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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.

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 (QuickOptTM) [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 ± 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.

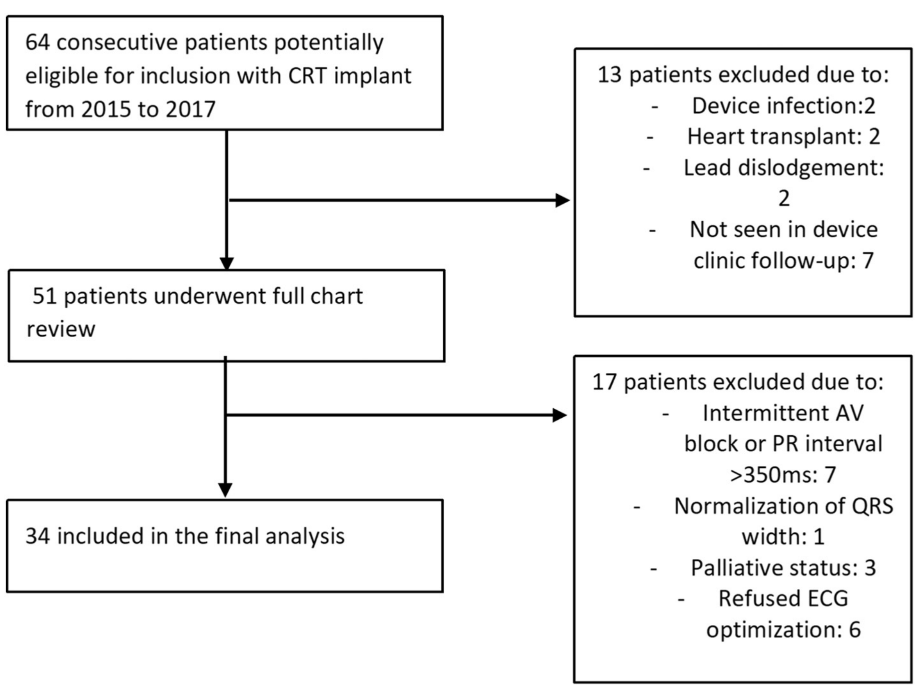

Fig. 1. Flow diagram for patient selection.

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 win 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

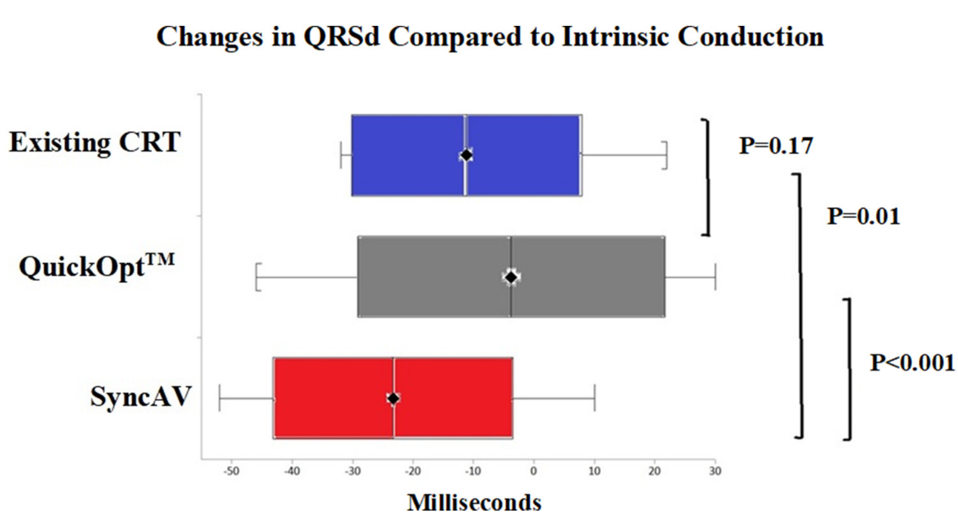

Fig. 2. The change in QRS duration (milliseconds) using existing CRT, QuickOptTM and SyncAV compared to intrinsic conduction.

