The influence of left ventricular pacing polarity on ventricular repolarization parameters in cardiac resynchronization therapy and its clinical reflections on ventricular tachyarrhythmias

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ABSTRACT

Objectives: This study aims to investigate the effects of the left ventricular (LV) pacing polarities on ventricular repolarization patterns and to examine novel parameters taking depolarization into account.

Patients and methods: This prospective study included a total of 54 patients (39 males, 15 females; mean age: 65.2±11.6 years; range, 40 to 89 years) with successful cardiac resynchronization therapy using quadripolar LV leads between January 2014 and February 2017. The patients were divided into two groups as the true bipolar group (n=25) and the unipolar/extended bipolar group (n=29). Ventricular repolarization parameters and novel markers, i.e., TpTe/QRS, Tpec/QRS, TpTe/(QRS × QTc) and Tpec/(QRS × QTc), were measured before implantation within 48 h following the procedure and at six months. Evaluation of ventricular tachyarrhythmias was performed using device records during follow-up.

Results: The median follow-up was 17.7 (range, 12.6 to 31.2) months. The mean ejection fraction was 23.3±5.5% in the bipolar group and 23.6±6.2% in the unipolar/extended bipolar group. Bipolar LV pacing was associated with higher Tpec/QTc values (acute, bipolar vs. unipolar, +0.011 vs. -0.0008, p=0.019; long-term, bipolar vs. unipolar, +0.005 vs. - 0.015, p=0.005, respectively). There was no significant difference between the groups in terms of other repolarization parameters. Bipolar pacing was associated with significantly higher novel markers values and more frequent sustained and non-sustained ventricular tachyarrhythmias.

Conclusion: The LV pacing polarity significantly affects Tpec/QTc, but not the other ventricular repolarization parameters. Novel arrhythmia predictors, i.e., TpTe/QRS, Tpec/QRS, TpTe/(QRS × QTc), and Tpec/(QRS × QTc), are more influenced in bipolar pacing associated with more frequent ventricular tachyarrhythmias.

Keywords: Cardiac resynchronization therapy, depolarization, pacing polarity, tachycardia, ventricular.

Despite enormous advances in pharmacological treatments in recent years, heart failure (HF) continues to occupy an important place among the leading causes of morbidity and mortality. Cardiac resynchronization therapy (CRT), which has created an important glimmer of hope in this regard, has become an established treatment procedure to improve clinical complaints and exercise tolerance, and to reduce all-cause mortality and hospitalizations in patients with mild-to-severe HF, reduced left ventricular (LV) systolic functions, and wide QRS complex, particularly with left bundle branch block (LBBB) morphology. Reverse remodeling and ventricular resynchronization are mechanisms of action of CRT. To correct these intra- and interventricular contraction disorders, three leads are placed in the right atrium, right ventricular apex, and LV epicardial surface (either retrograde via the coronary sinus [CS] or surgically). Consequently, cardiac output increases, pulmonary capillary wedge pressure decreases, and contractility is improved.

Providing different vector activation of different pacing configurations can affect ventricular
repolarization patterns. Quadripolar LV leads exhibit 10 variant pacing configurations in the clinical practice, although LV lead pacing polarity is mostly a modifiable parameter. Preference of pacing configuration is made taking into account the branch of the available CS, the risk of phrenic nerve stimulation, and optimization of LV pacing thresholds, whereas unipolar stimulation can be placed between the tip and generator, or between the pacing tip and the right ventricular coil or ring electrode (known as extended bipolar), Bipolar stimulation can be between distal and proximal electrodes or vice versa.[4]

Differences in mechanical activation sequence according to pacing polarities have been proven, resulting in different activation between the different layers of the myocardium, and this affect the ventricular repolarization patterns.[5] The difference in intrinsic repolarization between epicardium, midmyocardial M cells, and endocardium varies according to LV pacing polarities. Additionally, as a result of delayed activation and repolarization of midmyocardial M cells during epicardial biventricular pacing, the transmural dispersion of repolarization (TDR) can be significantly increased.[6] In the light of this knowledge, the influences of LV pacing polarity on ventricular repolarization parameters and its relationship with the likelihood of developing ventricular arrhythmias has become a matter of concern.

