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ECG-based evaluation of ventricular synchrony in left bundle branch area pacing through characterization of the activation sequence

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Left bundle branch area pacing (LBBAP) overcomes ventricular dyssynchrony induced by conventional right ventricular pacing (RVP). Despite QRS duration (QRSd) being the standard ECG marker for biventricular synchrony, it lacks insights into the ventricular activation sequence. Our aim is to assess biventricular synchrony by characterizing the ventricular activation sequence and introducing robust markers using the 12-lead ECG. A prospective single-center study was conducted, involving patients with pacemaker indication due to bradycardia. Patients were divided into LBBAP and RVP, and classified by baseline-QRS morphology. To assess biventricular synchrony, low frequency-based QRS analysis was performed to compute the ventricular activation sequence and precordial activation delay (pAD). Additional QRS markers including QRSd, QRS60, and QRS area (QRSa) were calculated. A total of 176 patients (107 LBBAP, 69 RVP) were included. The paced ventricular activation sequence indicated a more physiological pattern after LBBAP than RVP, with lower pAD values in narrow QRS, RBBB, and LBBB subgroups [−10(−20,14) vs. 26(5, 39) ms; −18(−30, −8) vs. 34(26, 55) ms; 10(−14, 25) vs. 32(12, 48) ms] ($p < 0.01$). In all subgroups, QRS60 showed lower values after LBBAP than RVP [52(41, 62) vs.73(65, 80) ms; 60(55, 66) vs. 77(67, 83) ms; 59(53, 64) vs. 77(74, 82) ms] ($p < 0.01$) and QRSa were also lower [53(38, 66) vs. 121(92, 143) µVs; 60(50, 89) vs. 124(97, 159) µVs; 62(52, 80) vs. 133(99, 148) µVs] ($p < 0.01$). pAD provides valuable insights into ventricular activation beyond paced-QRSd. Together with QRS60 and QRSa, pAD could be a promising tool to assess biventricular synchrony.

Keywords ECG markers, Ventricular activation synchrony, Left bundle branch area pacing

Left bundle branch area pacing (LBBAP) is a recent conduction system pacing strategy that improves ventricular synchrony when compared to conventional right ventricular pacing (RVP)[1]. RVP has long been the cornerstone treatment for patients with bradycardia who require pacemaker implantation. However, RVP results in a non-physiological ventricular activation, leading to ventricular dyssynchrony and increasing the risk of atrial fibrillation[2], ventricular dysfunction, and heart failure[2–5]. On the other hand, LBBAP has overcome these limitations by achieving a more synchronous ventricular depolarization, thus resulting in a narrower QRS complex compared to RVP[3,4].

The assessment of ventricular electrical synchrony is crucial in LBBAP patients. R-wave peak time in lead V6 (V6 RWPT)[6,7] and global RWPT[8] have been used to evaluate the presence of conduction system capture, and therefore to assess left ventricular synchrony. While QRS duration (QRSd) is the standard ECG marker for

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evaluating biventricular synchrony[9], it solely provides a measure of depolarization duration without indicating whether the electrical activation sequence of the ventricles is physiological. Moreover, accurately identifying the onset and end of the QRS complex is challenging, potentially introducing biases in the measurements[10,11]. Hence, there is a need for more robust ECG markers to further characterize the electrical biventricular synchrony in LBBAP patients.

The main target of this study is to comprehensively evaluate biventricular synchrony and characterize the activation sequence in patients who underwent pacemaker implantation (either RVP or LBBAP) through a standard 12-lead ECG depending on their baseline QRS morphology. We will provide a set of robust ECG parameters to assess ventricular synchrony more effectively including: precordial activation delay (pAD), accounting for information from the ventricular activation sequence; QRS60, reflecting the ventricular depolarization duration; and QRSa, comprising information of both QRS duration and amplitude. These markers, along with the characterization of the activation sequence, are expected to enhance and supplement the information provided by the standard ECG markers.

Methods

Study population

This is an observational, prospective, single-center study. From January 2022 to February 2023, a total of 176 consecutive patients who underwent a pacemaker implantation were included. The pacing strategy was determined by operators according to their clinical practice. Successful LBBAP or RVP implantation was an inclusion criterion to ensure that our findings focus on the outcomes of these pacing strategies. The exclusion criteria were: being under 18 years of age, pregnant women, patients with a LVEF less than 50%, or those with a non-specific intraventricular conduction disturbance present on the ECG. The Ethics Committee granted approval for the project and all participants signed an informed consent prior to enrollment and all methods were performed in accordance with the relevant guidelines and regulations.

Groups of study and pacemaker implantation

Two groups were defined according to the pacing strategy: the RVP and the LBBAP group. Each group was further subclassified into three subgroups based on the patient´s baseline QRS complex: narrow QRS (i.e. < 120 ms), right bundle branch block (RBBB), and left bundle branch block (LBBB), to assess the effect of RVP and LBBAP in each of these subgroups.

In the RVP group, bipolar active fixation electrodes with steroid liberation were employed. The stylet was manually preformed to reach the right ventricle mid-septum. In the LBBAP group, the 3830 lumen-less lead was advanced to the implantation site using the C315 His sheath (Medtronic Inc, Minneapolis, MN). The system was advanced 2 cm anteriorly and inferiorly from the His-bundle area into the right ventricle while searching for a "W pattern" in lead V1 of the surface ECG. Once identified, the sheath was rotated counterclockwise to maintain the electrode's orientation perpendicular to the ventricular septum. The electrode was then secured by performing 5–10 rapid clockwise rotations to penetrate the septum. As the electrode penetrated the septum, the "W" notch in V1 transitioned into a RBBB pattern. The precise positioning of the electrode relative to the sheath was verified using the fluoroscopy screen[12]. LBBAP was considered successful based on the standard criteria[9,13].

ECG acquisition, preprocessing, and delineation

12-lead ECGs were acquired with a sampling frequency of 1000 Hz and an amplitude resolution of 3.75 μV. Each patient underwent recording of two five-minute ECGs: the first one before implantation and the second one after 24 h of sequential pacing, either RVP or LBBAP (the pacemaker was programmed to ensure 100% ventricular pacing during this period). All ECGs underwent preprocessing, which included the removal of the 50-Hz powerline interference and baseline wander[14].

