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Dynamic atrioventricular delay programming improves ventricular electrical synchronization as evaluated by 3D vectorcardiography

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ABSTRACT

Background: Optimal timing of the atrioventricular delay in cardiac resynchronization therapy (CRT) can improve synchrony in patients suffering from heart failure. The purpose of this study was to evaluate the impact of SyncAV™ on electrical synchrony as measured by vectorcardiography (VCG) derived QRS metrics during biventricular (BiV) pacing.

Methods: Patients implanted with a cardiac resynchronization therapy (CRT) device and quadripolar left ventricular (LV) lead underwent 12-lead ECG recordings. VCG metrics, including QRS duration (QRSd) and area, were derived from the ECG by a blinded observer during: intrinsic conduction, BiV with nominal atrioventricular delays (BiV Nominal), and BiV with SyncAV programmed to the optimal offset achieving maximal synchronization (BiV + SyncAV Opt).

Results: One hundred patients (71% male, 40% ischemic, 65% LBBB, 32 ± 9% ejection fraction) completed VCG assessment. QRSd during intrinsic conduction (166 ± 25 ms) was narrowed successively by BiV Nominal (137 ± 23 ms, $p < .05$ vs. intrinsic) and BiV + SyncAV Opt (122 ± 22 ms, $p < .05$ vs. BiV Nominal). Likewise, 3D QRS area during intrinsic conduction (90 ± 42 mV ∗ ms) was reduced by BiV Nominal (65 ± 39 mV ∗ ms, $p < .05$ vs. intrinsic) and further by BiV + SyncAV Opt (53 ± 30 mV ∗ ms, $p = .06$ vs. BiV Nominal).

Conclusion: With VCG-based, patient-specific optimization of the programmable offset, SyncAV reduced electrical dyssynchrony beyond conventional CRT.

Introduction

Abnormalities in ventricular conduction of electrical impulses are present in approximately 30% of patients with heart failure. Cardiac resynchronization therapy (CRT) has been shown to reverse the adverse effects of electrical dyssynchrony, resulting in improved patient outcome [1,2]. However, a substantial portion of the patients who are selected according to current guidelines do not respond to CRT [3], in part due to poor device optimization [4].

Programmable CRT device settings for optimum therapy include atrioventricular delay (AVD), inter-ventricular delay, and left ventricular (LV) pacing site. Changes in these settings can significantly influence LV filling and ventricular electrical synchrony [5,6]. Post-implant optimization techniques relying on echocardiographic measurements to improve acute LV function are time consuming, costly, and may lead to a high degree of variability [6,7]. New device based-algorithms could possibly overcome these limitations, providing fast, in-clinic options for optimal, patient-specific device programming.

Abbreviations: AVD, atrioventricular delay; BiV, bi-ventricular; CRT, cardiac resynchronization therapy; HF, heart failure; LV, left ventricle; LBBB, left bundle branch block; NYHA, New York Heart Association; QRSd, QRS duration; RA, right atrium; RV, right ventricle; SyncAV™, proprietary algorithm for dynamic AVD programming; VCG, vectorcardiography.

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SyncAV™ is a new device-based algorithm designed to continually adjust the programmed AVD [8] to synchronize biventricular (BiV) pacing with the intrinsic AV conduction. When enabled, SyncAV extends the programmed AVD to automatically measure the AV conduction interval of an intrinsic beat (i.e., from right atrial [RA] to right ventricular [RV] lead). Subsequently, the new AVD is programmed to the measured intrinsic AV interval, shortened by an offset. This offset (nominal 50 ms) is programmable and can be tailored to enhance each individual patient's electrical response.

