Left Bundle Branch Area Pacing Generates More Physiological Ventricular Activation Sequences than Right Ventricular Pacing

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Abstract

Left bundle branch area pacing (LBBAP) has been proposed as a new physiological pacing modality to overcome ventricular dyssynchrony (VD) reported in bradycardic patients undergoing conventional right ventricular pacing (RVP). The standard non-invasive measure of depolarization synchrony is the QRS duration. However, a deeper understanding of not only the activation time but also the activation sequence is needed to evaluate the effects of RVP and LBBAP in the highly heterogeneous population of bradycardic patients. This study aimed to estimate the precordial ventricular activation from standard 12-lead ECGs of bradycardic patients with narrow QRS (physiological conduction) and right bundle branch block (RBBB, disturbed conduction) and use it to compare LBBAP vs RVP.37 RVP and 62 LBBAP ECGs recordings were collected before and after pacemaker implantation. Two different frequency-based methods for QRS complex analysis were used and the precordial activation sequence and activation delay (pAD) were estimated. Results showed more physiological activation sequences after LBBAP than after RVP, with lower pAD ($p<0.01$) after LBBAP in both narrow QRS [9(-25,13) vs 31(17,38)] and RBBB patients [-22(-42,-18) vs 39(31,61)]. The proposed ECG methodology could be used in clinical practice to map more physiological pacing targets in pacemaker implantation.

1. Introduction

Right ventricular pacing (RVP) is the most common treatment for patients suffering from bradyarrhythmias mostly caused by atrioventricular (AV) block and sinus node syndrome. Nevertheless, it is well known that conventional RVP is associated with cardiac systolic dysfunction and increased risk of atrial fibrillation and heart failure [1]. In this context, left bundle branch area pacing (LBBAP) has recently emerged as a feasible and safe alternative to RVP generating more physiological ventricular activation [2].

QRS duration is the standard measurement for ventricular synchrony [3] [4] [5]. It provides information about the ventricular activation time but not about the activation sequence. The use of methods rendering additional characterization could help to better assess the effects of RVP and LBBAP in bradycardic patients with physiological (narrow QRS) and disturbed (e.g. right bundle branch block, RBBB) ventricular conduction.

Previous studies have proposed techniques to measure ventricular synchrony and activation patterns in patients undergoing cardiac resynchronization therapy. These techniques have been applied on ultra-high-frequency (5000 Hz sampling frequency) 14-lead electrocardiograms (ECGs) using 16 different frequency bands within the 150-1000 Hz range [6]. Since the frequency content of the QRS complex is mostly contained in the 0-60 Hz band, here we will perform frequency analysis over frequency bands contained within such frequency range. Additionally, the same analysis will be conducted over frequency bands in the 150-400 Hz range. The activation times and sequences calculated with both methods in standard 12-lead ECGs of bradycardic patients with narrow QRS and with RBBB undergoing either LBBAP or RVP will be evaluated and compared.

2. Methods

2.1. Study population

12-lead ECG recordings from patients with narrow baseline QRS and RBBB indicated for antibradycardia therapy were collected at Lozano Blesa Clinical University Hospital (Zaragoza, Spain) at baseline and after 24 hours of continuous RVP (37 patients) or LBBAP (62 patients). ECGs were acquired at a sampling frequency of 1000 Hz and amplitude resolution of 3.75 μV. Table 1

shows the baseline characteristics of the patients included in the study.

Table 1. Baseline characteristics of the study population. AV = atrioventricular; SSS = sick sinus syndrome; AF = atrial fibrillation; RBBB = right bundle branch block

Variables	RVP	LBBAP	P-value
Age, y (mean $\pm$ SD)	78 ± 10	79 ± 8	0.54
Male sex, n(%)	65	61	0.72
Hypertension, n(%)	78	66	0.25
Diabetes, n(%)	38	26	0.27
Dyslipidemia, n(%)	59	558	0.98
Pacing indications, n(%)			
Complete AV block	30	44	0.17
AV block grade II	35	23	0.17
SSS	22	18	0.63
AF + ablation	3	5	0.6
Slow AF	11	8	0.65
Basal QRS, n(%)			
$<$120 ms	59	68	0.40
RBBB	41	32	0.40
Cardiomyopathy, n(%)	11	17	0.46

2.2. Signal processing

ECG preprocessing included removal of 50 Hz power-line noise and of baseline wander. Aspike cancellation strategy (only for those ECGs at post-implantation state) was implemented following the strategy described in [3] which is based on spike start and end identification and linear interpolation replacement.

Preprocessed ECG signals were delineated using a multi-lead wavelet-based approach [7] with updates in the derivative thresholds used to identify the onset and end of the QRS complex to better reproduce annotations by expert electrophysiologists. QRS fiducial, onset and end points were identified for each cardiac beat. QRS selection was performed to remove extrasystolic beats. The RR interval was calculated from consecutive QRS fiducial points. Beats contained in a 20-ms bin centered in the RR mode were selected and an initial median beat was calculated. Subsequently, only cardiac beats whose QRS complex showed a Pearson coefficient with the median beat above 0.95 were included to the final QRS selection.

