The impact of the left ventricular pacing polarity and localization during cardiac resynchronization therapy on depolarization and repolarization parameters

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Abstract

Objective: Reversal of myocardial activation sequence during cardiac resynchronization therapy (CRT) may increase the transmural dispersion of repolarization (TDR), which may lead to ventricular arrhythmias. Quadripolar left ventricular (LV) leads offer 10 different pacing configurations. However, little is known about the role of pacing polarity on repolarization patterns. Our study aimed to investigate the impact of LV pacing polarity on depolarization and repolarization parameters in the same substrate in the same patient group.

Methods: This study prospectively analyzed 20 patients who were consecutively admitted and underwent CRT-D implantation with quadripolar LV leads. Two bipolar pacing vectors and two unipolar vectors, also called extended bipolar pacing vectors, from the same pacing sites were selected for comparison. Electrocardiogram markers of depolarization and repolarization were measured and compared.

Results: Bipolar LV pacing was associated with a significantly shorter QRS duration (basal, unipolar vs. bipolar, 135.1±17.8 vs. 119.3±14.5, p<0.01; non-basal, unipolar vs. bipolar, 134.4±15.7 vs. 121.9±10.3, p<0.01) and Tp-Te value (Basal, unipolar vs. bipolar, 119.1±36.7 vs. 97.6±27.9, p<0.05; non-basal, unipolar vs. bipolar, 117.9±36.3 vs. 98.6±20.4, p<0.05) than those in unipolar pacing. LV pacing from basal and non-basal segments had no differential effect on the repolarization parameters.

Conclusion: The LV pacing polarity significantly affects QRS duration but not repolarization patterns regardless of the pacing site in the same substrate. From the perspective of basal and non-basal segments, the LV pacing site has no differential effect on the repolarization parameters. *(Anatol J Cardiol 2018; 19: 237-42)*

Keywords: cardiac resynchronization therapy, pacing polarity, quadripolar lead, transmural dispersion of repolarization, ventricular arrhythmias

Introduction

Cardiac resynchronization therapy (CRT) is well-established treatment for patients with symptomatic heart failure, reduced left ventricular (LV) ejection fraction (EF), and wide QRS (1). It improves symptoms and reduces the all-cause mortality (2, 3). However, despite these advantages, the rate of non-responders and sudden cardiac death remain high (4-6). Novel quadripolar LV leads offer 10 LV pacing configurations, and unipolar (extended bipolar) LV pacing is widely used to overcome technical issues such as phrenic nerve capture and stimulation thresholds. Using the best individual pacing configuration for each patient improves the hemodynamic response to CRT (7-9). Although the impact of LV pacing polarity on contractile functions has been investigated, little is known about the role of pacing polarity on repolarization patterns (10). Reversal of normal myocardial activation sequence during epicardial pacing, as it occurs during CRT, increases the transmural dispersion of repolarization (TDR) and may lead to ventricular arrhythmias (11, 12).

Potential antiarrhythmic and pro-arrhythmic impacts of the therapy remain controversial. CRT was associated with improvements in moderate to severe heart failure without pro-arrhythmia in MIRACLE ICD trial (13). The MADIT-CRT study investigators have also suggested that CRT-D reduces the risk of ventricular tachyarrhythmias (14, 15). Controversially, some recent studies have indicated the potential pro-arrhythmic effects of CRT (15). CRT may increase the QT interval and TDR, which have the potential to increase the risk of ventricular arrhythmias (16, 17). Increased TDR measured by the T_{peak}-T_{end} (Tp-Te) and Tp-Te/QT

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ratio has been associated with a higher incidence of ventricular arrhythmias in patients who have received a CRT-D (18). CRT with trans-septal LV endocardial CRT increases the physiological activation and is associated with a significant reduction in the TDR characteristics compared with those in conventional epicardial pacing in CRT (19).

