Improvement of electrical synchrony in cardiac resynchronization therapy using dynamic atrioventricular delay programming and multipoint pacing

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Abstract

Background: Optimization of cardiac resynchronization therapy (CRT) is often time-consuming and therefore underused in a clinical setting. Novel device-based algorithms aiming to simplify optimization include a dynamic atrioventricular delay (AVD) algorithm (SyncAV, Abbott) and multipoint pacing (MPP, Abbott). This study examines the acute effect of SyncAV and MPP on electrical synchrony in patients with newly and chronically implanted CRT devices.

Methods: Patients with SyncAV and MPP enabled devices were prospectively enrolled during implant or scheduled follow-up. Blinded 12-lead electrocardiographic acute measurements of QRS duration (QRSd) were performed for intrinsic QRSd (Intrinsic), bi-ventricular pacing (BiV), MPP, BiV with SyncAV at default offset 50 ms (BiVSyncAVdef), BiV with SyncAV at patient-specific optimised offset (BiVSyncAVopt), MPP with SyncAV at default offset 50 ms (MPPSyncAVdef), and MPP with SyncAV at patient-specific optimised offset (MPPSyncAVopt).

Results: Thirty-three patients were enrolled. QRSd for Intrinsic, BiV, MPP, BiVSyncAVdef, BiVSyncAVopt, MPPSyncAVdef, MPPSyncAVopt were 160.4 ± 20.6 ms, 141.0 ± 20.5 ms, 130.2 ± 17.2 ms, 121.7 ± 20.9 ms, 117.0 ± 19.0 ms, 121.2 ± 17.1 ms, 108.7 ± 16.5 ms respectively. MPPSyncAVopt led to greatest reduction of QRSd relative to Intrinsic (−31.6 ± 11.1%; \( p < .001 \)), showed significantly shorter QRSd compared to all other pacing configurations (\( p < .001 \)) and shortest QRSd in every patient. Shortening of QRSd was not significantly different between newly and chronically implanted devices (−51.6 ± 14.7 ms vs. −52.7 ± 21.9 ms; \( p = .99 \)).

Abbreviations: AVD, Atrio-ventricular delay; BiV, bi-ventricular; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; ICM, ischemic Cardiomyopathy; LV, left ventricle; LV1, left ventricular pacing vector 1; LV2, left ventricular pacing vector 2; LVEDV, left ventricular end-diastolic volume; LV-EF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MPP, Multipoint Pacing; MS, milliseconds; NICM, non-ischemic cardiomyopathy; NYHA, New York Heart Association; PCT, pacing capture threshold; PNS, phrenic nerve stimulation; QRSd, QRS duration; RA, right atrium; RV, right ventricle.

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Conclusion: SyncAV and MPP improved acute electrical synchrony in CRT. Combining both technologies with patient-specific optimization resulted in greatest improvement, regardless of time since implantation.

Whats new
Novel device-based algorithms like a dynamic AVD algorithm (SyncAV, Abbott) and multipoint pacing (MPP, Abbott) aim to simplify CRT optimization. Our data show that a combination of patient tailored SyncAV optimization and MPP results in greatest improvement of electrical synchrony in CRT measured by QRS duration, regardless if programmed in newly or chronically implanted devices. This is the first study to our knowledge to examine a combination of these device-based algorithms. The results help understanding the ideal ventricular excitation in heart failure.

KEYWORDS
atrioventricular delay, cardiac resynchronisation therapy, CRT optimization, multisite pacing, QRS duration

1 INTRODUCTION

Cardiac resynchronization therapy (CRT) is a well-established therapy for patients with heart failure, reduced left ventricular ejection fraction (LV-EF) and prolonged QRS duration (QRSD). However, despite advances in technology, still one third of CRT recipients are non-responders.1 Device settings for optimal therapy results include atrioventricular delay (AVD), ventriculoventricular delay (VVD), left ventricular (LV) pacing configurations, and LV multipoint pacing (MPP).

