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Spatial Dispersion of Activation and Repolarization Times Associated with Different Cardiac Pacing Modes

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Abstract

Various modes of ventricular pacing are currently applied to patients with an indication for permanent pacemaker implantation. The so-called physiological pacing modes, like His bundle pacing (HBP) and left bundle branch pacing (LBBP), stimulate the cardiac conduction system to induce efficient physiological activation. Other techniques, such as left ventricular septal pacing (LVSP) and right ventricular septal and apical pacing (RVSP and RVAP), stimulate the ventricular septum or right ventricular apex. 695 ultra-high-frequency electrocardiograms (UHF-ECG) from 176 patients with narrow QRS and pacemaker indication were analyzed to characterize their activation (AT) and repolarization (RT) time. AT and RT were grouped into three regions (R1: leads V1-V2; R2: V3-V4; R3: V5-V6). Overall, selective HBP (sHBP), nonselective LBBP (nsLBBP) and LVSP recordings had the closest AT and RT values to spontaneous rhythm recordings. For AT, the mean R1-R2 and R3-R2 differences with respect to spontaneous rhythm were, in absolute value, below 3, 16 and 10 ms for sHBP, nsLBBP and LVSP, respectively. For RT, the corresponding mean differences were below 11, 34 and 24 ms for sHBP, nsLBBP and LVSP. In conclusion, HBP, LBBP and LVSP render the closest ventricular AT and RT to the spontaneous rhythm in patients with physiological conduction (narrow QRS).

1. Introduction

Several cardiac pacing modes are applied to patients with symptomatic bradycardia who require permanent pacing to ensure adequate heart rate and prevent mortality. Conduction system pacing, namely His bundle pacing (HBP) and left bundle branch pacing (LBBP), have emerged as an alternative to conventional right ventricular pacing (RVP) [1], which has been reported to cause ventricular dyssynchrony with an increased risk of heart failure and decreased left ventricular ejection fraction.

Although HBP represents the most physiological stimulation mode, it presents limitations related to lead positioning, associated with 10%-20% implantation failure rate, and with high capture thresholds and consequent rapid power consumption. LBBP, defined by capture of the left bundle branch (LBB), appears as an effective alternative to overcome the limitations associated with HBP [2]. LBBP can be selective (only the LBB is captured), sLBBP, or nonselective (both LBB and the adjacent local septal myocardium are captured), nsLBBP, and has been shown to render high implantation success and low capture thresholds [3]. Pacing the His bundle as well as part of the myocardium is termed as non-selective HBP (nsHBP), whereas pacing of the His bundle exclusively is called selective HBP (sHBP).

The effects of sLBBP and nsLBBP in comparison to sHBP and nsHBP and to other pacing modes that stimulate the interventricular septum, like left ventricular septal pacing (LVSP) and right ventricular septal pacing (RVSP), or the right ventricular apex (RVAP) have not yet been fully characterized. Non-invasive markers measured from the electrocardiogram (ECG) have been proposed to quantify the ventricular activation characteristics and assess the effects of cardiac pacing. Among others, the index of electrical dyssynchrony (e-DYS), the local depolarization duration (Vdx), the mean of Vdx over leads (Vd) [4] and the dispersion of ventricular depolarization from inferred epicardial maps [5] have been proposed.

The aim of this study was to evaluate the changes induced by different cardiac pacing modes in the ventricu-

lar synchrony of the activation time (AT) and, importantly, also on the repolarization time (RT). To that end, we analyzed ECGs from patients with narrow QRS (physiological ventricular activation) referred for pacemaker implantation, acquired both before and after implantation.

2. Study Population

The study included patients referred for pacemaker implantation due to bradycardia. 695 ultra-high-frequency electrocardiograms (UHF-ECG, sampling frequency = 5 kHz) from 176 patients were acquired at the International Clinical Research Center at St Anne's University Hospital, Brno, Czech Republic and at the Cardiocenter of Faculty Hospital Kralovske Vinohrady and the Third Medical Faculty of Charles University, Prague, Czech Republic.

The distribution of recordings according to the pacing mode was: 50 recordings during sHBP, 160 during nsHBP, 87 during LVSP, 47 during nsLBBP, 13 during sLBBP, 102 during RSVP, 37 during RVAP and 199 during spontaneous rhythm.

14-lead UHF-ECG signals were recorded using a Ventricular Dyssynchrony Imaging (VDI) monitor (ISI Brno, Cardion, FNUSA, CZ, 2018). All patients underwent a pacing threshold test, during 12-lead ECG monitoring, to identify various patterns of ventricular activation (myocardial, HBP capture) before applying all cardiac pacing modes [6].

3. Methods

3.1. Preprocessing

Preprocessing of raw ECG signals included baseline wander and noise removal using high-pass and 50 Hz notch filters.