These issues have raised concern as to whether the LV pacing polarity might have a differential effect on repolarization patterns. Jame et al. (20) retrospectively evaluated 969 patients enrolled in the MADIT-CRT trial and demonstrated that patients with CRT-D with bipolar LV lead pacing polarity have a significantly lower risk of all-cause mortality and heart failure compared with those with unipolar/extended bipolar LV pacing. This retrospective analysis of pacing polarity did not demonstrate any difference in the incidence of ventricular arrhythmias. However, the impact on repolarization patterns was not investigated in this study. Finding a perfect match between patient groups is not always possible because patient variables and programing differences may have an impact on results.

Quadripolar LV leads offer more pacing configurations and facilitate the investigation of the impact of LV pacing polarity on both depolarization and repolarization parameters in the same substrate. Our study aimed to investigate the impact of LV pacing polarity on depolarization and repolarization parameters in relation to ventricular arrhythmias in the same patient group in the same substrate.

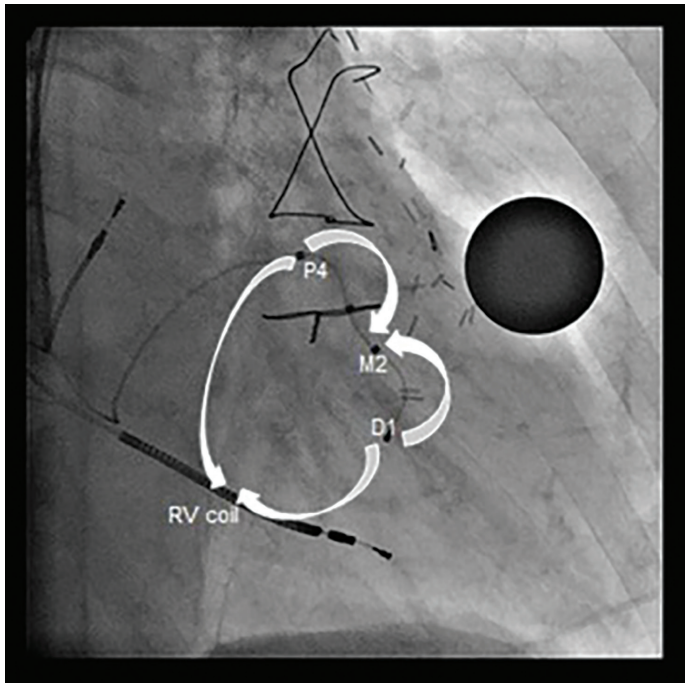

Figure 1. Right anterior oblique fluoroscopic view of the seventh patient, representing the four analyzed pacing vectors between the quadripolar left ventricular (LV) lead electrodes and right ventricular (RV) coil. Bipolar: non-basal, distal 1 (D1) to mid 2 (M2); bipolar: basal, proximal 4 (P4) to mid 2 (M2); unipolar: non-basal, distal 1 (D1) to RV coil; unipolar: basal, proximal 4 (P4) to RV coil

Methods

Patient population

This study was conducted at the department of cardiology, with the permission of the local ethical committee, and was performed in accordance with the Declaration of Helsinki. This study enrolled 26 consecutive patients with a standard indication for CRT implantation (left bundle branch block with QRS duration >120 ms; LV EF ≤ 35%; New York Heart Association functional class II, III, and ambulatory IV despite adequate medical treatment). The implantation protocol was successfully completed in 20 patients, and these patients were prospectively analyzed. According to the medical records and Holter ECG studies, none of these patients had a history of previous ventricular arrhythmic events. Primary prevention for sudden cardiac death was the only indication for CRT-D implantation.

Biventricular pacemaker implantation

Device implantation was performed in the cardiac catheterization laboratory following standard CRT implantation techniques. After a right ventricular (RV) shock lead was implanted in apical position, a quadripolar LV lead (The Quartet Model 1458Q, St. Jude Medical) and a right atrial lead were implanted, and capture thresholds from all electrodes were recorded. The four LV electrodes from the distal tip electrode to the proximal ring electrode were named D1, M2, M3, and P4, respectively.

