SyncAV fusion pacing [10]. Larger studies are now needed to confirm these findings in patients with RBBB.

This was a single center, retrospective analysis with a limited number of patients. The small number of patients with RBBB probably reflects the discouraging results from the available data regarding CRT in patients with non-LBBB morphology QRS prolongation and the limited indications for CRT in this specific population. The current study should serve as a proof-of-concept for fusion pacing as a potentially effective alternative for this group of patients and raise questions about the particularities of CRT programming and optimization in patients with RBBB. The degree to which fusion can be achieved with fixed AV delay adjustment in RBBB patients without a dynamic fusion pacing algorithm was not evaluated. Echocardiographic follow-up is performed at 6 months as per the current protocol for all CRTs at our institution. Longer-term follow-up with echocardiography as well as clinical heart failure outcomes are needed.

Conclusion

Biventricular fusion pacing is associated with improved electrical synchrony and increased LVEF when compared with traditional biventricular pacing in patients with underlying RBBB. This study demonstrated that a simple, ECG-based algorithm to optimize AV delays can significantly improve electrical synchrony in patients with RBBB. Larger studies are required to confirm these findings.

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Ethics approval

This study was approved by the McGill University Health Center Institutional Review Board.

Declaration of Competing Interest

Dr. Essebag has received honoraria from Abbott, Biosense Medical, Boston Scientific and Medtronic. All other authors have no relevant disclosures.

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