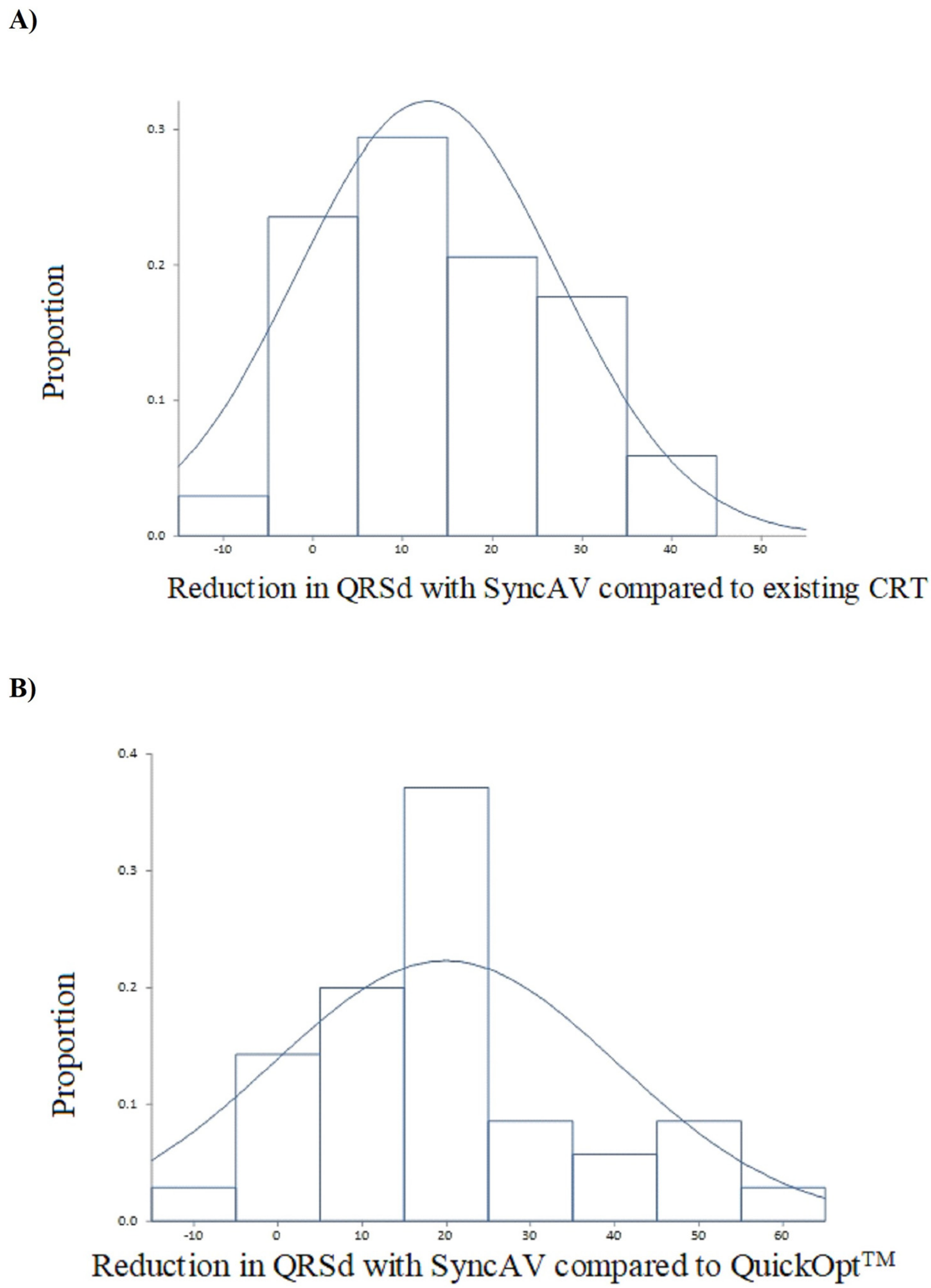

Fig. 3. The differences in the change in QRS duration achieved by SyncAV compared to A) existing CRT and B) QuickOptTM.

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, Karantezoupoulos 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

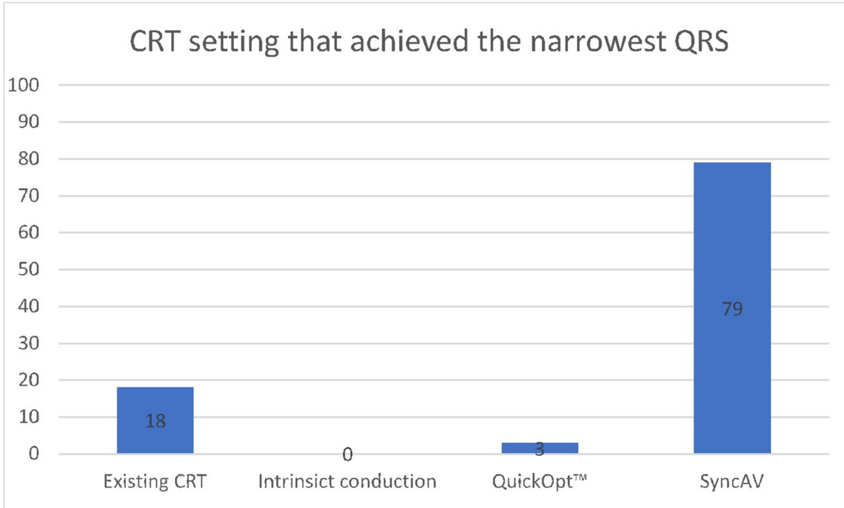

Fig. 4. Proportion of patients who achieved the narrowest QRS stratified by CRT setting.