Defining the LV lead electrode locations

After successful implantation, the final LV lead electrode positions were recorded in the longitudinal axis view [right anterior oblique (RAO): 20°-40°] and the short-axis view [left anterior oblique (LAO): 30°-40°]. The LAO view was used to define the LV electrode positions in the short-axis view of the LV wall, which is divided into three equal parts: anterior, lateral, and posterior. The RAO view, representing the long axis of the heart, was used to define the LV electrode positions as basal, mid-ventricular, or apical (Fig. 1). The electrode locations in the long axis view were divided into basal and non-basal groups. In addition to the electrode locations, the distances between the D1–P4 electrodes in the RAO views were measured.

Device optimization and ECG measurements

Subsequently, patients were brought to the ward, and the electrocardiogram (ECG) (25 mm/s, 10 mm/mV) was recorded under different biventricular pacing configurations. All patients were in sinus rhythm at the time of testing. Four LV pacing configurations with the longest electrode distance were selected for comparison. Patients with LV bipolar leads paced between the LV ring and LV tip were identified as True Bipolar, whereas those with LV bipolar leads paced between the LV tip or LV ring and RV coil or unipolar leads were identified as Unipolar/Extended Bipolar (20). Two bipolar pacing vectors (D1-M2, P4-M2) and two unipolar vectors, also called extended bipolar pacing

Table 1. Baseline characteristics of the study patients

Age, years	64±10.37
Male	15 (75)
LVEF, %	28±4.9
Etiology	
Ischemic	13 (65)
Non-ischemic	7 (35)
NYHA functional class	
II	4 (20)
III	16 (80)
Device	
CRT-D	20 (100)
CRT-P	0
AF	0
DM	6 (30)
HT	13 (75)
Hg, g/dL	12.2±1.7
Cr, mg/dL	1.03 ±0.15
Drugs	
ACE-I/ARB	20 (100)
Beta blocker	14 (70)
Amiodarone	1 (5)
Other QT prolonging drug	0
QRS morphology, LBBB	20 (100)

ACE-I - angiotensin-converting enzyme inhibitor; AF - atrial fibrillation; ARB - angiotensin II receptor blocker; DM - diabetes mellitus; HT - hypertension; LVEF - left ventricular ejection fraction; LBBB - left bundle branch block; NYHA - New York Heart Association.
Values are represented as mean±standard deviation or n (%)

vectors (D1-RVcoil, P4- RV coil), were selected. The LV pacing configurations with the longest inter-electrode distances were selected for comparison. A quick optimization module was used to program the pacing parameters for each configuration. Threshold tests were performed under 12-lead ECG monitoring to avoid anodal capture (21).

Both unipolar and bipolar pacing amplitudes were programed at the same output and 0.5 V above the threshold to minimize the initial capture area. The 12-lead QRS morphology was assessed to control the stable capture at the programed output. Patients with high pacing thresholds (>2 V) and patients who had capture problems with the selected electrodes were excluded from further analysis.

The ECGs of the patients were scanned and analyzed with digital calipers at 400% magnification by a blinded cardiologist. Lead V5 or lead II (if lead V5 was unsuitable) was used for analysis. The QT interval was defined as the time from the beginning of the QRS complex to the end of the T wave (19). The QT interval was corrected and measured according to the Bazett's formula

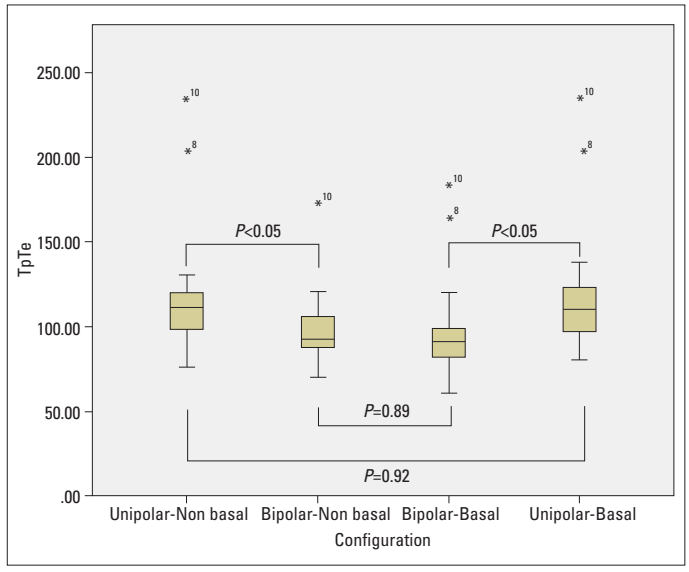

Figure 2. Box plot of Tp-Te values generated by unipolar and bipolar pacing from both basal and non-basal segments