With optimization of AVD, electrical synchrony can be improved leading to better mechanical synchrony.2 Echocardiography failed to show superiority of default settings for AV- and VV-delay optimization over default settings during long-term follow-up and current ESC guidelines have not recommended it as part of routine clinical care.3–5 On the other hand, several studies showed that electrical dyssynchrony can be improved by AVD optimization leading to better mechanical synchrony.2 Programming on the other hand is time consuming, often needs echocardiography as well as exercise testing and is therefore neglected in a real-world setting.3

A novel closed-loop, device-based algorithm (SyncAV, Abbott, Sylmar, CA, USA) is available in certain Abbott CRT devices. SyncAV continuously fuses intrinsic wavefronts propagating down the interventricular septum with right ventricular (RV)- and left ventricular (LV)-pacing by dynamically adjusting AVD. When enabled, SyncAV periodically extends the AVD and senses subsequent intrinsic atrial and ventricular events to measure intrinsic AVD. According to the measurements, AVD is reprogrammed to intrinsic AVD shortened by a programmable offset (10–60 ms, default 50 ms). Benefits of SyncAV have been described recently with acute improvement of electrical synchrony and structural reverse remodeling during follow-up in newly as well as chronically implanted CRT devices.6–8 With MultiPoint Pacing (MPP) (Abbott) it is possible to program two LV pacing configurations (LV1 and LV2) to deliver sequential or simultaneous pacing from two different sites along a single quadripolar lead and hence capture a broader LV area of excitable myocardium. Recent studies report an improvement of acute electrical synchrony and improved reverse remodeling during follow-up compared to conventional biventricular pacing.9,10

Whether combination of SyncAV and MPP leads to a greater improvement of electrical synchrony remains unknown. In the present work, we assessed whether using the novel technologies improves electrical synchrony in both newly and previously implanted CRT devices.

2 METHODS

2.1 Study population

We performed a prospective analysis in two cardiac centers in Germany: University Hospital Bergmannsheil Bochum and Hospital Lüdenscheid. All patients provided written informed consent. The study protocol conforms to the ethical guidelines of the 1964 Declaration of Helsinki and its later amendments. It was approved by the local ethics committee. Consecutive patients scheduled to receive a new implant or presenting with chronically implanted CRT defibrillator (Quadra Assura MP, CD 3371-40c/CD 3371-40qc, Abbott) or pacemaker (Quadra Allure MP, PM 3562, Abbott) with programmable MPP and SyncAV algorithm were included. All patients included in this study received a CRT device according to current ESC/EHRA guidelines.5,11 To be included in this analysis patients had to have a RA lead, a RV lead and a quadripolar LV lead (Quartet 1456Q, 1457Q, 1458Q, 1458QL, Abbott) placed in a posterolateral or lateral position. The location of LV lead was determined according to coronary venogram obtained during implant procedure. Patients with resting heart rate of > 100 bpm at rest, PR interval > 300 ms, underlying 2nd or 3rd degree heart block
TABLE 1  CRT setting definitions

| CRT setting | Ventricular pacing | Paced/sensed AVD (ms) | SyncAV offset (ms) |
|-------------|-------------------|----------------------|-------------------|
| Intrinsic   | –                 | Max/max              | –                 |
| BiV         | Simultaneous (LV + RV) from Cathode with latest RV-LV activation time | 130/100 | – |
| MPP         | LV1 to LV2 (5 ms) to RV (5 ms), first from Cathode with later RV-LV activation time | 130/100 | – |
| BiVSyncAV_{def} | Simultaneous (LV + RV) from Cathode with latest RV-LV activation time | dynamic | 50 |
| MPPSyncAV_{def} | LV1 to LV2 (5 ms) to RV (5 ms), first from Cathode with later RV-LV activation time | dynamic | 50 |
| BiVSyncAV_{opt} | Simultaneous (LV + RV) from Cathode with latest RV-LV activation time | dynamic | 10 - 60 |
| MPPSyncAV_{opt} | LV1 to LV2 (5 ms) to RV (5 ms), first from Cathode with later RV-LV activation time | dynamic | 10 - 60 |

Abbreviations: AVD, atrio-ventricular delay; BiV, bi-ventricular; CRT, cardiac resynchronization therapy; LV, left ventricle; MPP, multipoint pacing; RV, right ventricle.

and persistent atrial fibrillation or tachycardia were excluded. Demographics were collected from patient record.