Due to the pacemakers being programmed in monopolar pacing, the paced-ECGs exhibited a pacing stimulus artifact that was removed for subsequent paced-QRS analysis. A methodology based on identifying the start and the end of the spikes was implemented to eliminate these artifacts[15]. In brief, the absolute value of the ECG derivative was initially computed for each ECG derivation lead. The first sample exceeding a threshold of 200 mV/s during each cardiac beat was identified as a potential spike onset. A spike was considered valid only if more than 3 spike onset marks from the 12 ECG leads was found within a distance of 50 ms. The overall onset was defined as the earliest mark across the 12 ECG leads. The end of the spike was established to occur 20 ms after the spike onset. To confirm the presence of the spike, an ECG sample within the spike interval with a value below − 100 mV was required in each of the 12 ECG leads. Finally, the spike interval was replaced with the result of linearly interpolating the ECG signal immediately before and after the defined spike interval.

The QRS fiducial point as well as the QRS onset and end were automatically obtained from the preprocessed ECG signals using a multi-lead wavelet-based algorithm[16]. This algorithm reported an error margin of 6 ± 8.2 ms for QRS onset and 2.8 ± 8.7 ms for QRS end. The wavelet transform was employed to decompose the ECG signal into various frequency components, enhancing the accuracy of QRS complex delineation across each lead. For the global multi-lead marks, the first QRS onset mark and the last QRS end mark from the 12-lead analysis were determined with specific criteria of proximity between leads. In the case of the QRS fiducial point, the median of the fiducial points from the individual leads was calculated.

Beat selection

A selection process was performed to remove beats that did not present the dominant morphology (mainly extrasystoles and fused beats) in each ECG recording. This was accomplished by initially computing the RR intervals between consecutive QRS fiducial points. Beat segmentation was subsequently performed based on the QRS fiducial point and its corresponding RR interval.

Following beat segmentation, an RR histogram was built, and all the beats whose RR interval was within the 20 ms RR bin that contained the RR mode were selected. The median of these selected beats was set as a preliminary median beat. Each selected beat was then aligned with the preliminary median beat by shifting it by the number of samples leading to the maximum cross-correlation computed across all ECG leads[17]. Only QRS complexes presenting a Pearson correlation coefficient greater than 0.95 with the preliminary median beat were kept as final cardiac beat selection.

ECG-based markers describing activation synchrony

To evaluate the biventricular synchrony, we conducted two different analyses. Firstly, all selected final cardiac beats were included in a low-frequency analysis of the QRS complex in the precordial ECG leads. This aimed to determine the sequence of ventricular activation and, based on it, calculate a new proposed biventricular synchrony marker known as precordial activation delay (pAD). Secondly, a median beat computed from the final beat selection was used to assess biventricular synchrony using other markers like a new suggested duration-based marker named QRS60 and the QRSa.

Characterization of ventricular activation sequence and precordial activation delay

The ECG leads V1-V6 were employed to compute the ventricular activation sequences. Each ECG recording was bandpass-filtered in the following four frequency bands: 10–30, 20–40, 30–50, and 40–60 Hz, which jointly span the frequency range in which the QRS complex is contained. Next, the positive envelopes were computed from the Hilbert transform of the signals obtained after filtering in each of the frequency bands, Fig. 1B. The ventricular activation was defined within the window comprising from 120 ms before to 120 ms after the QRS fiducial point of every QRS complex. Only the ventricular activation windows from the cardiac beats selected as described in Sect. "Beat selection" were taken into consideration. The median of the selected positive envelopes was calculated for each of the four frequency bands. An amplitude normalization was applied by dividing each median envelope by its integral (area) for each frequency band. The average across all frequency bands was then calculated. For representation purposes, the resulting signal was normalized, with the peak amplitude set to one. This normalized signal is referred to as the low-frequency QRS (LF-QRS) and was computed for each precordial lead. The described methodology is illustrated in Fig. 1. The activation time for each ECG lead (AT_l) from V1 to V6 was computed as the time taken to achieve 50% of the LF-QRS total area.

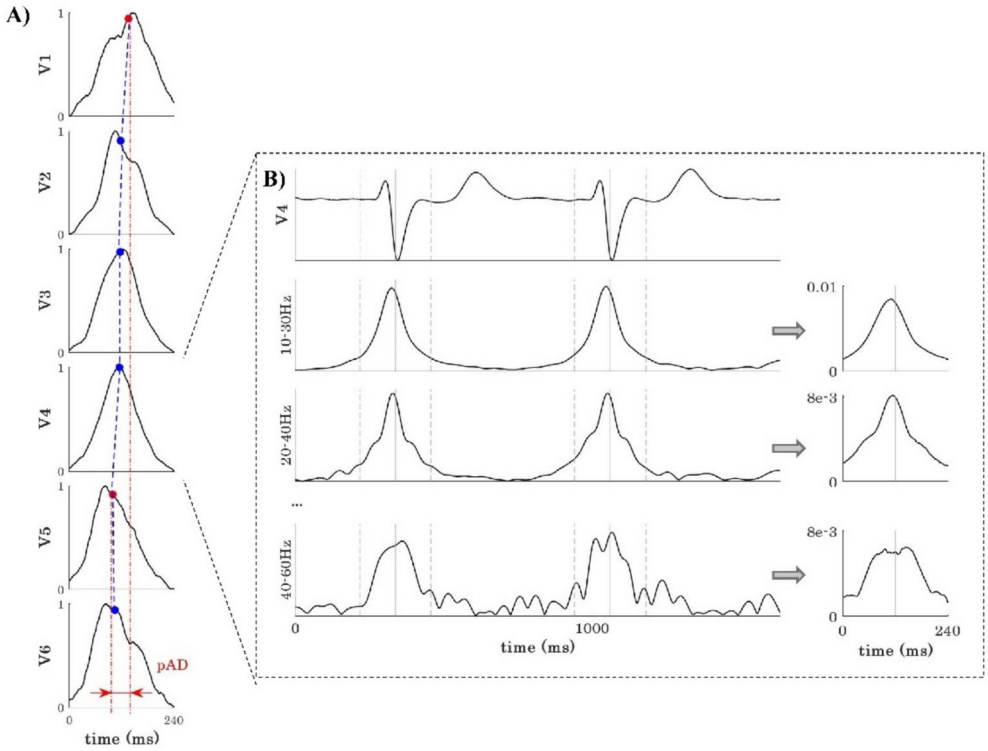

Fig. 1. (**A**) V1-V6 LF-QRS in black. Blue points indicate the AT_l Dash blue line represents the activation sequence constructed by linking AT_1-$_6$. AT_5 and AT_1, in red, are the first and last lead activated, respectively. pAD is the time difference between both shown with dash red lines. (**B**) V4 LF-QRS construction. On the left, V4 ECG signal and different band frequencies envelopes filtered. Grey solid lines correspond to QRS fiducial point. Grey dash lines correspond to start and end QRS window. On the right, median filtered QRS envelope. The normalized average of those generates V4 LF-QRS. LF-QRS: low-frequency QRS. AT_l: activation time of ECG lead l.