2.3. Ventricular activation sequences and pAD

Two frequency-based analyses of the QRS complex in precordial leads V1-V6 were conducted using: (1) high-frequency (HF) bands between 150 and 450 Hz (150-250, 200-300, 250-350, 300-400 and 350-450); (2) low-frequency (LF) bands between 10 and 60 Hz (10-30, 20-40, 30-50 and 40-60).

For LF and HF frequency analyses, the ECG recording was filtered in each of the described frequency bands. Positive envelopes of the selected QRS complexes were computed using the Hilbert transform, with the QRS complex extending from 120 ms before to 120 ms after the QRS fiducial point. In the HF analysis, an additional strategy was applied to avoid that the interpolation performed after applying the spike cancellation strategy could disrupt the QRS analysis.

For each of the two frequency analyses and for each precordial lead, the following steps were implemented. Median amplitude envelopes were calculated for each described frequency band. These were normalized by dividing the median amplitude envelope by its integral. The average over all frequency bands was subsequently computed and the resulting beat was normalized by the maximum amplitude. The obtained beats in each lead were denoted as HF-QRS and LF-QRS for HF and LF analysis, respectively.

A quality criterion was applied over HF-QRS complexes. If the median value of HF-QRS was superior to 0.35, the lead was discarded. A minimum of 3 leads was required for further analysis.

To compute the lead activation time (lAt), the sample with the maximum amplitude in each HF-QRS and LF-QRS was located. The first samples before and after it falling above 50 % of its amplitude were used to define the interval where the center of mass was computed in each lead. Precordial activation delay (pAD) was defined as the maximal time difference over V1-V6 lAt. pAD positive values indicated left ventricular activation delay and negative values indicated right ventricular activation delay. Shorter absolute pAD values represented faster and more synchronized ventricular activation.

Activation sequences were constructed by drawing the line connecting lAT values from V1 to V6. To compute the mean activation sequence over all patients in an analyzed group, the activation sequence of each patient was shifted so that the minimum lAt became 0 ms. Subsequently, the mean and 95% confidence intervals (CI) of lAt values for each lead were calculated.

To facilitate group comparisons, the activation sequences were centered in V2 to make them comparable between different patients groups.

2.4. Statistics

pAD data is presented as median (CI). Comparisons between post-implantation and basal states for each pacing technique were performed using Wilcoxon signed-rank test. Statistical differences between stimulation

techniques were analyzed using the Wilcoxon rank-sum (Mann–Whitney U) test. The χ^2 test was performed for comparisons of nominal data. P-values < 0.05 were considered as statistically significant. Activation sequences are displayed as mean and 95% CI.

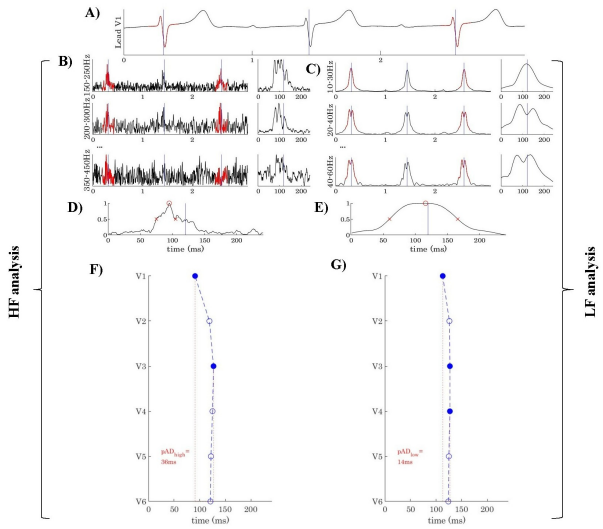

Figure 1. Activation sequence and pAD computation for a patient with narrow QRS at baseline. (A) ECG beats in lead V1. (B) HF and (C) LF analysis, with display of amplitude envelopes in different frequency bands and of the median amplitude envelope (selected beats in red). (D) HF-QRS and (E) LF-QRS complexes, with the red circle indicating maximum amplitude and red crosses, 50% of such amplitude. (F) HF-QRS and (G) LF-QRS activation sequences, with first and last activated leads in full circles.

3. Results

HF-QRS and LF-QRS analyses included 62 and 96 patients, respectively, with the difference being due to the applied quality criteria.

At baseline, no significant differences were observed between LBBAP and RVP patient groups. In narrow QRS patients, baseline activation sequences built with the two frequency methods showed highly synchronized V1-V6 activation sequences, both for LBBAP and RVP groups. In RBBB patients, the baseline activation sequences presented synchronized left ventricular activation and a remarkable delay in V1.

At post-implantation, significantly higher pAD values were found ($p<0.01$) for RVP than for LBBAP with both frequency analysis, as shown in Figure 2.