While the 12-lead ECG remains an essential standard for ventricular dyssynchrony quantification [9], parameters derived from 3D vectorcardiography (VCG) have been proposed as more sensitive guides to achieve CRT optimization and response [10,11]. VCG recordings incorporate the magnitude and direction of the electrical activity generated during a heartbeat. 3D QRS area, in particular, has been shown to be a superior predictor of CRT response compared to 12-lead ECG-derived QRS duration [12]. The influence of SyncAV programming on VCG-measured electrical synchrony has not been previously evaluated. In the present work, SyncAV performance was assessed acutely via VCG-derived QRS metrics during BiV pacing.

Methods

Study population

This study included data from two prospective studies that evaluated the effect of CRT with LV quadripolar lead technology on electrical synchronization (NCT02814214 and NCT02782598). Patients enrolled in either study were implanted, or had been implanted, with an Abbott CRT device (defibrillator or pacemaker) and a quadripolar LV lead (Quartet™ 1458Q) according to current CRT guidelines. The studies enrolled patients at least 18 years of age with a resting heart rate below 100 bpm, preserved atrioventricular conduction (PR < 300 ms), without permanent atrial tachyarrhythmia, and with no plans of pregnancy. The study protocols were approved by the local ethics committee of each participating institution.

Device programming

CRT devices were programmed to various pacing configurations, during which standard 12-lead ECGs were recorded with patients at rest and in supine position. Device settings used for the study are shown in Table 1. Test settings included intrinsic conduction, BiV pacing with fixed paced/sensed AVD of 140/110 ms (BiV Nominal), and BiV pacing with SyncAV on and programmed with optimal, patient-specific offsets (BiV + SyncAV Opt). SyncAV offsets were varied between 10 and 60 ms for each patient, and the optimal offset was defined based on maximal synchronization according to the corresponding VCG metric. All BiV settings were performed with simultaneous LV and RV pacing. LV pacing was performed from the cathode with the latest RV-LV activation time. After completion of acute ECG data collection, devices were reverted to the permanent settings previously established by the physician.

Table 1
Pacing configurations and settings tested.

Configuration	Paced/sense AVD [ms]	Pacing	No. of patients
Intrinsic	–	–	100
BiV nominal	140/110	RV + LV	100
BiV + SyncAV Opt	Dynamic, per SyncAV with patient-tailored offset	RV + LV	100

ECG collection and VCG analysis

ECG was acquired at a sampling frequency of 1000 Hz for at least 30 s per setting. From the 12-lead ECG, a 3D VCG was calculated using custom software to obtain signals along the orthogonal X, Y and Z axes [13]. Operators who performed VCG analysis and QRS measurements were blinded to the pacing configurations. QRS duration (QRSd) was measured from the earliest onset (QRS start) to the latest offset (QRS end) of the depolarization waveform in any of the X, Y and Z axes (Fig. 1). The QRS vector was expressed as the magnitude and angular direction of the point on the QRS loop with the greatest distance from the origin. The QRS amplitude was defined as the magnitude of this QRS vector. QRS area was defined as $(\text{QRS area}_x^2 + \text{QRS area}_y^2 + \text{QRS area}_z^2)^{1/2}$, where $\text{QRS area}_{x/y/z}$ are the integrals of the QRS waveform over time in each direction, from the time of QRS start to QRS end [10].

Statistical analysis

Categorical variables are expressed as number and percentage of patients. Continuous variables are expressed as mean ± standard deviation among patients. Differences in QRS duration, amplitude, and area among settings, as well as percent changes relative to intrinsic conduction, were assessed using one-way repeated measures ANOVA, followed by post hoc Tukey multiple comparison tests. Differences in QRS metrics among patient subpopulations were assessed using the Wilcoxon rank-sum test. As QRS angles were not normally distributed, the non-parametric, repeated measures Friedman test was used, followed by post hoc Wilcoxon signed-rank tests with Bonferroni correction. $P < .05$ was considered statistically significant. All analyses were performed in MATLAB (MathWorks, Natick, MA).