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 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 [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.

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.

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).

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

[1] Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, et al. Resynchronization-defibrillation for ambulatory heart failure trial I. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med 2010; 363(25):2385–95.

[2] Birnie DH, Tang AS. The problem of non-response to cardiac resynchronization therapy. Curr Opin Cardiol 2006;21(1):20–6.

[3] Exner DV, Birnie DH, Moe G, Thibault B, Philippon F, Healey JS, et al. Canadian Cardiovascular Society guidelines on the use of cardiac resynchronization therapy: evidence and patient selection. Can J Cardiol 2013;29(2):182–95.

[4] Asirvatham SJ. Cardiac resynchronization: is electrical synchrony relevant? J Cardiovasc Electrophysiol 2007;18(10):1028–31.

[5] Rickard J, Cheng A, Spragg D, Cantillon D, Chung MK, Tang WH, et al. QRS narrowing is associated with reverse remodeling in patients with chronic right ventricular pacing upgraded to cardiac resynchronization therapy. Heart Rhythm 2013;10(1): 55–60.

[6] Korantzopoulos P, Zhang Z, Li G, Fragakis N, Liu T. Meta-analysis of the usefulness of change in QRS width to predict response to cardiac resynchronization therapy. Am J Cardiol 2016;118(9):1368–73.

[7] Varma N, O'Donnell D, Bassiouny M, Ritter P, Pappone C, Mangual J, et al. Programming cardiac resynchronization therapy for electrical synchrony: reaching beyond left bundle branch block and left ventricular activation delay. J Am Heart Assoc 2018;7(3).

[8] Abraham WT, Gras D, Yu CM, Guzzo L, Gupta MS, Committee FS. Rationale and design of a randomized clinical trial to assess the safety and efficacy of frequent optimization of cardiac resynchronization therapy: the Frequent Optimization Study Using the Quick Opt Method (FREEDOM) trial. Am Heart J 2010;159(6):944–8 [e941].

[9] Parkash R, Philippon F, Shanks M, Thibault B, Cox J, Low A, et al. Canadian cardiovascular society guidelines on the use of cardiac resynchronization therapy: implementation. Can J Cardiol 2013;29(11):1346–60.

[10] Kligfield P, Badilini F, Rowlandson I, Xue J, Clark E, Devine B, et al. Comparison of automated measurements of electrocardiographic intervals and durations by computer-based algorithms of digital electrocardiographs. Am Heart J 2014;167 (2):150–9 [e151].

[11] Turagam MK, Velagapudi P, Kocheril AG. Standardization of QRS duration measurement and LBBB criteria in CRT trials and clinical practice. Curr Cardiol Rev 2013;9(1): 20–3.

[12] Tomlinson DR, Bashir Y, Betts TR, Rajappan K. Accuracy of manual QRS duration assessment: its importance in patient selection for cardiac resynchronization and implantable cardioverter defibrillator therapy. Europace 2009;11(5):638–42.

[13] Vancura V, Wichterle D, Ulc I, Smid J, Brabec M, Zarybnicka M, et al. The variability of automated QRS duration measurement. Europace 2017;19(4):636–43.

[14] Hadjis A, AlTurki A, Proietti R, Montemezzo M, Bernier M, Joza J, et al. Predicting response to cardiac resynchronization therapy: use of strict left bundle branch block criteria. Pacing Clin Electrophysiol 2019;42(4):431–8.

[15] Coppola G, Ciaramitaro G, Stabile G, DO A, Palmisano P, Carita P, et al. Magnitude of QRS duration reduction after biventricular pacing identifies responders to cardiac resynchronization therapy. Int J Cardiol 2016;221:450–5.

[16] Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, et al. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. New England Journal of Medicine 2013;369(15):1395–405.

[17] van Bommel RJ, Bax JJ, Abraham WT, Chung ES, Pires LA, Tavazzi L, et al. Characteristics of heart failure patients associated with good and poor response to cardiac resynchronization therapy: a PROSPECT (predictors of response to CRT) sub-analysis. Eur Heart J 2009;30(20):2470–7.

[18] Hasan A. How should echocardiography be used in CRT optimization? J Am Soc Echocardiogr 2010;23(8):867–71.

[19] Yang M, Li X, Yang D, Li Y, Zhou S, Liang J, et al. Cardiac resynchronization therapy improves myocardial conduction. Pacing Clin Electrophysiol 2019;42(2):238–46.

[20] Daubert C, Behar N, Martins RP, Mabo P, Leclercq C. Avoiding non-responders to cardiac resynchronization therapy: a practical guide. Eur Heart J 2017;38(19):1463–72.