The RBBB group showed more physiological activation sequences after LBBAP. This was reflected in less negative pAD values than at baseline, even if differences were not significant [HF-QRS:-26(-58,-7) vs -16 (-22,-10) ms, p=0.28; LF-QRS: -35(-50,-28) vs -22(-42,-18) ms, p=0.50]. After RVP, a significant activation delay was observed for RBBB patients using both frequency analyses [HF-QRS: -23 (-72,3) ms vs 20 (10,51) ms, $p<0.01$; LF-QRS: -23 (-70,-11) ms vs 39 (31,61) ms, p=0.01].

Narrow baseline QRS patients also presented left ventricle delay after RVP, but it only turned out to be significant when LF analysis was performed [HF-QRS: 15 (4,27) ms vs 29 (6,56) ms, p=0.19; LF-QRS: 7 (-12,16) ms vs 31 (17,38) ms, p=0.001]. After LBBAP, no significant differences were observed in LF-QRS analysis but pAD presented significant changes in HF-QRS analysis [HF-QRS: 12(-2,15) vs -7(-18,6), p=0.004; LF-QRS: 5(-10,13) vs 9(-25,13), p=0.24].

4. Discussion

The main findings of this study are: (1) in patients with physiological conduction (narrow QRS), LBBAP preserved activation synchrony but RVP did not; (2) in patients with disturbed conduction (RBBB), RVP led to significantly higher activation delays than at baseline, while LBBP reduced activation dyssynchrony; (3) LF-QRS rendered similar results to HF-QRS, thus confirming the suitability of studying frequency components up to 60 Hz for ventricular activation analysis.

The two frequency methods implemented in this study indicated that RVP increased dyssynchrony in ventricular activation, in line with previous studies. Significant differences in post-implantation pAD values were observed between LBBAP and RVP, with remarkably lower dyssynchrony found in patients treated with LBBAP but not in those treated with RVP. This applied to both patients with narrow QRS and with RBBB at baseline, thus supporting LBBAP as a more physiological pacing modality [8].

The RVP activation sequences in this study were similar to those shown in previous ultra-high-frequency studies [4, 5]. When pacing at the RV apex, inflow and outflow tract, the ventricular delays reported in [5] were of the same order as here, with mean values of 34, 19 and 33 ms, respectively, in a population with 14% RBBB patients and 32% without BBB. When performing left ventricular septal pacing (LVSP) and non-selective LBB pacing (nsLBBp) in a population with 21% RBBB patients and 32% without BBB, mean delays of –24 ms and –12 ms for each of the two pacing modalities were found. Our work showed median pAD values after RVP of 31 ms and 29 ms for narrow QRS patients and 39 and 20 ms in RBBB patients using LF-QRS and HF-QRS analyses.

The two frequency analyses rendered consistent results and showed that LBBAP improves cardiac depolarization synchrony but RVP does not, with this holding both for patients with narrow QRS at baseline and for RBBB pa-

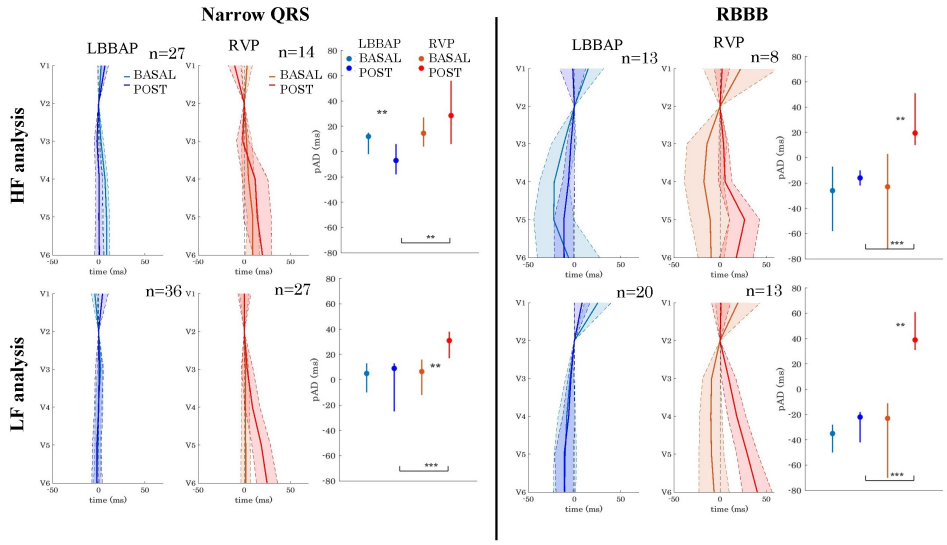

Figure 2. Mean (CI) activation sequences and median (CI) of pAD for LBBAP and RVP groups at baseline and post-implantation states for HF-QRS and LF-QRS analyses.

tients. While the LF-QRS analysis could be applied to all QRS complexes, the HF-QRS analysis was restricted to 62, as all other complexes did not satisfy the quality criteria. These results suggest the use of LF-QRS analysis to characterize the effects of pacing in bradycardic patients. The developed method, derived from the study of 12-lead ECG recordings, could be applied to improve the identification of pacing sites for more physiological ventricular activation.

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