Potential proarrhythmic effects of CRT are still controversial and various mechanisms have been proposed. One of the main mechanisms is the reversal of the myocardial activation sequence, which increases QT and TDR.[7] Furthermore, it has been suggested that the proarrhythmic mechanism of unidirectional block and re-entry may be corrected by changing the activation sequence within the scar areas.[8] In contrast, antiarrhythmic properties of CRT are advocated by leading to LV reverse remodeling, electrical stabilization of myocyte membranes, and bringing about a decrease in myocardial wall stress.[9]

It has been previously documented that long-term clinical outcomes of different LV pacing polarity, unipolar/extended bipolar configuration are associated with a higher incidence of HF/death, and all-cause mortality in patients with LBBB, compared to true bipolar.[10] Although the effect on ventricular repolarization patterns has not been studied, no significant difference is observed in terms of ventricular tachyarrhythmic (VTA) events.[10] In our study, we aimed to investigate the effects of different LV pacing polarities on ventricular repolarization patterns and to examine the novel arrhythmia predictive parameters taking depolarization into account and its relationship with VTA events.

**PATIENTS AND METHODS**

This single-center, prospective study was conducted at Dokuz Eylül University, Department of Cardiology and Medical Park Izmir Hospital, Department of Cardiology between January 2014 and February 2017. A total of 54 patients (39 males, 15 females; mean age: 65.2±11.6 years; range, 40 to 89 years) with successful CRT with biventricular pacemaker implantation using quadripolar LV leads according to the conventional CRT indications were included in the study. The only indication for CRT-defibrillator (D) implantation was considered the primary prevention from sudden cardiac death (SCD). Inclusion criteria were as follows: (i) patients with a standard indication of CRT according to the New York Heart Association (NYHA) Class II-IV despite optimal medical therapy with a LV ejection fraction (LVEF) of ≤35% and a QRS duration of >130 msec, irrespective of the QRS morphology; and (ii) patients with a LVEF of ≤35% regardless of the NYHA functional class who required ventricular pacing and had a CRT indication due to a QRS duration of >130 msec, irrespective of the QRS morphology. Exclusion criteria were as follows: patients with a QRS duration of <130 msec, a history of ventricular arrhythmia event or SCD according to medical history and Holter electrocardiographic [ECG] records, Wolff-Parkinson-White (WPW) syndrome, arrhythmogenic right ventricular dysplasia, Brugada syndrome, or a history of channelopathy, failure of the CS cannulation or implantation procedure. A written informed consent was obtained from each patient. The study protocol was approved by the Dokuz Eylül University, School of Medicine, Ethics Committee (date/no: 16.11.2016-61804747000/1056). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The CRT-D device implantation and identifying the LV pacing configurations in terms of polarity were performed in the cardiac catheterization laboratory using standard transvenous approach of CRT device implantation techniques. Following an apically right ventricular shock lead implantation, a quadripolar LV (The Quartet Model 1458Q, St. Jude Medical, St.
Paul, Minnesota, USA) and the right atrium leads were implanted, respectively, and capture thresholds were recorded simultaneously. The identification of LV electrodes was determined as the Distal 1(D1), Mid 2(M2), Mid 3(M3), and Proximal 4(P4), respectively, starting from the distal tip electrode. Then different pacing configurations offered by the quadripolar LV lead were defined as follows: True Bipolar: D1 to M2, D1 to P4, M2 to P4, M3 to M2, M3 to P4 and P4 to M2 configurations; Unipolar (or extended bipolar): D1 to RV coil, M2 to RV coil, M3 to RV coil and P4 to RV coil configurations (Figure 1). The patients were divided into two groups as the true bipolar group (n=25) and the unipolar/extended bipolar group (n=29).

The 12-lead ECGs were recorded before CRT device implantation within 48 h following the procedure and six months after the procedure. All ECGs were scanned digitally and evaluation was made at 400% magnification. The measurements were performed by a blinded cardiologist. The onset of the QT interval was determined as the first portion (deflection) of the QRS complex, and the end was identified as the point where the isoelectric line intersected the tangent slope of the T wave. The longest interval of entire leads wherein the T wave was obviously selected (usually V2 or V3) was regarded to be the QT interval. The acquired QT value was corrected to heart rate using the Bazzet formula (QTc). The QT peak interval was defined as the interval from the onset of the QRS to the peak of the positive T wave or the bottom of a negative T wave. In case of a biphasic T wave, the first peak was selected as a reference point for measurement. The TpTe interval was calculated by subtracting the QT peak interval from the QT interval. TpTe was averaged after measuring TpTe in all 12 leads. The TpTe value was corrected according to the Bazzet formula and Tpec was obtained. The QT and TpTe dispersions were calculated from the difference between the longest and shortest of the mentioned intervals in 12-lead ECG. The TpTe/QT, Tpec/QTc, TpTe/QRS, Tpec/QRS, TpTe/(QRS × QTc), Tpec/(QRS × QTc) values were also calculated.\[11\]