Pacing artifacts were removed by a semi-automated algorithm, updated from the one described in [7], consisting of the following steps:
1. Orthogonal leads XYZ were obtained from the standard 12-lead ECG signal by using the Kors transformation matrix [8]. The vector magnitude was then computed as:

$$v(n) = \sqrt{x(n)^2 + y(n)^2 + z(n)^2} \qquad (1)$$

where $x(n)$, $y(n)$, $z(n)$ are the orthogonal leads and $v(n)$ is the vector norm.
2. The vector magnitude slope, dv/dt, was approximated from the differences between consecutive samples. The onset and end of the pacing artifact were identified as the first and last samples satisfying the following conditions:

$$\frac{dv}{dt} > \alpha_{onset}$$
$$\frac{dv}{dt} < \alpha_{end} \qquad (2)$$

where α_{onset} and α_{end} are the thresholds for the pacing stimulus onset and end. Here, $\alpha_{onset} = 0.5$ and α_{end}=-0.5 mV/ms.
3. The pacing artifact was removed and replaced with the result of linearly interpolating the signal between the onset and end of the identified artifact window.

QRS complexes for each recording were detected and clustered according to their morphology, discriminating between paced beats and irregular patterns (as extra-beats) [9]. Delineation of ECG waves was performed by using a wavelet-based single-lead automatic system [10].

3.2. Representative beat

A representative beat for each recording was defined as the median of all the beats that presented the main beat morphology. The applied algorithm followed these steps:
1. RR intervals, RR_i, were computed from the QRS detection marks of each beat i.
2. The statistical mode of the RR interval histogram, computed with bins of 20 ms, was selected for each recording. The beats whose RR interval lay within the histogram bin containing the mode were selected and used to obtain the first candidate for median beat.
3. All the selected beats were aligned with respect to the initially calculated median beat.
4. The rank correlation between the median beat candidate and each beat was calculated. A beat was discarded if the correlation coefficient was below 0.85.
5. A median beat was computed as the median of all the finally selected beats.

ECG measurements were obtained from this median beat.

3.3. Activation and repolarization time

The AT was obtained for each individual lead from the onset of the QRS complex to the time point corresponding to the steepest negative slope of the voltage-time relationship (i.e. minimum dV/dt) within the QRS complex. Similarly, the RT was determined as the time point corresponding to the maximum of dV/dt within the upstroke of the T wave from the onset of the QRS complex (Figure 1).

Three ventricular regions were defined from the six precordial leads: R1 (septal/right ventricular leads V1 and V2); R2 (anteroapical leads V3 and V4); and R3 (anterolateral leads V5 and V6). The average of AT (RT, respectively) over the two leads of each region was computed. The difference of AT (or RT) measurements in R1 and R3 were computed with respect to the corresponding measurement in R2.

The dispersion of the AT (RT, respectively) values over the three regions was calculated as a marker of
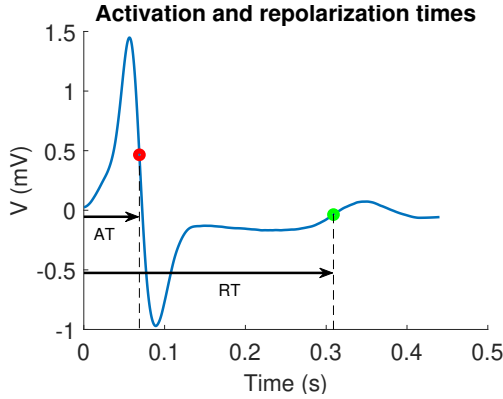
Figure 1. ECG beat with identified time points used to compute AT (red) and RT (green).

Figure 2. Mean value for AT and RT in R1 and R3 with respect to R2 for spontaneous rhythm, sHBP, nsHBP, sLBBP, nsLBBP, LVSP, RVSP and RVAP.

dyssychrony in electrical activation (repolarization, respectively).

3.4.   Statistical analysis

Measurements of regional AT and RT and of their spatial dispersion were compared for different pacing modes. Values are presented as mean over recordings. The Mann-Whitney U test (or Wilcoxon rank-sum test) was used to compare the values between different pacing modes. Statistical differences were considered significant if the associated p-value was <0.05. MATLAB R2017a (9.2) was used for the analysis.

4.   Results

4.1.   Activation and repolarization times for each pacing type

Figure 2 presents the average differences in AT and RT for the septal region R1 and the anterolateral region R3 with respect to region R2, individually for each cardiac pacing mode and the spontaneous rhythm. No significant R1-R2 differences ($p > 0.8$) were found for AT and RT between sHBP (-8.22 and 8.58 ms) and spontaneous rhythm (-8.30 and 18.31 ms).

The two modes of LBBP, i.e. sLBBP and nsLBBP, had similar RT behavior, especially in terms of the average R3-R2 difference (-25.01 and -20.66 ms, $p > 0.5$).