2.2  | Data collection

With a resting patient in a supine position, various CRT programming were performed for 1 min and standard 12-lead ECG was recorded during the final 10 s of each programming. QRS duration was measured manually from digital ECGs (50 mm/s sweep speed and 10 mm/mV scale) using electronic calipers by three observers blinded to the settings. Time from the earliest deflection from isoelectric line to the latest return to isoelectric line was measured in all 12 ECG leads and the greatest value was used. The measurements taken from all three observers were averaged. QRSd measurements were performed in five different settings: (i) intrinsic conduction (Intrinsic); (ii) biventricular pacing (AVD paced/sensed 130/100 ms; VV-delay 0 ms) (BiV); (iii) multipoint pacing (AVD paced/sensed 130/100 ms; VV-delay 5 and 5 ms) (MPP); (iv) biventricular pacing with SyncAV ON (offset: 60, 50 [default], 40, 30, 20, 10 ms); and (v) multipoint pacing with SyncAV ON (offsets: 60, 50 [default], 40, 30, 20, 10 ms). To compare the SyncAV default offset (50 ms) with the individualized offset providing the narrowest (=optimal) QRSd in each patient at BiV and MPP mode, the offsets were labelled BiVSyncAV_{def}, MPPSyncAV_{def}, BiVSyncAV_{opt}, and MPPSyncAV_{opt}. RV-LV activation times were defined as conduction delays from RV sensing to LV sensing at each LV electrode (D1, M2, M3, P4) using the device based automatic measurement (VectSelect). Biventricular pacing was performed from the cathode with the latest RV-LV activation time with simultaneous LV and RV pacing and a fixed AV delay paced/sensed of 130/100 ms. For MPP, pacing configurations with large anatomical electrode separation (>30 mm) and first cathode to pace from later RV-LV activation time were chosen and programmed with delays LV1 to LV2 5 ms and LV2 to RV 5 ms. Table 1 provides an overview of programming details. Pacing amplitude safety margin of 1.0 V above threshold at 0.5 ms was programmed for all testing without phrenic nerve stimulation (PNS) present. After completion of ECG collection, devices were reverted to previous permanent settings.

2.3  | Statistical analysis

All statistical analysis was performed using IBM SPSS Statistics version 24.0.0 on mac.

Categorical variables were expressed as number and percentages (normal distribution) or median and interquartile range (non-normal distribution) and compared by chi square test or fisher exact test. Continuous variables were stated as mean ± standard deviation and compared with unpaired t-test/ANOVA for normally distributed variables and Mann-Whitney U-test for non-normally distributed variables. All statistical analyzes were two-sided and p < .05 was considered statistically significant.