Results

Patient characteristics

Of 120 patients enrolled in 5 centers, 7 patients experienced ECG recording system malfunction, while transient ECG signal artifacts during one or more pacing mode prohibited accurate QRS annotation in 13 other patients. The remaining 100 patients (age: 67 ± 10 years; 71% male; ejection fraction 32 ± 9%; 40% with ischemic cardiomyopathy, 22% 1st degree AV block) with CRT-D (94%) and CRT-P (6%) were evaluated at a post-implant time of 1.5 ± 2.2 years (range 0.0–14.4 years). Baseline clinical characteristics are listed in Table 2. All patients were in sinus rhythm at the time of ECG recordings. The right ventricular (RV) lead was placed in the apex (63%) or septum (37%), and the quadripolar LV lead was placed in a lateral (38%), posterolateral (24%), or anterolateral (38%) branch of the coronary sinus. The mean baseline PR interval was 193 ± 44 ms (range 115–320 ms) and mean QRSd during intrinsic conduction was 166 ± 25 ms (range 101–248 ms). Representative VCG loops for a subset of CRT settings in a single patient are shown in Fig. 1.

Vectorcardiographic evaluation of biventricular pacing with SyncAV

The SyncAV offsets resulting in minimal QRSd, QRS amplitude, and QRS area were 34 ± 16, 46 ± 15, and 44 ± 14 ms, respectively. The impact of SyncAV offset optimization on each VCG metric, relative to the optimal offset for each patient, is illustrated in Fig. 2. Programming the offset ±10 ms away from the optimum resulted in population-wide elevations in QRSd, amplitude, and area of 7.5%, 9.1%, and 11.5%, respectively.

The effect of biventricular pacing with and without SyncAV on VCG parameters is shown in Fig. 3. Relative to the QRSd during intrinsic conduction (166 ± 25 ms), BiV Nominal reduced QRSd by 17 ± 14% ($p < .05$ vs. intrinsic) to 137 ± 23 ms ($p < .05$ vs. intrinsic). Activating SyncAV with an optimized offset (BiV + SyncAV Opt) reduced QRSd by 26 ± 10% relative to intrinsic ($p < .05$ vs. BiV Nominal) to 122 ± 22 ms ($p <$