Evaluation of VTA events was performed based on the recorded ECG readings and clinical records. Device therapies were analyzed in two main categories as anti-tachycardic pacing (ATP) or shock. In case of both ATP and shock delivery in the same arrhythmia episode, the episode was evaluated in the shock category. Ventricular tachyarrhythmia detected by the device and terminated spontaneously without any therapy was recognized as non-sustained ventricular tachycardia (NSVT). Ventricular tachycardia (VT) or ventricular fibrillation (VF) episodes which met the device detection criteria and underwent therapy (ATP or shock) were considered to be sustained VTAs. Electrical storm was defined as ≥3 VTA episodes within 24 h. Tachyarrhythmic events treated by the device as a result of atrial fibrillation (AF) or supraventricular tachycardia (SVT) were identified as inappropriate and not included in the analysis. The VTA detection criteria of the device and therapy settings were programmed in accordance with the nominal settings at the time of implantation and, if necessary, changed only at the discretion of the cardiologist.

**Statistical analysis**

Statistical analysis was performed using the PASW 17.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables were presented in mean ± standard deviation (SD) or median (interquartile range [IQR]), while categorical variables were presented in number and frequency. For the comparison of independent variables with the dependent variables, the Mann-Whitney U test was used, since non-parametric conditions were provided for numerical variables. The chi-square test was used to compare categorical variables. A p value of <0.05 was considered statistically significant.
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RESULTS

The median follow-up was 17.7 (range, 12.6 to 31.2) months. The mean age was 64.7±12.3 in the true bipolar group and 65.7±11.2 in the unipolar/extended bipolar group. The mean LVEF was 23.3±5.5% in the true bipolar group and 23.6±6.2% in the unipolar/extended bipolar group. The baseline characteristics of both groups were comparable (Table 1).

To analyze the difference acute effects of CRT on ventricular repolarization parameters and the novel arrhythmia markers between the groups, pre-procedural ECGs were compared to ECGs at 48 h after CRT device implantation. Compared to the pre-procedural values, an increase in the TpTe/QRS, Tpec/QRS, TpTe/(QRS x QT) and Tpec/(QRS x QTc) values in the acute period was more prominent in the bipolar group (p=0.026, p=0.018, p=0.016, and p=0.013, respectively). The TpTe/QT and Tpec/QTc values were found to be acutely increased after the procedure in the bipolar group, while a decrease was observed in the unipolar group (p=0.089 and p=0.019).

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| Table 1 | Baseline demographic and clinical characteristics of study population |
|---------|-------------------------------------------------------------------|
|         | True bipolar (n=25) | Unipolar/extended bipolar (n=29) | p          |
| Age (year) | 64.7±12.3 | 65.7±11.2 | 0.755 |
| LVEF (%)   | 23.3±5.5  | 23.6±6.2  | 0.853 |
| DM         | 7 28      | 8 27.58    | 0.973 |
| HT         | 8 32      | 9 31       | 0.939 |
| Sex        |            |            | 0.565 |
| Male       | 19 76     | 20 69      |        |
| Female     | 6 24      | 9 31       |        |
| Etiology   |            |            | 0.542 |
| Ischemic   | 10 40     | 14 48      |        |
| Non-ischemic | 15 60   | 15 52      |        |
| NYHA Class |            |            | 0.567 |
| I-I        | - -       | 1 3.44     |        |
| II         | - -       | 1 3.44     |        |
| II-III     | 1 4       | 3 10.34    |        |
| III        | 22 88     | 21 72.41   |        |
| Ambulatory IV | 2 8     | 3 10.34    |        |
| Baseline rhythm |        |            | 0.499 |
| AF         | 2 8       | 4 13.8     |        |
| SR         | 23 92     | 25 86.2    |        |
| QRS morphology |        |            | 0.560 |
| LBBB      | 24 96     | 28 96.55   |        |
| RBBB      | 1 4       | 1 3.44     |        |
| Device     |            |            |        |
| CRT-D      | 25 100    | 29 100     |        |
| CRT-P      | - -       | - -        |        |
| Drugs      |            |            |        |
| ACE-I/ARB  | 23 92     | 26 89.65   | 0.893 |
| Beta blocker | 24 96   | 28 96.55   | 1.000 |
| MRA        | 14 56     | 17 58.62   | 0.923 |
| Amiodarone | 13 52     | 8 27.58    | 0.067 |
| Digoxin    | 5 20      | 2 6.89     | 0.229 |