For RVAP, the mean differences with respect to R2 of both AT and RT were longer for R1 (28.62 and 31.27 ms) than for R3, whereas for RVSP the reverse was observed (-17.65 and -20.21 ms for R1). These differences were statistically significant ($p < 0.01$). For LVSP, AT and RT at R1 and R2 were very close, as can be seen in Figure 2. The mean R1-R2 differences for AT and RT were less than 1 ms (-0.82 and 0.15 ms).
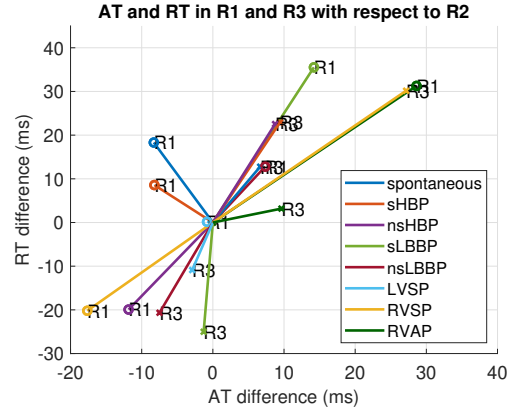
4.2.   Comparison of cardiac pacing and spontaneous rhythm

For the following analysis, the average AT and RT values of each pacing modality are compared to those computed for spontaneous rhythm. The differences are denoted by Δ_{AT} or Δ_{RT}. Thus, values close to zero indicate that the pacing mode has AT or RT values similar to spontaneous rhythm.

Pacing	R1-R2		R3-R2	
	Δ_{AT} (ms)	Δ_{RT} (ms)	Δ_{AT} (ms)	Δ_{RT} (ms)
sHBP	0.09	-9.73	2.84	10.12
nsHBP	-3.55	-38.24	2.10	9.76
sLBBP	22.50	17.21	-7.93	-37.79
nsLBBP	15.66	-5.52	-14.14	-33.44
LVSP	7.48	-18.16	-9.54	-23.67
RVSP	-9.35	-38.52	20.52	17.38
RVAP	36.92	12.96	3.00	-9.60

Table 1.   Differences between average values from AT and RT for R1-R2 and R3-R2 with respect to spontaneous rhythm.

Δ_{AT} and Δ_{RT} evaluated in R1 and R3 with respect to R2 are shown in Table 1. The highest differences with the spontaneous rhythm in terms of AT dispersion were found for RVAP (36.92 ms in R1-R2) and in terms of RT dispersion for RVSP (-38.52 ms, in R3-R2).

This analysis confirmed the observations from Figure 2. The lowest difference with the spontaneous rhythm in both AT and RT dispersion measured as R1-R2 was found for sHBP, nsHBP and nsLBBP. For R3-R2, sHBP, nsHBP and RVAP had the closest behavior to spontaneous rhythm in terms of both AT and RT dispersion.

5.   Discussion and conclusions

Different cardiac pacing strategies are currently being used in patients with an indication for permanent pacemaker. Since electrical dyssynchrony has been shown to be associated with heart failure and increased mortality [11], it is important to determine which modality of pacing leads to an electrical behavior closest to the physiological one in patients with normal conduction (narrow QRS).

Here, we measured AT, RT and the AT and RT differences between R1 and R2 and between R3 and R2. HBP, LBBP and LVSP led to the closest ventricular AT and RT values to those measured under spontaneous rhythm. Overall, patients subject to sHBP had the lowest values of Δ_{AT} and Δ_{RT}. LBBP or LVSP, which present advantages in terms of higher implantation success and lower capture thresholds, rendered slightly higher differences than HBP. Other techniques, such as conventional RVSP showed responses that were further away from the physiological one. Moreover, HBP led to an activation sequence similar to that of spontaneous rhythm, with the first activated region being R1, followed by R2 and finally R3. The activation sequence for LBBP, however, started in R3 and was followed by R2. R1 was the latest activated region, which could be expected due to the direct stimulation of the LBB, generating a delayed right ventricular activation.

Our results in terms of AT dispersion are in line with those of previous works. In [4, 6], ventricular dyssynchrony was characterized using markers from UHF-ECG recordings and HBP was found to preserve ventricular synchrony to an extent similar to that of spontaneous rhythm, in agreement with our findings. In [12], right ventricular pacing was compared with physiological pacing, including nsHBP. In line with our results, the authors found that right ventricular pacing produced greater electrical dyssynchrony than HBP strategies. On the other hand, RT dispersion has been scarcely investigated, thus precluding the comparison of our results with previous studies.

Although LBBP and LVSP render somewhat larger dispersion in AT and RT than HBP, they may still be the preferred pacing modality, as they can overcome limitations of HBP, including difficulties in accessing the stimulation site or the requirement of high pacing thresholds.

Acknowledgements

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