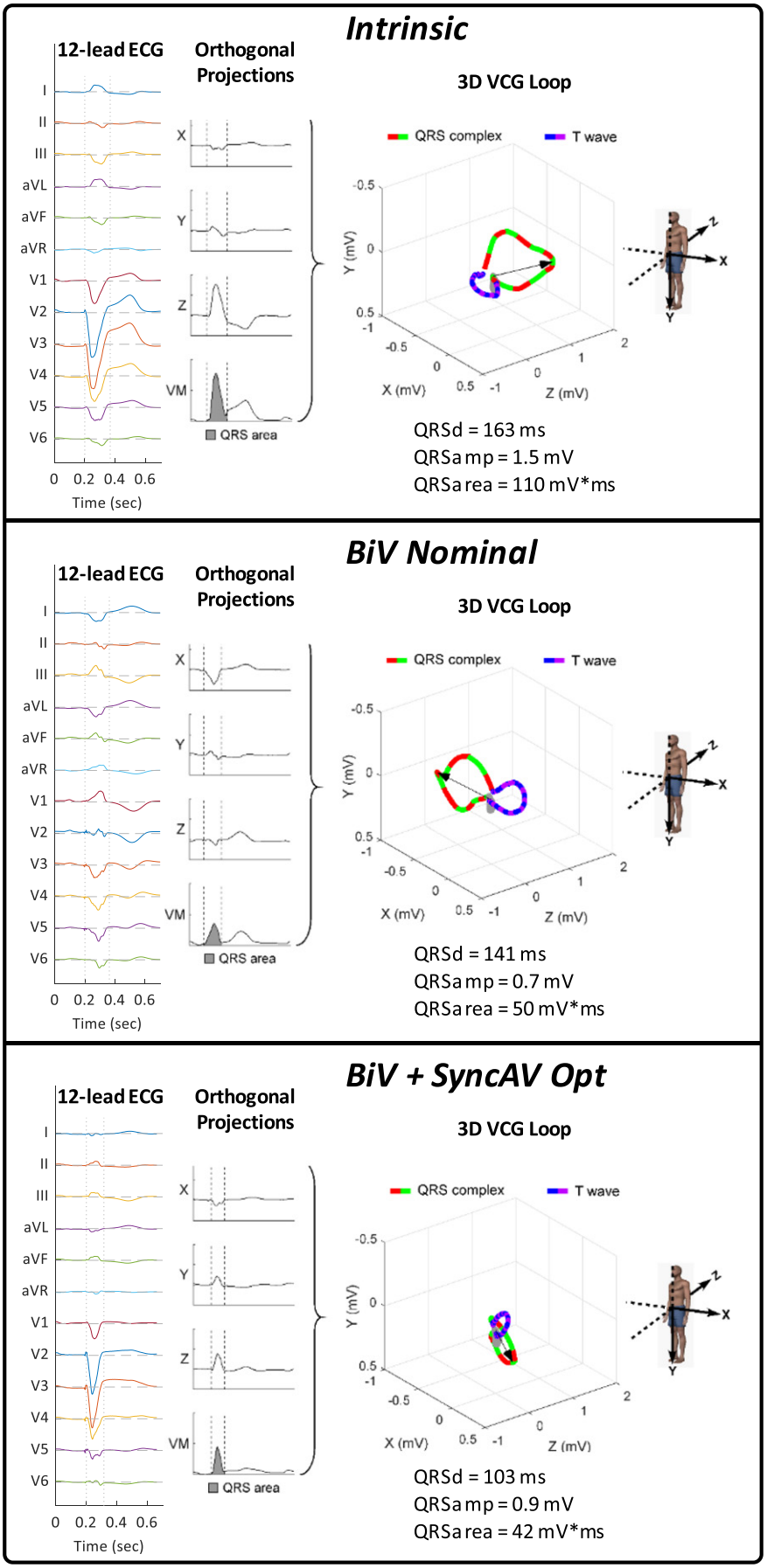

Fig. 1. Sample ECG and VCG analysis. Example 12-lead ECG, orthogonal VCG projections, and 3D VCG loops for intrinsic conduction, BiV Nominal, and BiV + SyncAV Opt.

Table 2
Baseline patient demographics.

Characteristic	All patients
Patient, No.	100
Age, yr	67 ± 10
Male, n (%)	71 (71)
Ischemic, n (%)	40 (40)
LBBB, n (%)	65 (65)
NYHA class, n (%)	
I	10 (10)
II	62 (62)
III	28 (28)
LVEF, %	32 ± 9
PR, ms	193 ± 44
QRSd, ms	166 ± 25
RV paced – LV sensed conduction time, ms	
D1	157 ± 28
M2	164 ± 30
M3	167 ± 31
P4	172 ± 34
Comorbidities, n (%)	
Hypertension	61 (61)
Diabetes mellitus	32 (32)
Renal disease	9 (9)
History of smoking	43 (43)

.05 vs. intrinsic and BiV Nominal). QRS amplitude during intrinsic conduction was 1.47 ± 0.55 mV, with a reduction during BiV Nominal of 16 ± 48% ($p < .05$ vs. intrinsic) to 1.14 ± 0.49 mV ($p < .05$ vs. intrinsic). BiV + SyncAV Opt resulted in the greatest reduction in QRS amplitude of 23 ± 26% relative to intrinsic ($p < .05$ vs. BiV Nominal) to 1.09 ± 0.48 mV ($p < .05$ vs. intrinsic, $p = .72$ vs. BiV Nominal). QRS area during intrinsic conduction was 90 ± 42 mV * ms, with a reduction during BiV Nominal of 18 ± 60% ($p < .05$ vs. intrinsic) to 65 ± 39 mV * ms ($p < .05$ vs. intrinsic), and during BiV + SyncAV Opt of 37 ± 29% ($p < .05$ vs. BiV Nominal) to 53 ± 30 mV * ms ($p < .05$ vs. intrinsic, $p = .06$ vs. BiV Nominal). The reductions in QRS duration, amplitude, and area, relative to intrinsic conduction, for each setting were not significantly different between patients without LBBB (e.g. RBBB, IVCD) and with LBBB ($p > .05$).