The marker pAD was defined as the maximum time difference between the AT_l values calculated across the V1-V6 leads, as shown in Fig. 1A. Positive pAD values indicate a delay in the left ventricular activation, while negative pAD values describe a delay in the right ventricular activation. Small absolute pAD values denote a fast and synchronized ventricular activation.

The activation sequence was constructed by linking AT_l from V1-V6 with a line, as displayed in Figs. 1A and 2B. To determine the median activation sequence across patients within a group, the individual activation sequences were aligned by subtracting the minimum AT_d. This alignment ensured that all sequences started at 0 ms for the ECG lead with the earliest activation in each patient's recording. Median, 25th, and 75th percentiles were then computed over patients for each V1-V6 AT_l. For representation purposes, the representative activation sequences of each group were centered in V2, which facilitated the comparisons between patient groups.

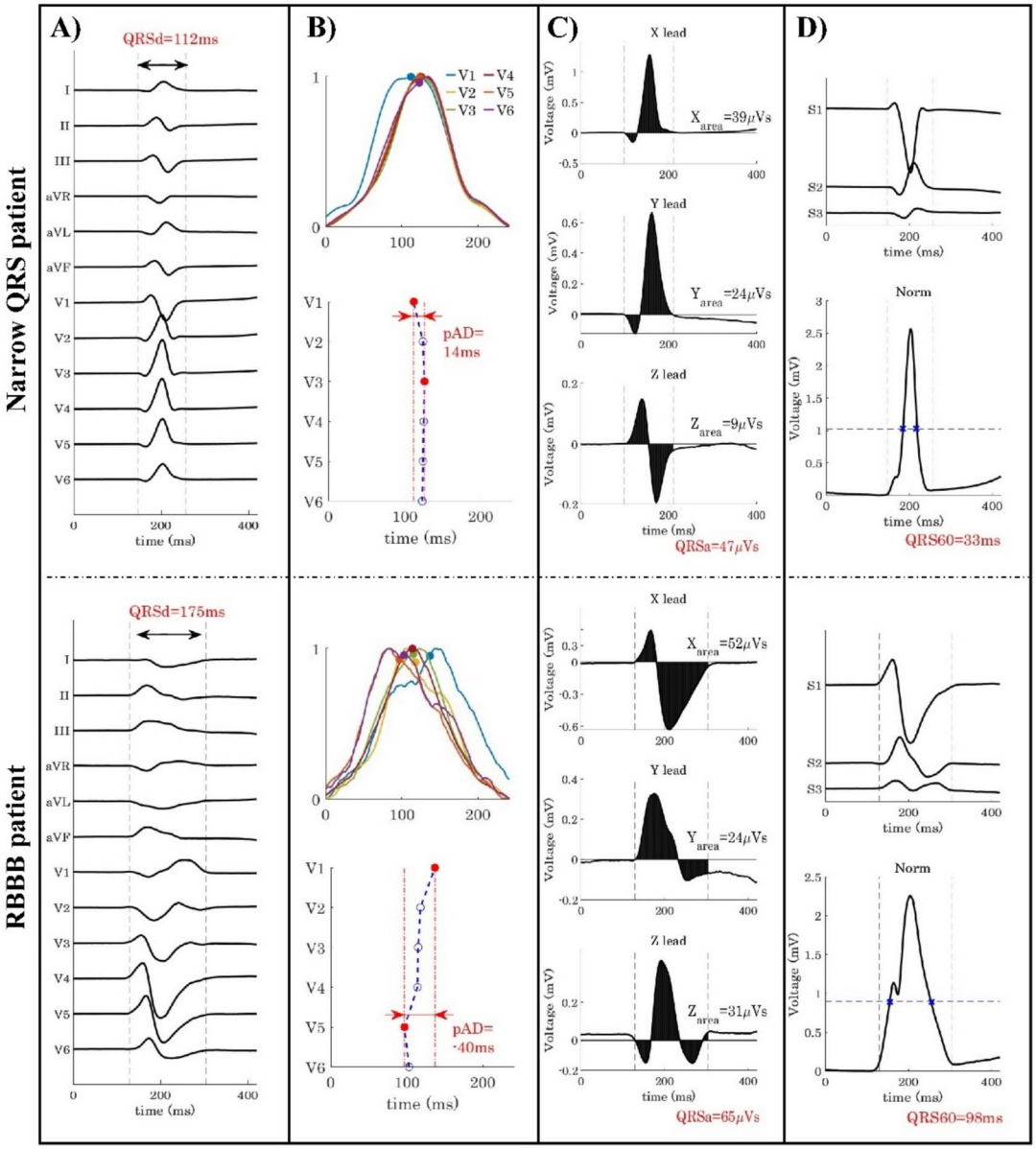

Fig. 2. Calculation of the ECG depolarization descriptors. Upper row shows a representative narrow QRS patient example and bottom row a RBBB patient example. (**A**) QRSd is computed from QRS onset and end delineated in the 12-lead standard ECG. Dash black lines represent QRS onset and QRS end. (**B**) V1-V6 LF-QRSs and each lead activation time as a circle mark. V1-V6 line-linking showing the first and last lead activated in red and pAD value. (**C**) Calculation of QRSa from individuals X, Y and Z orthogonal leads positive and negative areas of the delineated QRS. (**D**) First three components of the SVD of the QRS and the norm of these components. QRS60 is the temporal interval between the two blue crosses. RBBB: Right bundle branch block: QRSd: QRS duration; LF-QRS: Low-frequency QRS; QRSa: QRS area; SVD: Singular value decomposition.

We defined $AT_{6,s}$ as AT_6 calculated as the time from the pacing spike, to allow for an appropriate comparison with V6 RWPT.

QRS60 and QRS area

To compute QRS60 and QRSa, a representative baseline-QRS and paced-QRS from each patient were calculated from the final cardiac beat selection (as defined in Sect. "Beat selection") of the baseline and paced-ECG recordings, respectively.

The following descriptors were computed:

- **QRS60**, based on singular value decomposition (SVD). SVD was applied to the representative median beat in the eight independent ECG leads (I, II, V1, V2, V3, V4, V5, V6). The first three components of the SVD decomposition allowed to construct a three-dimensional space in which more than 99% of the ECG energy was represented[18]. The magnitude of the 3D vector from QRS onset to QRS offset was computed. The maximum of this norm was identified and the duration of the time interval during which the magnitude of the norm was above 60% of its maximum was defined as QRS60. Figure 2D shows the described methodology. Large QRS60 values indicate a highly dispersed activation, while low QRS60 values represent a synchronized depolarization.
- **QRS area (QRSa)** was computed as described by Plesinger et al.[19]. In brief, each 12-lead median beat was transformed into a 3-orthogonal-lead beat, using the Kors conversion matrix to compute the vectorcardiographic X, Y and Z leads. The area under the QRS complex was computed in each of the X, Y and Z leads (represented in Fig. 2C) and QRSa was calculated as:

$$QRS_a = \sqrt{X_{area}^2 + Y_{area}^2 + Z_{area}^2}$$

Clinical established biomarkers

Baseline and paced-QRS duration (QRSd) were measured from the automatically delineated QRS onset to QRS end in the computed median beat using a multi-lead approach[16], as shown in Fig. 2A. V6 RWPT and global V6 RWPT were measured for each patient undergoing LBBAP before any signal processing following the Kielbasa et al. approach[8].