SD: Standard deviation; LVEF: Left ventricular ejection fraction; DM: Diabetes mellitus; HT: Hypertension; NYHA: New York Heart Association; AF: Atrial fibrillation; SR: Sinus rhythm; LBBB: Left bundle branch block; RBBB: Bundle branch block; CRT-D: Cardiac resynchronization therapy-defibrillator; CRT-P: Cardiac resynchronization therapy pacemaker; ACE-I: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; MRA: Mineralocorticoid receptor antagonist.
respectively). We revealed no statistically significant difference in the QRS duration between the groups (median: -18.66 vs. -13.22 msec, respectively; p=0.515). When the early changes in other ECG parameters were compared, no statistically significant difference was revealed according to the LV pacing polarity (Table 2).

Statistically significant differences in the LV pacing polarity between the groups persisted at six months; however, there was a marked decline in the median values of ventricular repolarization parameters and novel markers, compared to the acute phase. Compared to the pre-procedural values, the increase in the TpTe/QRS, Tpec/QRS, TpTe/(QRS × QT) and Tpec/(QRS × QTc) values at six months was higher in the bipolar group (p=0.023, p=0.004, p=0.052, and p=0.006, respectively). Although the median value of Tpec/QTc decreased compared to the acute phase, the increase from baseline persisted at six months in the bipolar group, while a decrease from baseline was observed in the unipolar/extended bipolar group (bipolar vs. unipolar: +0.005 vs. -0.015, respectively; p=0.005). At six months, no statistically significant difference in the QRS duration was revealed between the groups (median: -20.10 vs. -13.59, respectively; p=0.302). When the long-term changes in other ECG parameters were compared, no statistically significant difference was revealed according to the LV pacing

| Electrocardiographic measurements | Polarity     | Median | Interquartile range | p*  |
|----------------------------------|-------------|--------|---------------------|-----|
| ΔT-2 TpTe interval (ms)          | Unipolar    | + 11.08| 46.49               | 0.147|
|                                  | Bipolar     | + 13.83| 22.47               |      |
| ΔT-2 Tpec (ms)                   | Unipolar    | + 7.59 | 41.62               | 0.125|
|                                  | Bipolar     | + 16.12| 19.85               |      |
| ΔT-2 TpTe dispersion (ms)       | Unipolar    | + 12.95| 58.62               | 0.855|
|                                  | Bipolar     | + 10.44| 49.02               |      |
| ΔT-2 QTc (ms)                    | Unipolar    | + 52.00| 105.07              | 0.931|
|                                  | Bipolar     | + 38.95| 54.67               |      |
| ΔT-2 Tp-Te/QT                   | Unipolar    | - 0.006| 0.05                | 0.089|
|                                  | Bipolar     | + 0.012| 0.04                |      |
| ΔT-2 Tpec/QTc                   | Unipolar    | -0.0008| 0.04                | 0.019|
|                                  | Bipolar     | + 0.011| 0.03                |      |
| ΔT-2 QRS duration (ms)          | Unipolar    | - 13.22| 23.66               | 0.515|
|                                  | Bipolar     | - 18.66| 15.12               |      |
| ΔT-2 QT dispersion (ms)         | Unipolar    | + 21.98| 46.94               | 0.391|
|                                  | Bipolar     | + 33.85| 42.42               |      |
| ΔT-2 (TpTe)/QRS                 | Unipolar    | +0.08  | 0.25                | 0.026|
|                                  | Bipolar     | +0.15  | 0.13                |      |
| ΔT-2 (Tpec)/QRS                 | Unipolar    | +0.12  | 0.25                | 0.018|
|                                  | Bipolar     | +0.17  | 0.18                |      |
| ΔT-2 (Tpec)/(QRS x QTc) (ms⁻³)  | Unipolar    | +1*10⁻⁴| 0.00                | 0.013|
|                                  | Bipolar     | +2*10⁻⁴| 0.00                |      |
| ΔT-2 (TpTe)/(QRS x QTc) (ms⁻³)  | Unipolar    | +1*10⁻⁴| 0.00                | 0.016|
|                                  | Bipolar     | +2*10⁻⁴| 0.00                |      |

* Mann Whitney U test; ΔT-2: Change between before and after the procedure (within 48 hours); QTc: QT interval corrected according to the Bazett formula; TpTe: Difference between QT and QT peak interval; Tpec: TpTe interval corrected according to the Bazett formula.
polarity (Table 3). Figure 2 shows the acute and long-term difference of CRT’s impact on Tpec/QRS according to LV pacing polarity, as an example of novel arrhythmia markers.