The QRS vector angle (Fig. 4) during intrinsic conduction was 79 ± 39°, indicating depolarization directed toward the LV. The QRS vector angle shifted toward the RV during BiV Nominal pacing (109 ± 36°, $p < .05$ vs. intrinsic). BiV + SyncAV Opt exhibited a mean QRS vector angle between intrinsic and BiV Nominal (95 ± 39°, $p < .05$ vs. intrinsic, $p < .05$ vs. BiV Nominal).

Discussion

VCG analysis has been recently used as a tool for CRT patient selection and predictor of response [12–15]. VCG QRS metrics have been shown to identify delayed LV activation and dyssynchrony, distinguishing candidates who may particularly benefit from CRT. The key outcome of this work highlights the improvement in 3D electrical synchrony achieved by the SyncAV device-based algorithm in an acute setting, evaluating patients immediately after and well beyond CRT implant. BiV pacing with an optimized SyncAV offset resulted in a greater reduction of QRS duration, QRS amplitude, and QRS area than BiV Nominal pacing. The reduction in VCG-derived QRS duration, relative to intrinsic conduction, observed during BiV pacing with optimized SyncAV (26 ± 10%) was consistent with ECG-based observations in previous studies by Varma et al. (24 ± 8%) and Thibault et al. (20 ± 10%) [8,16]. While patient individualization of the SyncAV offset is recommended, the mean optimal offset centered around its nominal value of 50 ms.

Improvements in ventricular electrical synchronization are the cornerstone of CRT. In the long-term, these improvements induce reverse remodeling, alleviation of patient symptoms, and reduction in overall mortality [17]. Studies have shown that acute reduction in QRSd resulting from device timing optimization may increase patients' benefit from CRT, and result in superior long-term clinical outcome [18]. The significant reductions in VCG QRSd, QRS amplitude, and QRS area indicate superior electrical resynchronization by the patient-specific SyncAV algorithm, relative to conventional programming with static AVD. The study also highlights the potential future application of VCG metrics for real-time, in-clinic optimization of device-based CRT algorithms.

VCG analysis also provides the main direction of electrical activation across the heart in the form of the mean QRS angle. As expected in predominantly LBBB hearts, the QRS angle during intrinsic conduction pointed slightly toward the LV (79 ± 39°), which could be attributed to late right-to-left activation. BiV Nominal pacing rotated the QRS angle by 30° toward the RV (109 ± 36°). This shift could be due to the left-to-right wavefronts resulting from LV pacing. Interestingly, by leveraging the intrinsic wavefront while stimulating wavefronts from both the RV and LV, BiV + SyncAV Opt exhibited a mean angle (95 ± 39°) between those of intrinsic conduction and BiV Nominal pacing. This centered RV + LV angle of BiV + SyncAV Opt was associated with a significantly smaller QRS area, suggesting faster, more synchronized ventricular depolarization. Both the reduced QRS area and rotated activation angle toward the RV have been shown to improve hemodynamic response [19,20].