3  | RESULTS

3.1  | Baseline characteristics

A total of 81 eligible patients who received an MPP and SyncAV enabled CRT device between March 2014 and March 2020 were included. Twenty-one patients were excluded due to atrial fibrillation, nine due to loss of required AV conduction, and 18 were lost to follow-up since implantation. The remaining 33 patients were prospectively evaluated. Mean age was 68.3 ± 10.4 years and 25 (76%) were male. Ischemic cardiomyopathy was the underlying cardiac disease in 18 (54.5%) patients, while 15 patients (45.5%) suffered of dilated cardiomyopathy. At implant, 11 patients (33.3%) were at NYHA Class II and 22 patients (66.7%) at NYHA Class III. The mean LV-EF at implant was 26.7% ± 6.3%. Implanted device type was CRT-D in 30 (90.9%)
patients and CRT-P in 3 (8.9%) patients. Seven patients (21.2%) were enrolled the day after implantation and 26 (78.8%) during scheduled follow-up. Mean time since implant was 2.1 ± 1.6 years (range: 0–4.7). As underlying conduction abnormality LBBB, right bundle branch block (RBBB), and non-specific intraventricular conduction delay (IVCD) were observed in 30 (90.9%), 2 (6.1%), and 1 (3.0%) patients, respectively. Heart rate at rest was 65.6 ± 12.3 beats/min (range 48–88 beats/min) with a PR interval of 217 ± 32.7 ms (range: 146–295 ms) and an intrinsic QRS of 160.4 ± 20.6 ms (range 135–220 ms). Atrial pacing during programming was not observed in any patient. Desired LV pacing configurations for all BiV and MPP programming modes were possible at 1.0 V above threshold without PNS. Baseline demographic characteristics are listed in Table 2.

### 3.2 Electrical synchronization

Representative 12-lead ECG signals are shown in Figure 1. The QRSd of intrinsic conduction was 160.4 ± 20.6 ms. Relative to intrinsic conduction, BiV pacing reduced QRSd by 11.1% ± 15.2%.

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**TABLE 2** Baseline characteristics and acute measurement results (n = 33)

| Characteristics                                          | Value                        |
|----------------------------------------------------------|------------------------------|
| Age at implant (years)                                   | 68.3 ± 10.4                  |
| Sex, male, n (%)                                         | 25 (76%)                     |
| CRT-D Implant, n (%)                                     | 30 (90.9%)                   |
| Time of enrollment                                       |                              |
| Immediately after implantation, n (%)                    | 7 (21.2%)                    |
| During scheduled follow-up, n (%)                        | 26 (78.5%)                   |
| Time post implant, y (range)                             | 2.1 ± 1.6 (0–4.7)            |
| Ischemic Cardiomyopathy, n (%)                           | 18 (54.5%)                   |
| NYHA Class at implant                                    |                              |
| NYHA 2, n (%)                                            | 11 (33.3)                    |
| NYHA 3, n (%)                                            | 12 (66.7)                    |
| Left ventricular ejection fraction (%) at implant        | 26.7 ± 6.3                   |
| Conduction abnormality                                   |                              |
| Left Bundle Branch Block, n (%)                          | 30 (90.9)                    |
| Right Bundle Branch Block, n (%)                         | 2 (6.1)                      |
| IVCD                                                     | 1 (3.0)                      |
| Resting heart rate (beats/min)                           | 65.6 ± 12.3, (range 48–88)   |
| Intrinsic PR interval (ms), (range)                      | 217 ± 32.7, (146–295)        |
| Conduction times RV-LV sensed                            |                              |
| D1                                                       | 107.1 ± 41.1                 |
| M2                                                       | 115.2 ± 40.6                 |
| M3                                                       | 114.2 ± 42.5                 |
| P4                                                       | 116.1 ± 41.9                 |
| QRSd (ms)                                                | 160.4 ± 20.6, (135–220)      |
| Intrinsic QRSd, (range)                                  |                              |
| BiV                                                     | 141.0 ± 20.5                 |
| MPP                                                     | 130.2 ± 17.2                 |
| BiVSyncAV_{def}                                          | 121.7 ± 20.9                 |
| MPPSyncAV_{def}                                          | 121.2 ± 17.1                 |
| BiVSyncAV_{opt}                                          | 117.0 ± 19.0                 |
| MPPSyncAV_{opt}                                          | 108.7 ± 16.5                 |
| PCT (V) at 0.5 ms for LV1 (range)                         | 1.2 ± 0.5, (0.5–2.25)        |
| PCT (V) at 0.5 ms for LV2 (range)                         | 1.4 ± 0.9, (0.5–2.5)         |