Correlation with established clinical markers

A linear correlation analysis was performed to assess how the proposed markers correlate with QRSd and evaluate the additional information they provide on ventricular electrical synchrony. ΔpAD, ΔQRS60, ΔQRSa, and ΔQRSd were computed as the difference between the paced and baseline values of the markers. For ΔpAD, absolute values were considered to ensure a fair comparison independent of the sign, as both negative and positive values render the same information regarding the degree of activation synchrony, as long as the absolute magnitude is equal.

Additionally, the linear correlation between V6 RWPT and global RWPT with pAD and $AT_{6,s}$ was analyzed in patients undergoing LBBAP. Pearson correlation analysis was used to determine the correlation coefficient (R).

Statistical analysis

The descriptive characteristics of the groups were summarized as mean and standard deviation (SD), or frequencies and percentages, as appropriate. Results for pAD, QRS60, QRSa and QRSd were presented as the median along with 25th and 75th percentiles. To compare between baseline and paced-QRS complex for each pacing technique, the Wilcoxon signed-rank test was employed. The Mann–Whitney U test was used to assess differences between pacing techniques. χ^2 test was performed for comparisons of nominal data. All the analyses were performed in R V.4.2.0. The statistical significance was set at $p < 0.05$.

Results

Clinical characteristics

A total of 176 patients were prospectively enrolled in this study, with 69 patients in the RVP and 107 in the LBBAP group. The mean age was 78 ± 7 years old, 109 (62%) were male and the main indication for pacemaker implantation was AV block, 133 (76%). A total of 74 patients (42%) presented a narrow QRS (i.e. < 120 ms), 71 (40%) presented RBBB, and 31 (18%) LBBB. A total of 107 patients underwent left bundle branch area pacing (LBBAP), with 67 patients meeting the criteria for left bundle branch pacing (LBBP) and the remaining 40 classified as left ventricular septal pacing (LVSP). The clinical characteristics of the patients are presented in Table 1.

Ventricular activation sequences: precordial activation delay

Biventricular synchrony assessed through the ventricular activation sequence and quantified by pAD in both the baseline-ECG and paced-ECG, was compared between the different groups (LBBAP and RVP) and patient subgroups (narrow QRS, RBBB and LBBB) as shown in Fig. 3. pAD values were analyzed in each of the 3 subgroups (narrow QRS, RBBB and LBBB) and compared from baseline to paced-ECG:

- Patients with narrow QRS at the baseline-ECG displayed comparable activation patterns and simultaneous activation from V1 to V6, resulting in near zero pAD values in both LBBAP and RVP groups: 6(−9, 14) and 4(−11, 17) ms, respectively, ($p = 0.89$). The paced ECG in the LBBAP group showed lower (negative) pAD values when compared to baseline-ECG (−10(−20, 14) vs. 6(−9, 14) ms, $p = 0.03$) due to a delay in V1 and

Variables	LBBAP (n = 107)	RVP (n = 69)	*P*-value
Age, y (mean ± SD)	78 ± 7	79 ± 7	0.47
Male, n (%)	67 (63%)	21 (61%)	0.78
Hypertension, n (%)	79 (74%)	57 (83%)	0.17
Diabetes, n (%)	37 (35%)	22 (32%)	0.65
Dyslipidemia, n (%)	57 (53%)	38 (55%)	0.86
Pacing indications, n (%)			
AV block	79 (74%%)	54 (78%)	0.50
SSS	21 (20%)	10 (14%)	0.38
AF with bradycardia	6 (6%)	4 (6%)	0.96
Basal QRS, n (%)			
Narrow QRS	43 (40%)	31 (45%)	0.53
RBBB	47 (44%)	24 (35%)	0.23
LBBB	17 (16%)	14 (20%)	0.45
V6 RWPT, ms (mean ± SD)	148 ± 28	–	–
Global RWPT, ms (mean ± SD)	71 ± 15	–	–

Table 1. Clinical characteristics of the study population. *AV* Atrioventricular; *SSS* Sick sinus syndrome; *AF* Atrial fibrillation; *RBBB* Right bundle branch block; *LBBB* Left bundle branch block, *RWPT* R-wave peak time.

a similar ventricular pattern from V2 to V6. In contrast, the paced-ECG in the RVP group showed a progressive delay from V1 to V6, resulting in increased pAD values when compared to baseline-ECG (26(5, 39) vs. 4(−11, 17) ms, $p < 0.01$). When comparing the paced-ECG of the LBBAP and RVP groups, pAD values were lower for LBBAP (−10(−20, 14) vs. 26(5, 39) ms, $p < 0.01$) (Fig. 3A).

- Patients with RBBB at the baseline-ECG presented an activation sequence with delayed activation in V1 and, therefore, negative pAD values in both groups (LBBAP: −26(−41,−17), RVP: −25(−41, −18) ms, $p = 0.81$). The paced-ECG in the LBBAP group showed a reduction in the V1 delay, thus resulting in smaller negative pAD values when compared to baseline-ECG (−18(−30, −8) vs. −26(−41, −17) ms, $p = 0.02$). Conversely, in the paced ECG of the RVP group, an increase in the activation delay in V6 resulted in positive pAD values (34(26, 55) vs. −25(−41, −18) ms, $p < 0.01$). When comparing the paced ECGs of both pacing groups, the pAD values were lower for LBBAP (−18(−30, −8) vs. 34(26, 55) ms, $p < 0.01$) (Fig. 3B).
- Patients with LBBB at the baseline-ECG showed a delayed activation in V6, with positive pAD values in both groups (LBBAP: 38(19, 57), RVP: 36(13, 52) ms, $p = 0.87$). The paced-ECG in the LBBAP group showed a reduction in the V6 delay, leading to reduced pAD values (10 (−14, 25) vs. 38 (19, 57) ms, $p < 0.01$). However, the paced-ECG in the RVP group showed no significant changes with respect to baseline (32 (12, 48) vs. 36 (13, 52) ms, $p = 0.75$). When comparing the paced ECGs from both pacing groups, pAD displayed lower values for LBBAP (10 (−14, 25) vs. 32 (12, 48) ms, $p < 0.01$) (Fig. 3C).