(20). The QT peak interval was the time interval measured from the beginning of the QRS to the peak of the positive T wave or the nadir of the negative T wave (22). The Tp-Te interval was defined as the difference between the QT interval and QT peak interval. The Tp-Te/QT was also measured and analyzed. The repolarization parameters obtained during bipolar and unipolar LV pacing from basal and non-basal segments were compared.

Statistical analysis

Mean±standard deviation (SD) were used for descriptive statistics. Categorical data were summarized as frequencies and percentages. The repolarization parameters between pacing modes were compared using paired two-tailed Student's t-tests. In all analyses, p<0.05 was considered statistically significant. Statistical analysis was performed using SPSS 17.0 software (SPSS IBM, Chicago, IL, USA).

Results

The implantation protocol was successfully completed in 20 of the 26 patients. Two patients in whom the proximal LV electrode (P4) could not be inserted into the branch of the coronary sinus (CS) were excluded. To minimize the initial capture area, three patients with high pacing thresholds (>2 V) and one patient with phrenic nerve capture in selected electrodes were also excluded. No patient was excluded due to procedure-related complications. The baseline characteristics of the remaining 20 patients are shown in Table 1. The mean age of the patients was 64±10 years, and a majority of them (65%) had ischemic dilated cardiomyopathy.

The quadripolar LV lead was placed in the lateral branch in 12 patients, in the posterolateral branch in four patients, and in

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Table 2. Comparison of repolarization parameters and QRS intervals generated by unipolar and bipolar pacing from both basal and non-basal segments

		Unipolar	Bipolar	*P*		Basal	Non-basal	P
QRS	Basal	135.1±17.8	119.3±14.5	<0.015	Unipolar	135.1±17.8	134.4±15.7	0.893
	Non-basal	134.4±15.7	121.9±10.3	<0.014	Bipolar	119.3±14.5	121.9±10.3	0.532
Tp-Te	Basal	119.1±36.7	97.6±27.9	<0.052	Unipolar	119.1±36.7	117.9±36.3	0.921
	Non-basal	117.9±36.3	98.6±20.4	<0.052	Bipolar	97.6±27.9	98.6±20.4	0.892
Tp-Te/QT	Basal	0.26±0.06	0.23±0.06	0.142	Unipolar	0.26±0.06	0.28±0.10	0.543
	Non-basal	0.28±0.10	0.23±0.03	0.063	Bipolar	0.23±0.06	0.23±0.03	0.812
QTc	Basal	449.0±43.3	431.0±47.5	0.223	Unipolar	449.0±43.3	441.5±52.1	0.623
	Non-basal	441.5±52.1	429.0±47.5	0.432	Bipolar	431.0±47.5	429.0±47.5	0.834

QTc - QT corrected; Tp-Te - Difference between QT and QT peak interval
The repolarization parameters between both pacing modes were compared using paired two-tailed Student's t-tests

the anterolateral branch in four patients. In two patients, due to angulation of the branch of the CS, the D1 and P4 electrodes were located in different segments of the left ventricle in the LAO view. In all other patients, the D1 and P4 electrodes were located in the same segments. In all patients, the P4 electrodes were located in basal segments and the D1 electrodes were located in non-basal segments of the left ventricle (mid-ventricular location in 13 patients; apical location in seven patients). The mean distance between the D1 and P4 electrodes was 43.17±3 mm in the RAO view. The mean pacing capture threshold was 1.1±0.6 V and pulse width was 0.45 ms.