Abbreviations: BiV, bi-ventricular; CRT, cardiac resynchronization therapy; def, default; IVCD, intra-ventricular conduction delay; MPP, multipoint pacing; LV, left ventricle; opt, optimal; PCT, pacing capture threshold; QRSd, QRS duration; RV, right ventricle.
to 141.0 ± 20.5 ms (p < .001). With MPP a further reduction by 7.2% ± 8.1% to 130.2 ± 17.2 ms (p < .001) was observed. Programming the SyncAV algorithm at the default 50 ms offset in a BiV pacing mode, a further shortening of QRSd compared to BiV pacing alone of was achieved by 11.8% ± 7.5% to 121.7 ± 20.9 ms (p < .001). ECG optimization of SyncAV offset during BiV pacing resulted in an additional 3.8% ± 3.5% shortening of QRSd to 117.0 ± 19.0 ms (p < .05). Relative to MPP alone, combining SyncAV at the default 50 ms offset with MPP reduced QRSd further by 6.8% ± 6.9% to 121.2 ± 17.1 ms (p < .001). Optimization of SyncAV during MPP led to a further reduction by 10.3% ± 6.0% to 108.7 ± 16.5 ms. Compared to BiVSyncAVopt, MPPSyncAVopt resulted in significantly shortened QRSd 108.7 ± 16.5 ms versus 117.0 ± 19.0 ms (p < .001). Greatest overall QRSd reduction relative to intrinsic conduction was achieved by MPP with a patient tailored SyncAV offset (−31.6% ± 11.1%; p < .001), see Table 2. For each pacing configuration, QRSd is illustrated in Figure 2 and respective changes relative to intrinsic conduction in Figure 3. Fusion of CRT and intrinsic conduction with shortening of QRSd was present in all patients while MPPSyncAVopt showed the most significant shortening in each individual patient.
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3.3 | MPP SyncAV offset optimization

The MPP SyncAV offset most frequently associated with narrowest QRSd was between 20 and 40 ms as illustrated in Figure 4. An offset of 50 or 60 ms was not associated with narrowest QRS in our cohort. QRSd for offsets 60, 50, 40, 30, 20, and 10 ms were 125.1 ± 17.3 ms, 121.2 ± 17.1 ms, 114.9 ± 15.7 ms, 115.1 ± 18.7 ms, 114.8 ± 20.1 ms, 118.1 ± 19.2 ms, respectively. An offset of 60 ms led to a significantly longer QRSd compared to all other offsets (p < .01). Offset of 50 ms resulted in significantly longer QRSd compared to offsets 40, 30, and 20 ms (p < .01), but not compared to 10 ms (p = .16). QRSd for 10 ms offset was significantly longer compared to offsets 40, 30, and 20 ms (p < .05). Patient-tailored optimization of SyncAV offset was associated with a significant shortening in QRSd compared to default setting (108.7 ± 16.5 ms vs. 121.2 ± 17.1 ms, p < .001).

3.4 | Electrical synchronization in QRS non-responders

BiV pacing alone prolonged QRSd in 5 (15.1%) patients and shortening of QRSd was less than 10% in another 5 (15.1%) patients compared to intrinsic conduction. These patients are QRS non-responders and could be considered possible non-responders to BiV. By using MPPSyncAVopt, QRSd shortened significantly in these 10 (30.3%) patients relative to baseline (146.9 ± 19.8 ms vs. 113.3 ± 13.0 ms, p < .001).

During MPP, QRSd prolonged in two (6%) patients and shortening was less than 10% in six (18.2%) patients. These patients could be considered possible non-responders to MPP. By using MPPSyncAVopt, QRSd shortened significantly in these eight (24.2%) patients relative to baseline (145.0 ± 21.6 ms vs. 114.0 ± 13.4 ms; p < .001).

All patients with MPPSyncAVopt showed >10% shortening of QRSd compared to the baseline ECG.