Biventricular synchrony *from QRS60, QRS area and QRS duration*

QRS60, QRSa and QRSd were evaluated in each patient subgroup from baseline and paced ECGs, as shown in Fig. 5. This allowed the characterization of ventricular depolarization through three different features involving information about the duration and/or amplitude of the QRS.

- Patients with narrow QRS at the baseline-ECG presented comparable QRS60, QRSd and QRSa between both groups ($p = 0.09$, $p = 0.29$ and $p = 0.19$, respectively). The paced-ECG in the LBBAP group ECG showed a non-significant tendency towards increase in QRS60 when compared to the baseline ECG (48(41, 57) vs. 52(41, 62) ms, $p = 0.07$) and an increase in both QRSa (42(33, 51) vs. 53(38, 66) μVs $p < 0.01$) and QRSd (103(91, 109) vs. 119(106,126) ms, $p < 0.01$). On the other hand, the RVP group displayed a significant increase after pacing in the three depolarization descriptors: QRS60 (45(37, 51) vs. 73(65, 80) ms, $p < 0.01$); QRSa: (38(32, 48) vs. 121(92, 143) μVs $p < 0.01$); and QRSd (92(87, 106) vs. 158(147, 170) ms, $p < 0.01$). When the paced-ECGs of the LBBAP and RVP groups were compared, QRS60, QRSa and QRSd values were found to be lower for LBBAP (QRS60: 52(41, 62) vs. 73(65, 80) ms; QRSa: 53(38, 66) vs. 121(92, 143) μVs and QRSd: 119(106, 126) vs. 158(147, 170) ms, $p < 0.01$) (Fig. 4A).
- Patients with RBBB at the baseline-ECG presented similar basal values of QRS60, QRSd and QRSa between the LBBAP and RVP groups ($p = 0.19$, $p = 0.46$ and $p = 0.23$, respectively). The paced-ECG in the LBBAP group displayed lower values of QRS60 and QRSd than the baseline ECG (81(68,96) vs.60(55, 66) ms and 152(139, 164) vs. 131(119, 147) ms, $p < 0.01$, respectively) while QRSa did not show significant differences (61(46, 78) vs. 60(50, 89) μVs $p = 0.35$). In the RVP group, pacing resulted in a significant increase in QRSa and QRSd (52(43, 80) vs. 124(97, 159) μVs $p < 0.01$, and 150(139, 155) vs. 170(155, 178) ms, $p < 0.01$, respectively), while QRS60 did not change (74(63, 88) vs. 77(67, 83) ms, $p = 0.54$). When comparing the paced-ECGs of both groups, QRS60, QRSa and QRSd values were found to be significantly lower for LBBAP (QRS60: 60(55, 66) vs. 77(67, 83) ms; QRSa: 60(50, 89) vs. 124(97, 159) μVs and QRSd: 131(119, 147) vs. 170(155, 178) ms, $p < 0.01$), (Fig. 4B).

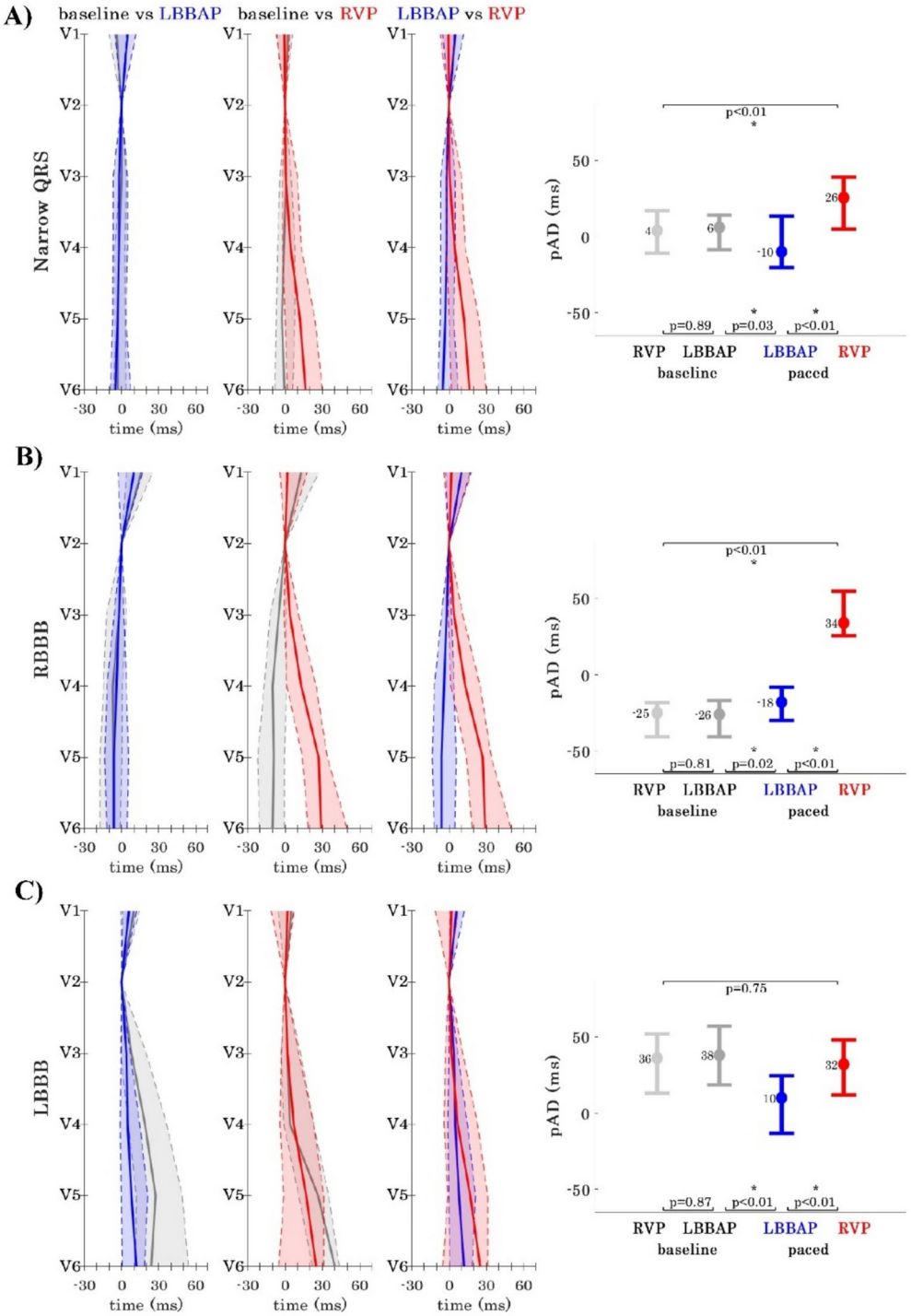

Fig. 3. Median, 25th, and 75th percentiles of ventricular activation sequences at baseline (in grey), LBBAP (in blue) and RVP (in red) and corresponding pAD median, 25th and 75th percentiles values in baseline (**A**) narrow QRS (**B**) RBBB and (**C**) LBBB population. LBBAP: left bundle branch area pacing; RVP: right ventricular pacing; LBBB: left bundle branch block; RBBB: right bundle branch block.