Table 2 shows the ECG parameters generated by unipolar and bipolar pacing from both basal and non-basal segments. Bipolar LV pacing was associated with a significantly shorter Tp-Te value than that in unipolar pacing from both sides of the LV (basal, unipolar vs. bipolar, 119.1±36.7 vs. 97.6±27.9, p<0.05; non-basal, unipolar vs. bipolar, 117.9±36.3 vs. 98.6±20.4, p<0.05) (Fig. 2). LV pacing from basal and non-basal segments had no differential effect on the repolarization parameters (bipolar Tp-Te, basal vs. non-basal, 97.6±27.9 vs. 98.6±20.4, p=0.89; unipolar Tp-Te, basal vs. non-basal, 119.1±36.7 vs. 117.9±36.3, p=0.92) (Fig. 2). The mean baseline Tp-Te/QT ratio was 0.25±0.05. Although the Tp-Te/QT ratios were lower with bipolar pacing, the differences were not significant (basal, unipolar vs. bipolar, 0.26±0.06 vs. 0.23±0.06, p=0.14; non-basal, unipolar vs. bipolar, 0.28±0.10 vs. 0.23±0.03, p=0.06). There was no significant difference between the QTc intervals (Table 2).

The QRS intervals in all patients significantly reduced following both unipolar and bipolar CRT (p<0.01). However, the QRS reduction was more prominent with bipolar pacing than with unipolar pacing (basal, unipolar vs. bipolar, 135.1±17.8 vs. 119.3±14.5, p<0.01; non-basal, unipolar vs. bipolar, 134.4±15.7 vs. 121.9±10.3, p<0.01). The LV pacing site had no impact on the QRS duration (bipolar, basal vs. non-basal, 119.3±14.5 vs. 121.9±10.3, p=0.53; unipolar, basal vs. non-basal, 135.1±17.8 vs. 134.4±15.7, p=0.89).

Discussion

The present study investigated the impact of LV pacing polarity and LV pacing site on the repolarization parameters in the same patient group. The main findings can be summarized as follows:

(i) The LV pacing polarity has a differential effect on the QRS duration and repolarization parameters in the same substrate.

(ii) The LV pacing site has no differential effect on the repolarization parameters from the perspective of basal and non-basal segments.

The spread of activation in the ventricle is different during unipolar and bipolar pacing. A unipolar wave front attenuates with the square of the distance, and a bipolar wave front attenuates with the third power of the distance (22). The size and shape of the virtual electrode is also influenced by the pacing polarity (23, 24). The point of initial capture on the epicardium may be the same, but the sub-epicardial layers captured by the virtual electrode may be different. Furthermore, the myocardium of patients with heart failure is electrically and mechanically heterogeneous. The presence of scars may lead to changes in conduction vectors and may change the transmural activation sequence.

Different pacing configurations may produce a different vectoral activation and may affect the ventricular repolarization patterns. Yang et al. (25) reported a significant difference in the mechanical activation sequence between unipolar and bipolar LV pacing during CRT. They observed a higher basal endocardial strain and more uniform global strain with bipolar pacing. The difference in the mechanical activation sequence between pacing polarities indicates the differential activation of different layers of the myocardium, which may have an impact on ventricular repolarization. There is an intrinsic repolarization difference among the epicardium, mid-myocardial M cells, and endocardium. Delayed activation and repolarization of mid-myocardial M cells during biventricular pacing leads to a prominent increase in QT and TDR (12).

Our observation on QRS duration is consistent with that in a previous study that evaluated the changes in the electromechanical parameters during different pacing configurations using a quadripolar lead (26). In this study, the shortest QRS durations were most commonly associated with the bipolar pacing modes (D1-M2, P4-M2), whereas the longest QRS duration was most commonly associated with the unipolar mode (P4-RV). In our study, the QRS reduction was more prominent with bipolar pacing, and the LV pacing site had no impact on the QRS duration.

The differential effect of bipolar or unipolar pacing on the QRS duration might play a role on the results of our study. Shorter Tp-Te observed with bipolar pacing could be related to shorter QRS durations with bipolar pacing rather than the effect of bipolar pacing on repolarization patterns. Because the QRS duration has nearly equal effects on both the Tp-Te and QT duration, this might explain the statistically equal values of Tp-Te/QT between the two groups.