Considering VTAs, we observed that both sustained and NSVTs were higher in the true bipolar group. A detailed analysis revealed that sustained VTAs were observed in 22 patients, 14 (63.6%) of which were bipolar and eight (36.4%) were unipolar (p=0.034). Similarly, NSVTs were found to be significantly higher in the true bipolar group (73.7%), whereas 26.3% were in the unipolar group (p=0.003). In terms of VF, there was no significant difference between the groups (p=0.313). Furthermore, there

### Table 3
Electrocardiographic changes in long-term based on left ventricular pacing polarity

| Electrocardiographic measurements | Polarity | Median  | Interquartile range | p*  |
|-----------------------------------|----------|---------|---------------------|-----|
| Δ1-3 TpTe interval (ms)           | Unipolar | -6.05   | 35.63               | 0.196 |
|                                  | Bipolar | +6.21   | 28.15               | 0.075 |
| Δ1-3 Tpec (ms)                    | Unipolar | -3.02   | 35.04               | 0.075 |
|                                  | Bipolar | +5.71   | 26.88               | 0.472 |
| Δ1-3 TpTe dispersion (ms)         | Unipolar | +9.99   | 57.72               | 0.472 |
|                                  | Bipolar | +0.81   | 29.81               | 0.472 |
| Δ1-3 QTc (ms)                     | Unipolar | -1      | 81.80               | 0.952 |
|                                  | Bipolar | +4      | 59.77               | 0.952 |
| Δ1-3 Tp-Tc/QT                     | Unipolar | -0.014  | 0.02                | 0.062 |
|                                  | Bipolar | -0.004  | 0.03                | 0.005 |
| Δ1-3 Tpec/QTc                     | Unipolar | -0.015  | 0.02                | 0.005 |
|                                  | Bipolar | +0.005  | 0.03                | 0.005 |
| Δ1-3 QRS duration (ms)            | Unipolar | -13.59  | 22.13               | 0.302 |
|                                  | Bipolar | -20.10  | 16.77               | 0.302 |
| Δ1-3 QT dispersion (ms)           | Unipolar | -2.86   | 31.58               | 0.788 |
|                                  | Bipolar | +2.96   | 29.43               | 0.788 |
| Δ1-3 (TpTe)/QRS                   | Unipolar | +0.03   | 0.13                | 0.023 |
|                                  | Bipolar | +0.08   | 0.14                | 0.023 |
| Δ1-3 (Tpec)/QRS                   | Unipolar | +0.03   | 0.16                | 0.004 |
|                                  | Bipolar | +0.12   | 0.14                | 0.004 |
| Δ1-3 (Tpec)/(QRS x QTc) (ms⁻¹)    | Unipolar | 0       | 0.00                | 0.006 |
|                                  | Bipolar | +2*10⁻⁴ | 0.00               | 0.006 |
| Δ1-3 (TpTe)/(QRS x QTc) (ms⁻¹)    | Unipolar | 0       | 0.00                | 0.052 |
|                                  | Bipolar | +2*10⁻⁴ | 0.00               | 0.052 |

* Mann Whitney U test; Δ1-2: Change between before and after the procedure (within 48 h); Δ1-3: Change between before and long term after the procedure (at 6 month); Tpec: TpTe interval corrected according to the Bazzet formula; TpTe: Difference between QT and QT peak interval; Tpec: TpTe interval corrected according to the Bazzet formula.
was no significant difference between the two groups in respect of shock delivery and ATP (p=0.499 and p=0.191, respectively). A comparison of ventricular arrhythmias between the groups is summarized in Table 4. Electrical storm was observed in five (9.25%) patients, including four in the bipolar group and one in the unipolar group. Four of them (80%) occurred within the first 100 days.