- In patients with LBBB at the baseline-ECG, no differences were found in the baseline-ECG between the LBBAP and RVP groups ($p=0.27$, $p=0.65$ and $p=0.54$, respectively). LBBAP reduced QRS60 (73(63, 85) vs. 59(53,64) ms, $p=0.05$), QRSa (98(77, 120) vs. 62(52, 80) μVs $p<0.01$) and QRSd (153(133,166) vs. 126(117,134) ms, $p<0.01$) with respect to baseline. In the RVP group, the paced-ECG had similar QRS60 and QRSd values than the baseline ECG (74(72,84) vs. 77(74,82) ms, $p=0.55$ and 148(140, 169) vs. 59(151,168) ms, $p=0.51$, respectively) and QRSa showed a non-significant increase (102(84, 127) vs. 133(99, 148) μVs $p=0.10$). When the paced ECGs of the two groups were compared, QRS60, QRSa and QRSd values were

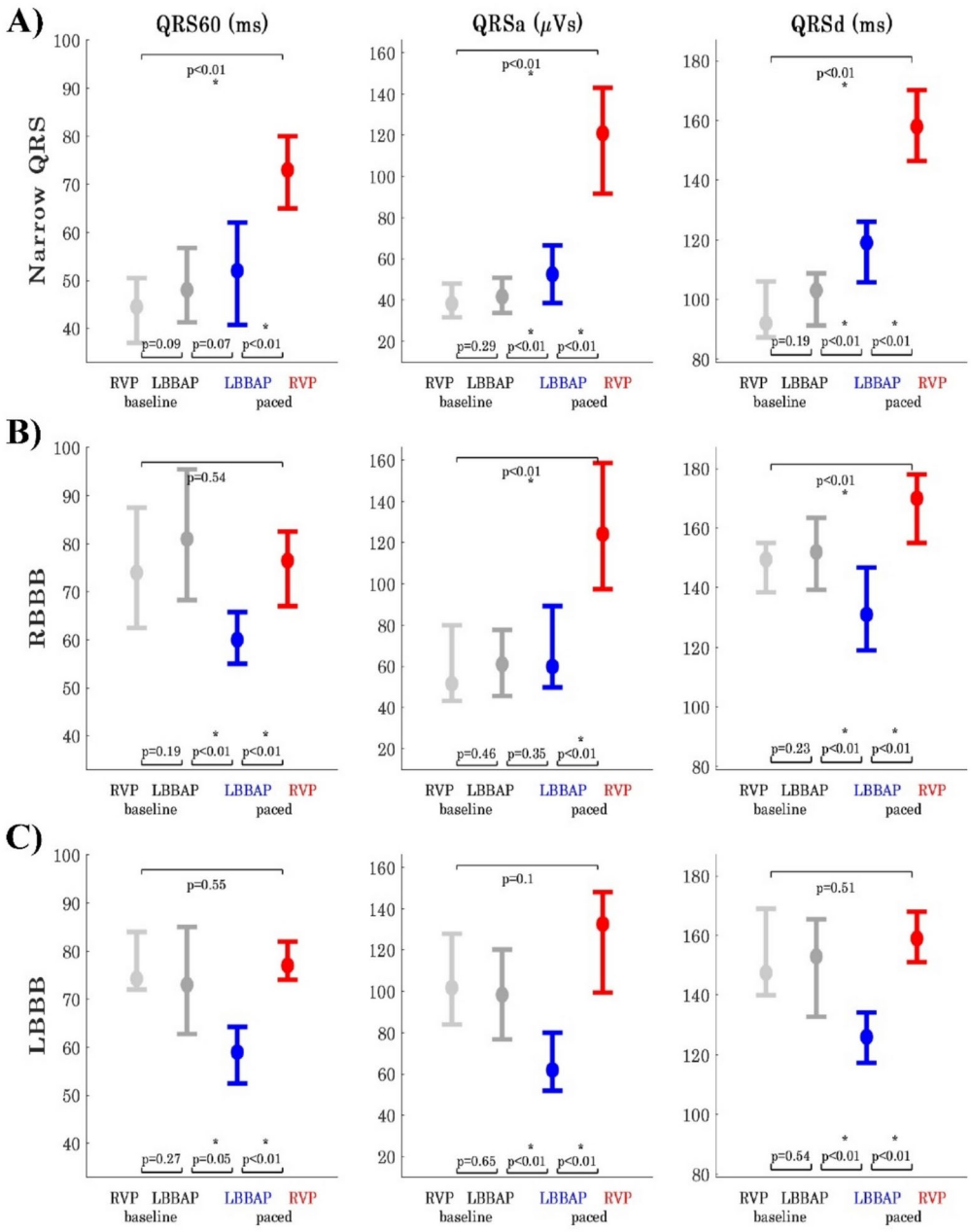

Fig. 4. Median, 25th and 75th percentiles of QRSd, QRSa, and QRS60 markers computed in baseline (**A**) narrow QRS, (**B**) RBBB and (**C**) LBBB patients. QRSd: QRS duration; QRSa: QRS area; LBBB: left bundle branch block; RBBB: right bundle branch block.

found to be significantly lower for LBBAP than for RVP (QRS60: 59(53,64) vs. 77(74, 82) ms; QRSa: 62(52, 80) vs. 133(99, 148) μVs and QRSd: 126(117, 134) vs. 159(151, 168) ms, $p < 0.01$), (Fig. 4C).

Correlation between our proposed metrics and established clinical markers

Linear correlation between ΔQRSd and the three metrics ΔQRS60, ΔQRSa and ΔpAD showed R values of 0.75, 0.62 and 0.43, respectively ($p < 0.01$). All parameters displayed a positive correlation with ΔQRSd but still providing complementary information showing the most pronounced association in ΔQRS60 followed by ΔQRSa and ΔpAD. In case of pAD, also its sign provides complementary information about the ventricular activation direction. To clarify this, an example is presented in Fig. 5A where, a narrow baseline-QRS exhibits similar baseline and LBBAP paced-QRSd (101 and 109 ms, respectively) but notable differences were observed in their activation sequences, changing from a progressive activation from V1 to V6 to a delayed V1 activation, as well as in their pAD values varying from + 7 to − 11 ms, respectively.