3.5 | Difference of synchronization according to baseline characteristics

Although the number of included Non-LBBB patients was low (9.1%), intrinsic QRSd was significantly shorter in patients with Non-LBBB compared to patients with LBBB (142.7 ± 26.1 ms vs. 162.1 ± 19.7 ms, p < .05). MPPSyncAVopt achieved the greatest QRSd reduction in Non-LBBB patients compared to intrinsic conduction (117.7 ± 19.4 ms vs. 142.7 ± 26.1 ms, p < .05). Shortening of QRSd with a patient-tailored offset (MPPSyncAVopt) was significantly higher in LBBB compared to Non-LBBB patients (LBBB: −33.1% ± 10.4% vs. Non-LBBB: −17.0% ± 8.3%, p < .05), although the final absolute value of QRSd with MPPSyncAVopt did not differ significantly between these two groups (LBBB: 107.8 ± 16.3 ms vs. Non-LBBB: 117.7 ± 19.4 ms, p = .48).

Shortening of QRSd with MPPSyncAVopt was significantly higher in patients with longer intrinsic QRSd (Spearman-Rho = −0.585, p < .001) as illustrated in Figure 5. At time of enrolment, QRSd was ≤150 ms in 10 (30.3%) patients. A reduction of QRSd with MPPSyncAVopt, however, was still significant compared to QRSd at baseline (139.5 ± 11.9 ms vs. 102.3 ± 12.9 ms, p < .001). The intrinsic PR-interval had no influence on the amount of QRSd shortening during MPPSyncAVopt (QRSd reduction PR-interval <200 ms: −31.9% ± 14.2% vs. with PR-interval ≥200 ms: −31.3% ± 7.6%, p = .87). Additionally, there was no correlation between intrinsic PR-interval and optimal SyncAV offset with MPP (p = .421).

There was no significant difference in shortening of QRSd with best possible programming between ischemic- (ICM) and non-ischemic cardiomyopathy (NICM) (ICM: −30.1% ± 10.3% vs. NICM: −31.9% ± 14.2%).
The significantly reduces LVESV and increases LV-EF in Additionally, once AVD $−=±$ This is compara-
In the present study, compared to empiric $p$
Dotted diagram illustrating significant relation
algorithm demonstrated better clinical outcome
$±$ $p$
SyncAV
Varma et al.
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SyncAV
QRSd with optimal programming (MPPSyncAVopt).
FIGURE 5
$−$
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QRSd shortening between patients with baseline LV-EF $≥25%$ and LV-EF $<25%$ at implant was not significant either (LV-EF $≥ 25%$: $−37.0\% \pm 9.0\%$ vs. LV-EF $< 25%$: $−30.5\% \pm 12.4\%, p = .18$).

4 | DISCUSSION

Improvement of electrical synchrony is associated with structural reverse remodeling in CRT recipients and electrical as well as mechanical synchrony are both predictors for long-term outcome in CRT. Measurement of QRSd as performed in our study is an easy and inexpensive assessment of electrical synchrony and CRT optimization. Improvement of AV delay has been a cornerstone for optimizing CRT for a very long time.

Echocardiographic guided AVD optimization however did not improve outcome compared to nominal settings and proved to be very time consuming with limited reproducibility. Additionally, once AVD is manually optimized at rest, it remains static and does not change according to different ambulatory conditions. The one-time in-clinic adjustment of a fixed AV delay does not take physiologic or autonomic changes of intrinsic AV conduction into account and therefore cannot be considered to be an ideal setting for different clinical scenarios.

In contrast, AV delay may be optimized by fusion between intrinsic RV depolarization and biventricular pacing. This fusion leads to a shortening of QRSd, which is a surrogate for LV activation time and is associated with LV reverse remodeling, better response to CRT and a reduction in cardiovascular hospitalization and mortality.