These findings collectively indicate that there are differences in the capture and activation of ventricles. Naturally, factors that influence depolarization patterns may also affect repolarization patterns. It was previously reported that reversal of the direction of activation affects the action potential curve and T wave morphology even in the absence of any difference in final repolarization time (12). There is an intrinsic repolarization difference between the epicardium, mid-myocardial M cells, and endocardium. Different vectoral activations of the left ventricle with different transmural activations during unipolar and bipolar pacing might be responsible for our findings. We observed a significant difference in the Tp-Te values between unipolar and bipolar LV pacing from both basal and non-basal segments.

The underlying heart disease and localizations of myocardial scars can contribute to the electrophysiological effects of biventricular pacing. The pacing site and vectoral relationship between the poles and myocardial scars can affect the results. Therefore, we compared recordings from two different sites and selected pacing configurations with the longest inter-electrode distances for comparison. We assessed the impact of basal and non-basal pacing on repolarization patterns in the same patient group using a quadripolar LV lead. Data on the role of the LV pacing site during conventional CRT is controversial. Kleemann et al. (27) suggested that different LV lead positions were not associated with an increase in ventricular arrhythmias. Kutyifa et al. (28) analyzed the association between the LV lead position and the risk of ventricular arrhythmias in patients enrolled in a MADIT-CRT trial and found that posterior or lateral lead locations were associated with a decreased risk of arrhythmic events compared with anterior LV lead positions. In contrast, the incidence of ventricular arrhythmias in patients with an apical LV lead location was similar to that in patients with a non-apical lead location (28). Consistent with this clinical study, we observed no difference in terms of repolarization patterns between basal and non-basal pacing of the same substrate.

Study limitations

We must acknowledge that our observation is limited by the longitudinal aspect of the left ventricle, and the impact of pacing sites along the short axes of the heart would be different. We also emphasize that the main aim of our study was to investigate the impact of pacing polarity. Two different pacing sites with the longest inter-electrode distances were selected to verify findings.

Another limitation of our study is the small sample size and bias in the ischemic etiology. A majority of our patients (65%) had ischemic cardiomyopathy, and 11 of them had a history of anterior myocardial infarction. As noted above, the presence of large ischemic scars and heterogeneity of the myocardial substrate may have affected our results. Nevertheless, our study population reflected the general patient population receiving CRT. Due to the relatively small number of patients, no subgroup analysis on ischemic and non-ischemic patients was performed.

We selected only lead V5 (or lead II if V5 was not eligible) for measuring the repolarization parameter. Analysis of a single lead might have influenced the accuracy of ventricular repolarization. However, previous studies showing the association between increased Tp-Te interval and Tp-Te/QT ratio and ventricular arrhythmias during CRT have also used one-lead measurements, and these parameters are widely accepted (18, 29).

Only acute responses to CRT were examined in our study, but long-term electrical and mechanical remodeling could modify the results (30). In addition, analyzing the changes in the repolarization patterns at a long-term follow-up could be very valuable, particularly among the CRT responders.

Conclusion

LV pacing polarity significantly affects the QRS duration but not repolarization patterns regardless of the pacing site. Bipolar LV pacing is associated with a shorter QRS duration and Tp-Te values compared with those in unipolar LV pacing. From the perspective of basal and non-basal segments, the LV pacing site has no differential effect on the repolarization parameters. Our study was designed to reveal the differential effect of pacing polarity in the same substrate. Different than the results from daily clinical practice, our results represent acute electrical changes elegantly measured under the low pacing amplitudes. In addition, we were unable to make a clinical conclusion according to the results of our study. Further randomized controlled studies are required to determine whether these changes are associated with arrhythmic risk in patients with CRT.

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Analysis &/or interpretation – A.Ö., E.Ö.; Literature search – E.E.Ö., A.Ö.; Writing – E.E.Ö., E.Ö.; Critical review – Ö.S., L.G.

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