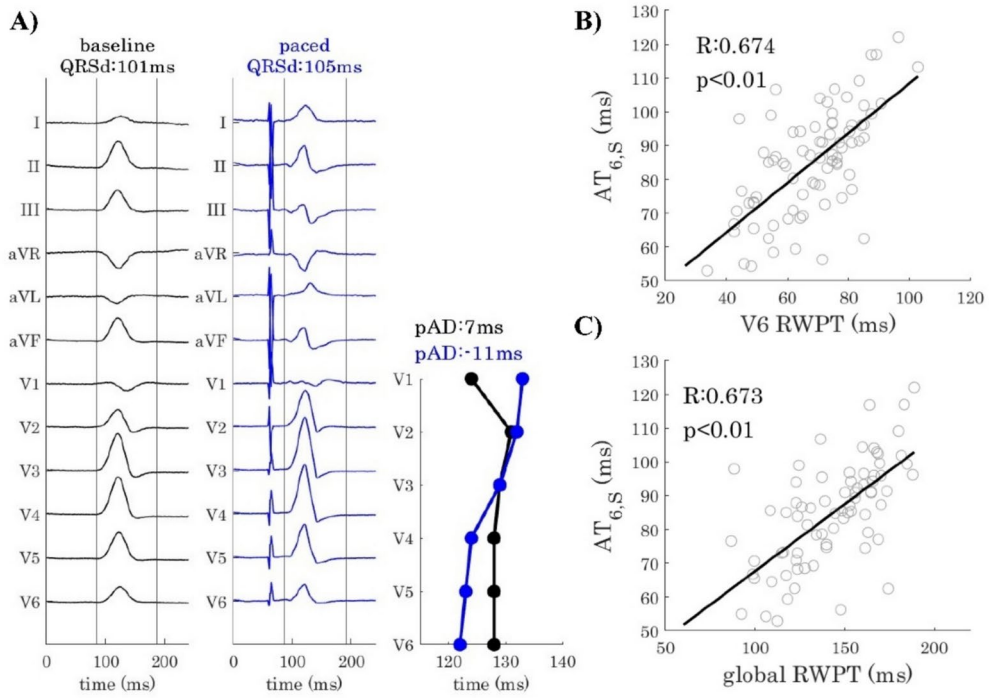

Fig. 5. (**A**) Narrow baseline-QRS in black and after LBBAP in blue and corresponding ventricular activation sequences and pAD values. Ventricular activation sequences showed progressive activation from V1 to V6 at baseline (black) with pAD value of 7 ms while paced-QRS displayed delayed V1 activation (blue) with pAD value of − 11 ms. (**B**) Linear correlation analysis $AT_{6,s}$ with V6 RWPT and (**C**) global RWPT. QRSd: QRS duration; QRSa: QRS area; pAD: precordial activation delay, RWPT: R-wave peak time.

Otherwise, V6 RWPT and global RWPT showed strong linear correlation with $AT_{6,s}$ (R = 0.674, $p < 0.01$ and R = 0.673, $p < 0.01$; Fig. 5B). In contrast, no clear correlation was observed with pAD (R = 0.208, $p = 0.06$ and R = 0.152, $p = 0.19$).

Discussion

LBBAP is an emerging strategy that provides a more synchronous left ventricular activation than conventional RVP. In this context, it is key to identify markers capable of measuring biventricular synchrony. So far, paced-QRSd is the only validated tool for this purpose. Despite being an easy-to-obtain marker, it is not without limitations[10,11]. This study delves deeper into the analysis of the QRS complex to evaluate biventricular synchrony based on the baseline QRS morphology by characterizing the ventricular activation sequence. Additionally, introduces three reproducible markers, derived directly from a standard 12-lead ECG: pAD, QRS60, and QRSa. The main findings are:

i. Ventricular activation sequences constructed from precordial QRS are identified as more physiological following LBBAP compared to RVP, offering a deeper understanding of how pacing affects ventricular depolarization.
ii. pAD, QRS60 and QRSa obtained from standard 12-lead ECG analysis serve as effective tools to assess ventricular activation synchrony in LBBAP.
iii. pAD derived from precordial LF-QRS analysis provides additional information compared to paced-QRSd, yielding new insights into both the direction and the delay of ventricular depolarization.
iv. QRS60 and QRSa show a moderately strong correlation with QRSd and may address some of the limitations associated with its measurement.

To accurately assess the effects of LBBAP, given the high variability in the QRS morphology among patients undergoing pacemaker implantation, we categorized them into three subgroups: narrow QRS, RBBB, and LBBB. This categorization enabled a detailed analysis of ventricular depolarization changes after LBBAP.

The marker pAD provides information not only about the synchrony of ventricular activation but also about its direction. After LBBAP, pAD showed median negative values for the three analyzed populations, suggesting a delay in the activation of the right ventricle, which is consistent with the appearance of a pseudo-RBBB in the paced ECG following LBBAP[9,13]. In patients with narrow baseline QRS, the ventricular activation sequences revealed a delay in V1 compared to their baseline. Patients with a baseline RBBB did not exhibit a significant change in the activation sequence after LBBAP, because the delay in V1 was already present in the baseline ECG, but the significantly lower pAD values suggest an improvement in biventricular synchrony despite the persistence of the RBBB. Conversely, in the LBBB subgroup, a more synchronized ventricular activation was

obtained after LBBAP, as the delay present in V5-V6 at the baseline ECG was corrected. Following RVP, we identified positive pAD values for the three subgroups studied indicating a left ventricle delay. The initial depolarization occurred in the right ventricle being V1-V2 the first leads activated and a significant delay was observed in V6, which refers to left ventricle late depolarization. This is explained by the slow conduction of the electrical wave propagation originating from the paced right ventricular septum, generating a substantial delay in the left ventricle and implying an interventricular dyssynchrony[20].

The introduction of this novel parameter (i.e. pAD) represents a new approach to the characterization of ventricular activation when compared to QRSd. While QRSd is only a temporal-based marker indicating the duration of the ventricular depolarization, pAD offers information about both the direction of the activation, by its positive or negative sign, and the delay, by its magnitude. This also explains the low correlation observed with V6 RWPT and global RWPT, as pAD is measuring dispersion of activation times, which is related to synchrony. By incorporating information from leads V1 to V6, pAD encompasses both ventricles, rather than focusing solely on the left ventricle as V6 RWPT and global RWPT. In contrast, $AT_{6,s}$, which measures activation time from the pacing spike, would be expected to show a stronger correlation with V6 RWPT and global RWPT, as we have shown in Fig. 5B.