Different device-based algorithms for dynamic fusion of intrinsic conduction with biventricular or left ventricular pacing have been developed. The Adaptiv CRT (aCRT) algorithm (Medtronic Inc., Minneapolis, MN, USA) periodically assesses intrinsic conduction and optimizes AV timing by providing left ventricular only pacing during normal AV conduction or biventricular pacing during prolonged AV conduction. The aCRT algorithm demonstrated better clinical outcome compared to echocardiography-optimized biventricular pacing after 6 months and better response to CRT compared to empiric programming of AVD. Another device-based algorithm is the Respond CRT system based upon the SonR sensor by Microport CRM. A sensor embedded in the right atrial lead picks up cardiac muscle vibrations that reflect heart sounds as a surrogate for cardiac contractility. By measuring real-time LV contractility, it automatically adjusts AV- and VV delays during rest and exercise. In the Respond CRT trial the SonR algorithm showed a better response compared to echocardiographic guided CRT optimization and a 35% risk reduction in heart failure hospitalization. The SyncAV algorithm is a device-based algorithm that dynamically adjusts AVD, synchronizing AV conduction with biventricular pacing. Fusion of fast intrinsic His-Purkinje conduction with slow pacing cardiomyocyte propagation leads to reduced overall ventricular depolarization time, demonstrated by QRSd. Benefits for SyncAV compared to empiric programming have been reported previously. In the present study, magnitude of QRSd reduction with BiVSyncAVopt confirms these data, regardless of time since implantation. A recent study was also able to show that SyncAV significantly reduces LVESV and increases LV-EF in CRT recipients.

To the best of our knowledge, this is the first study to investigate the influence of an ECG-optimized SyncAV offset together with MPP technology on electrical dyssynchrony. In patients with BBB, large areas of slow conduction or block can be found. While capturing larger areas of the left ventricle by MPP a better and more physiological wavefront propagation can be expected. By ensuring a large anatomical separation of pacing poles, this benefit seems to be even greater as the probability to pace a scarred area is lower. For delivering MPP from a single quadripolar LV lead, multiple studies showed immediate improvement of electrical synchrony and hemodynamic response compared to BiV. Pacing from two electrodes with large anatomical spacing resulted in greatest benefits compared to other MPP pacing configurations during a long-term follow-up. Our results are in line with this data as QRSd was significantly shortened by MPP compared to BiV alone. Pacing from two LV locations with large anatomical separation was feasible at an acceptable threshold in all patients (see Table 2) and as recently reported, therapy costs and reduction in battery longevity seem to be at a tolerable level for use of MPP.

The progressive reduction in QRSd by ECG-optimized SyncAV offsets is conclusive with previously published data. Varma et al. reported a QRSd reduction by BiV pacing alone, BiV pacing with SyncAV at default setting of 50 ms and BiV pacing with ECG optimized SyncAV offset of 12%, 18%, and 24%, respectively. This is comparable to the QRSd reduction for these settings of 12%, 24% and 27% in our study. Greatest QRSd shortening of 32% in our study was achieved by MPP with ECG optimized SyncAV offset (MPPSyncAVopt). Thus, a combination of both technologies seems to be favorable to ensure...
physiological wavefront propagation without disturbances in areas with slow conduction.

Patient-specific programming seems to be crucial as out of the box settings for SyncAV do not account for different intrinsic wavefront propagations in individual patients as suggested by widely ranging PR-intervals (146–295 ms) and intrinsic QRSd (135–220 ms). PR intervals did not influence the reduction of QRSd when ECG guided optimization of SyncAV offset was performed. This effect is likely due to individual optimization of SyncAV and therefore optimal fusion of intrinsic conduction and pacing in every individual patient. In contrast to aCRT, a pure AV optimization algorithm, offsets of ≥50 ms did not result in shortest QRSd in any of our patients. The additional LV pacing site of MPP seems to address any intra-LV activation delays across the two LV electrodes, enabling an accelerated LV propagation and thus leading to shorter LV offsets. The importance of patient-specific optimization is pointed out in Figure 4 as there is a range of individual optimal SyncAV offsets rather than an optimal default SyncAV offset.