Clinical implications

The most important clinical implications of this study are that SyncAV improves electrical resynchronization beyond conventional BiV pacing, and that VCG can be used to optimize individual programming of the SyncAV offset. The advantage of VCG, compared to other

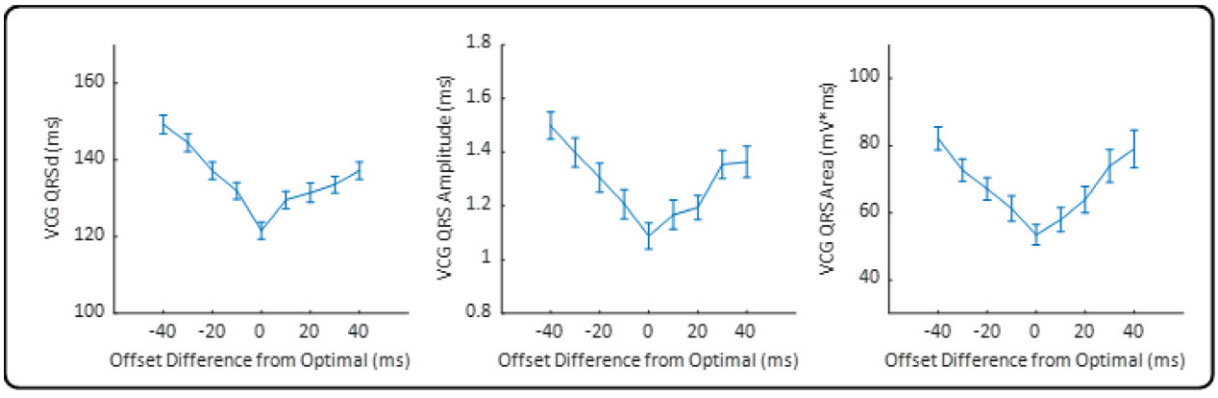

Fig. 2. Impact of SyncAV offset optimization on VCG metrics. QRS duration (left), QRS amplitude (center), and QRS area (right) vs. SyncAV offset are shown for all patients ($N = 100$). Metrics are shown across all SyncAV offsets, relative to the optimal offset for each patient (0 ms). Plots show mean ± standard error across all patients.