Although using an ultra-high-frequency technology, in contrast to our low-frequency analysis in standard ECGs, recent works[21–23] have focused on analyzing the ventricular synchrony by quantifying the direction of the ventricular sequences. Thus, the ability of pAD to determine both the direction and the delay in the activation of different ventricular areas could potentially become a useful intraprocedural tool in the future. More specifically, it could help to target specific septum location to position the LBBAP lead providing a more synchronous and physiological biventricular depolarization.

The values of our proposed pAD marker fall within ranges reported by the electrical dyssynchrony index proposed in recent works[21,23] which analyzed the pacing strategies effect. In agreement with our results, negative values (from – 30 to – 10 ms) were shown following LBBAP[23] and activation sequences with delayed lateral leads were found after RVP[22]. Our approach not only analyzed the pacing effects but also focused on attaining similar baseline populations by studying subgroups based on baseline-QRS morphology (narrow QRS, RBBB, and LBBB) which resulted in a better characterization of the pacing effect (either LBBAP or RVP). Additionally, pAD utilizes common V1 to V6 leads from standard 12-lead ECG and employs standard recording frequency ranges (200–1000 Hz). In contrast, the electrical dyssynchrony index requires 14-lead ultra-high-frequency technology, needing specialized equipment to record frequency ranges up to 5000 Hz and eight precordial leads.

An analysis of additional markers (i.e. QRSa and QRS60) has been conducted to achieve a more comprehensive characterization of the effects of pacing on ventricular activation. These markers provide information regarding the duration and area of the QRS complex, complementing and enhancing the information provided by QRSd, while overcoming some of its limitations. Accurate identification of the start and end of the QRS complex is crucial for QRSd, a task that could sometimes be challenging and subject to important biases[10]. We propose QRS60 as a new duration marker that could overcome the bias associated with measuring the onset and the termination of the QRS complex. This marker is a more robust marker to assess biventricular synchrony given that potential discrepancies in the QRS complex delineation should not affect QRS60 values at all. Our results revealed significantly lower QRS60 values after LBBAP compared to RVP in the three QRS subgroups in agreement with the results for QRSd. Additionally, QRS60 has shown a strong positive correlation with QRSd, as both descriptors provide information of QRS duration. It should be noted that QRSd significantly increased after LBBAP in narrow baseline-QRS patients. In contrast, although QRS60 showed a trend towards increase, this change wasn't statistically significant. This is likely because QRS60 includes the most representative part of the ventricular activation, but may not capture the activity in the last activated areas, which are characterized by smaller size and slower activation.

Concerning QRSa, it has been previously used as a predictor for therapy response in cardiac resynchronization therapy, showing a superior performance to QRSd in predicting cardiac and total mortality in these patients[24,25]. However, it has been scarcely used to investigate the effects of pacing in bradycardia patients undergoing LBBAP. We have employed it to compare LBBAP and RVP effects on biventricular synchrony. All the analyzed subgroups exhibited higher QRSa values after RVP than LBBAP, confirming previous results[26]. Although QRSa showed good correlation with QRSd, it still offers complementary information to QRSd since it considers QRS amplitude. Based on these results QRSa could potentially be an appropriate marker to assess biventricular synchrony in LBBAP.

Although narrow QRS and LBBB baseline-ECG patients' results were as expected, the RBBB subgroup demonstrated an interesting reduction in pAD following LBBAP. We propose that this improvement may be related to the development of a pseudo-RBBB pattern after LBBAP[7]. This could be due to the fact that LBBAP leads to early recruitment of the basal right ventricular septum and improves biventricular synchrony through earlier activation of the right ventricle, mimicking an incomplete RBBB[27].

pAD, QRS60, and QRSa are not only robust and reproducible markers but also feasible for real-time computation from standard ECGs. The computation of these markers is highly efficient, with QRSa, QRS60 and pAD calculated in less than one millisecond. Further refinement of the algorithms would be warranted to reduce the computational demand even more and to integrate the specialized software with the ECG acquisition. This process would be seamless and would not interfere with routine clinical practice.

By providing a comprehensive assessment of biventricular synchrony, these markers offer valuable new insights and address some of the limitations associated with traditional analyses based solely on paced-QRS duration. The accessibility to the LF-QRS methodology for ventricular activation sequence construction and pAD evaluation, which doesn't require any specific equipment beyond a 12-lead ECG, could significantly contribute to its widespread use during LBBAP implants, thereby allowing for a more precise characterization of ventricular activation. Moreover, this technology holds promise for future applications in guiding the placement of the

LBBAP lead pacemaker in real-time, potentially serving as a valuable clinical tool for analyzing biventricular synchrony during the implant procedure.

Limitations

This study was conducted at a single-center. Moreover, no validation for the presented markers was performed due to the absence of an established gold standard for biventricular synchrony beyond paced-QRSd. Nevertheless, the results obtained from RVP enhance the credibility of our work, as this pacing strategy effectively induced ventricular dyssynchrony, in line with findings from electrophysiological studies[20]. This was reflected in pAD, QRS60 and QRSa. Further studies are needed to determine whether these markers can help to improve clinical outcomes by guiding the procedure.

Conclusions

The findings of this study suggest that pAD (derived from LF-QRS activation sequences), QRS60 and QRSa, are useful parameters to assess biventricular synchrony in LBBAP patients. While QRSd is only a temporal-based marker, pAD offers information about the direction and the delay of ventricular activation. QRS60 and QRSa are robust markers that provide additional information regarding QRS amplitude, both presenting good correlation with QRSd. All three demonstrated a more physiological ventricular depolarization in LBBAP than in RVP. The accessibility of these markers through a standard 12-lead ECG analysis could foster widespread integration within the LBBAP field, with potential utility during LBBAP implants.

Data availability

The datasets generated and analysed during the current study are not publicly available because they contain sensitive medical information obtained under patient consent, specifically for the purposes of this study, but are available from the corresponding author on reasonable request.

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Author contributions

C.S.-B.: Data collection, analysis, results interpretation, and manuscript preparation. A.M.: Study design, results interpretation, and manuscript review. J.M.-P.: Clinical data collection, clinical procedures, and manuscript review. M.C.-R.: Clinical procedures and manuscript review. P.V.-M.: Data collection. I.M.-P.: Clinical procedures. L.S.-V.: Clinical data collection. I.J.-G.: Clinical data collection. G.V.M.-C.: Clinical data collection. J.R.R.-A.: Manuscript review. E.P.: Study design, results interpretation, and manuscript review. J.R.-M.: Study design, results interpretation, and manuscript review.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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