Several studies were able to show that LBBB and a broader QRSd at implant were predictors for better outcome in CRT recipients. Our results support these data as there was a significant correlation between QRSd and magnitude of improvement. Patients with a mean QRSd of ≤150 ms did not respond well to BiV or MPP with fixed AVD in our cohort. However, in comparison to large studies where electrical synchrony in patients with an intrinsic QRSd ≤150 ms and empiric programming did not improve greatly from CRT, our results showed a significant reduction of QRSd with MPPSyncAVopt in this subgroup as well. This suggests that our programming strategy with easy performable ECG-optimized SyncAV offset and MPP could reduce non-response in this subset of patients. Investigating effects of our programming strategy prospectively in patients with a QRS duration smaller than 150 ms could be of interest.

As expected, absolute reduction of QRSd was significantly higher in patients with underlying LBBB compared to Non-LBBB. However, patients with Non-LBBB improved significantly with MPPSyncAVopt as well. Additionally, there was no significant difference in final QRSd between LBBB and Non-LBBB that can be achieved by MPPSyncAVopt programming. A possible explanation for the higher absolute reduction of QRSd in LBBB could be a higher intrinsic QRSd in patients with LBBB at implant (p < .05). Therefore, even with very limited sample size, this could suggest that with MPPSyncAVopt even patients with Non-LBBB and shorter QRSd at baseline can benefit greatly from this programming strategy.

Ginks et al. reported patients with NICM improved significantly more often compared to ICM with conventional biventricular pacing. However, LV activation pattern improved for ICM with multipoint pacing and was not different from NICM anymore. This confirms our results as there was no difference in benefit from MPPSyncAVopt between ICM and NICM in our cohort.

Future developments should consider an automatic algorithm to test for possible MPP vectors with large anatomical spacing and optimize SyncAV offset on a regular basis. An automatic algorithm would not only facilitate clinical workflow but make a valuable contribution to regularly adjust offset during possible changes of intrinsic wavefront propagation.

5 LIMITATION

To evaluate effects of SyncAV and MPP, only acute QRSd measurements were performed while patients were at rest in a limited sample size. Close relation of electrical and mechanical synchrony has been described previously. However, large randomized long-term trials combining both technologies with assessment of echocardiography, clinical data and mortality are needed to further investigate the effect on reverse remodeling and outcome. To evaluate this, a larger study population is needed. To examine clinical effects, especially on CRT non-responders, a follow-up of at least 12 months would be beneficial with comparison of different programming strategies in randomized groups. Research into the effect of our programming strategy upon CRT non-responders with chronically implanted devices could be performed as well.

In addition, examining QRSd with the same programming at different situations and during a follow-up would be very interesting to testify the programming strategy. Research into effects of SyncAV during exercise and a long-term follow-up is underway (ClinicalTrial.gov identifiers NCT03768804 and NCT04100148).

The sample size of patients with non-LBBB is especially small and the results of this subgroup, especially in comparison to the group of patients with LBBB, need to be looked at very carefully. These patients have not been excluded, as this study was supposed to test CRT optimization in a real-world setting. During routine follow-up, non-LBBB are often not treated with special attention regarding optimization strategies. In order to see if this sub-group of patients would profit from our programming strategy as much as LBBB patients would profit, they have been included and looked at as well.

6 CONCLUSION

SyncAV and MPP improved acute electrical synchrony in CRT. The combination of both technologies with patient-tailored optimization resulted in greatest improvement in newly as well as chronically implanted CRT devices. Both technologies proved to be an easy usable, time-effective ECG-based programming strategy optimizing effects of CRT and led to favorable results in all subgroups analyzed.

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CONFLICT OF INTEREST

The authors Schiedat, Karosiene, Bogossian, Zarse, Hanefeld, Mügge declares that there is no conflict of interest. Authors Dr Mijic, Dr Lemke and Dr Kloppe has received consultancy fees/speaking honoraria from Abbott.
DATA AVAILABILITY STATEMENT
All data can be made available upon request.

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