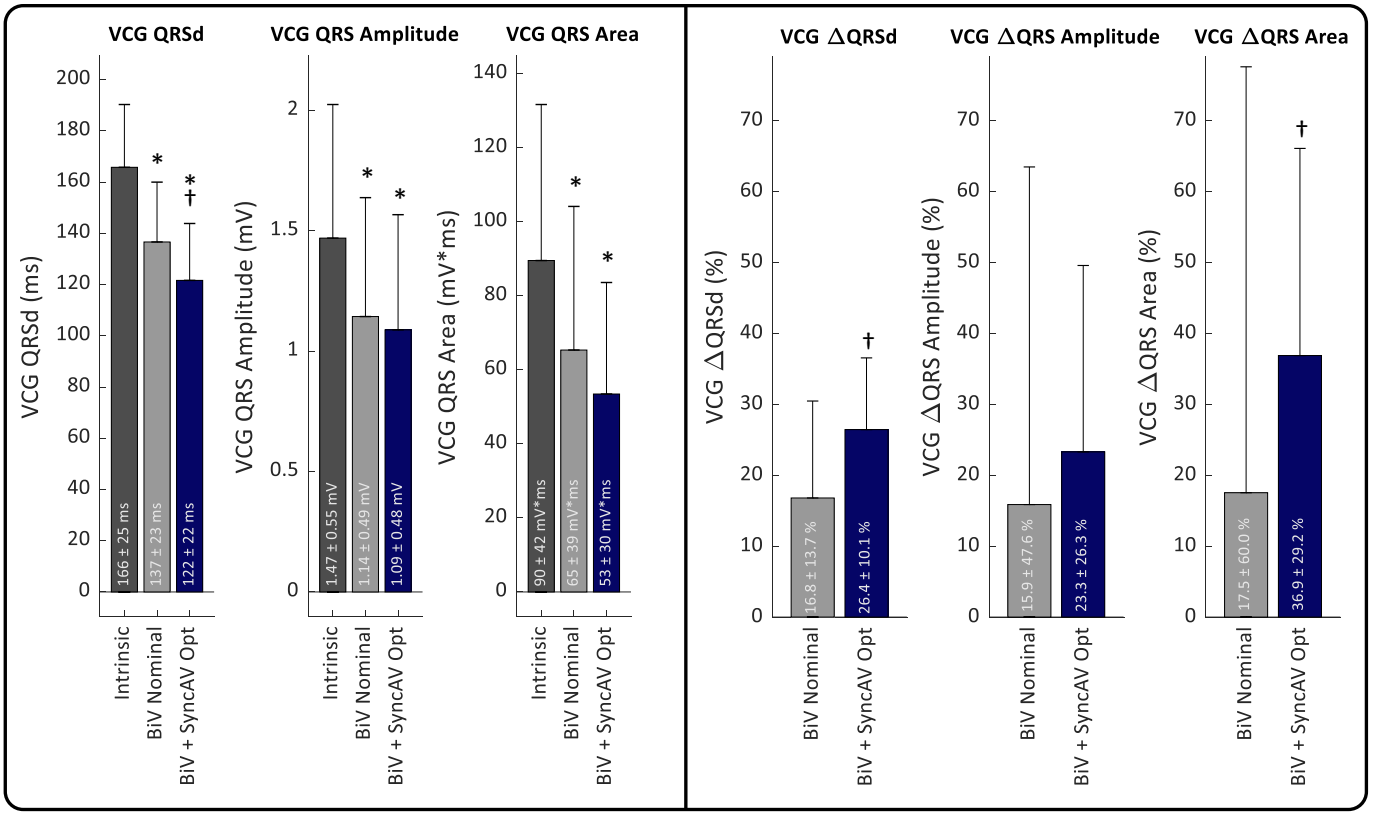

Fig. 3. Effect of biventricular pacing with SyncAV on VCG metrics. Absolute QRS duration (QRSd), amplitude, and area (Left). Percent reduction in QRS duration, amplitude, and area with respect to intrinsic conduction (Right). N = 100 patients. Bars show mean ± standard deviation. P < .05 is indicated by * vs. Intrinsic, † vs. BiV Nominal.

techniques like blood pressure or echocardiography, is that it is a simple, non-invasive technique that can be readily available in any clinic. The study also provides further evidence, beyond earlier studies [8,16], that if programmed adequately, SyncAV results in better electrical synchronization by fusing the BiV pacing activation with the intrinsic activation wavefront. Unlike other synchronization-enhancing features that require multiple LV pacing sites, SyncAV only adjusts the timing of ventricular pacing, with negligible impact on battery longevity.

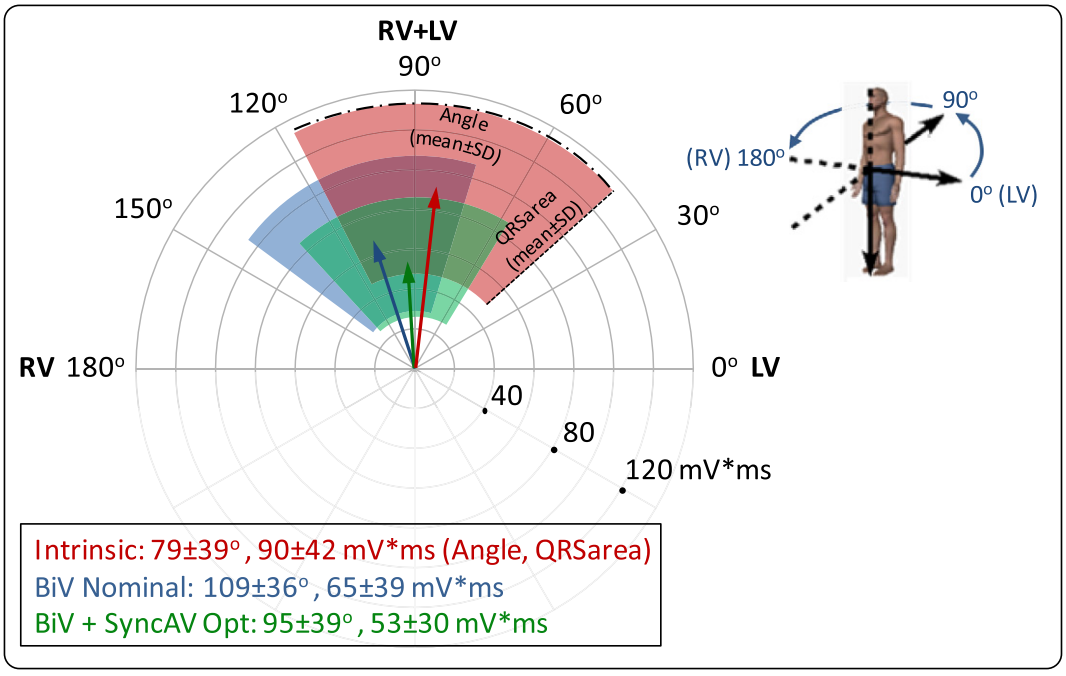

Fig. 4. Magnitude and direction of the maximum QRS vector. Vector magnitudes represent 3D QRS area; vector angles represent the direction in the transversal plane (0° LV → 180° RV). The shaded regions illustrate the mean ± SD for the magnitude and angle. BiV + SyncAV Opt yielded the smallest QRS area, with an angle in between intrinsic conduction and BiV Nominal.

Limitations

In the present work, SyncAV was evaluated only acutely and at rest. Therefore, the capacity of SyncAV to continuously adjust AVD to changes in a patient's intrinsic conduction, has not been taken into account. Although studies have shown the long-term clinical benefit of acute QRS reduction in CRT patients [18], the long-term impact of dynamic AV delay programming has yet to be evaluated. In addition, although the optimal LV lead position for each patient was judged by each center's implanting strategy without a uniform implant protocol or LV lead location, the range of lead sites highlights the broad applicability of SyncAV. Similarly, the broad range of post-implant VCG evaluation time-points highlights the synchronizing ability of SyncAV, despite the potential pre-existing impact of years of CRT.

Furthermore, optimal SyncAV offsets were selected based on individual VCG metrics, which introduces a bias in our analysis. The scope of this manuscript was to present how SyncAV settings could be optimized following any metric of interest (e.g. QRS duration, amplitude, area, or vector angle) and demonstrate the subsequent benefits to resynchronization. A future in-clinic strategy may include real-time VCG analysis to assess a range of offsets with a specific VCG optimization target in mind.

Conclusion

VCG measurements demonstrated an improvement in electrical synchrony by biventricular pacing with VCG-optimized SyncAV, as shown by a reduction in QRS duration, amplitude, and area, relative to biventricular pacing with nominal AVD. Biventricular pacing with SyncAV resulted in a shift of the QRS vector angle back toward intrinsic conduction, indicating that some of the benefit of SyncAV may come from fusion of intrinsic conduction with BiV-paced activation.

Disclosures

EE received a post-doctoral research fellowship from the Cardiac Arrhythmia Network of Canada (CANet). JM, NB and LM are employees of Abbott. FP, CP, BT and LC received research grants and/or are consultants with Abbott. NV reports consulting fees/honoraria from Abbott, Boston Scientific, Biotronik, and Medtronic. This study was funded by Abbott.

Declaration of competing interest

JM, NB and LM are employees of Abbott. FP, CP, BT and LC received research grants and/or are consultants with Abbott. NV reports consulting fees/honoraria from Abbott, Boston Scientific, Biotronik, and Medtronic. This study was funded by Abbott.

Acknowledgements

EE received a post-doctoral research fellowship from the Cardiac Arrhythmia Network of Canada (CANet).

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