### DISCUSSION

The CRT considered a crucial treatment modality for HF may be pro-arrhythmic, since pacing from epicardium increases TDR.[7] In responders to CRT, this early increase has been shown to decrease in the long-term, presumably as a result of reverse remodeling.[12] In the present study, our objective was to investigate the impact of CRT on conventional and recently defined ventricular repolarization parameters from the perspective of different LV pacing polarities in both acute and long-term and to examine novel arrhythmia predictive parameters taking depolarization into account. We also attempted to identify whether there were reflections on arrhythmic events.

Different pacing polarities lead to different distribution of activation in the ventricle. The activation wave of a bipolar depolarization detracts with the third force of the distance, while a unipolar wave attenuates with the square of the distance.[13] This difference caused by polarity particularly influences the initiation of the re-entry mechanism in the scar tissue. Although the first capture point in the epicardium can be the same, the subepicardial layers captured by the virtual electrode may differ. Additionally, the presence of scar tissues may affect the conduction vectors and can change the transmural activation sequence within such heterogeneous myocardium.[14] Yang et al.[5] reported a higher basal endocardial strain with bipolar pacing and found more uniform global strain compared to unipolar pacing. They also revealed that there were differences in the mechanical activation sequence in terms of LV pacing polarity, probably affecting vectoral activation and ventricular repolarization patterns.

Myocardial activation sequence reverses during biventricular pacing in conventional CRT patients. As a consequence of this reverse activation, early repolarization of epicardium, delayed activation and repolarization of midmyocardial M cells lead to a significant increase in TDR.[7] The Increased TDR can be measured non-invasively using parameters, such as Tpeak-Tend (TpTe or Tpe) and Tp-Te/QT.[15] Furthermore, it was shown that the QT dispersion which reflects regional heterogeneity in myocardial repolarization is associated with life-threatening arrhythmias and SCD. However, TpTe has been demonstrated to be superior to QT and QT dispersion in predicting VTs.[16] The TDR seems to play a key arrhythmogenic role not only in CRT’s HF patients, but also in those with SCD, myocardial infarction, long QT syndrome, and Brugada syndrome.[17] Recently,

| Polarity                  | Polarity | n  | %   | p*  |
|--------------------------|----------|----|-----|-----|
| Sustained VTA            | Unipolar | 8  | 36.4| 0.034|
|                         | Bipolar  | 14 | 63.6|     |
| Ventricular fibrillation | Unipolar | 5  | 71.4| 0.313|
|                         | Bipolar  | 2  | 28.6|     |
| NSVTA                    | Unipolar | 5  | 26.3| 0.003|
|                         | Bipolar  | 14 | 73.7|     |
| VTA with shock delivery  | Unipolar | 4  | 66.7| 0.499|
|                         | Bipolar  | 2  | 33.3|     |
| VTA terminated with ATP  | Unipolar | 6  | 75  | 0.191|
|                         | Bipolar  | 2  | 25  |     |

* Pearson chi-square; VTA: Ventricular tachyarrhythmia; NSVTA: Non-sustained ventricular tachyarrhythmia; ATP: Anti-tachycardia pacing. 
Tpec (TpTe corrected according to the Bazett formula) was suggested to be a more sensitive measurement in predicting the risk of SCD and Tpec of more than 90 msec was determined to be associated with an approximately three-fold increased risk.\(^\text{[18]}\) In the light of these data, we investigated both Tpec and Tpec/QTc value that, to the best of our knowledge, has not been evaluated previously.

In our study, Tpec/QTc showed a significant post-procedural increase in the true bipolar group, while a decrease was observed in the unipolar/extended bipolar group. The difference between the two groups decreased in the long-term, but remained statistically significant. There was no significant difference in the remaining ventricular repolarization parameters between the groups. As a clinical reflection of this observation, four of five patients with electrical storm were in the true bipolar LV configuration. Sustained and NSVTs were observed more frequently in the bipolar group. The greater influence of Tpec/QTc in the early period after CRT supports that a significant part of the increase in TDR is temporal. The point that draws our attention in this regard is that electrical storm occurred in four (80%) of our five patients within the first 100 days.

In another aspect, TDR does not take into account depolarization and action potential in HF patients whose myocardium are electrically and mechanically heterogeneous and transmural activation sequence is abnormal due to scar tissues. Recently, it has been suggested that, in arrhythmogenic right ventricular dysplasia and Brugada syndrome, QT/QRS ratio defined as cardiac electrophysiological balance index can be used to predict arrhythmia, as it takes depolarization into consideration.\(^\text{[19]}\) In this context, it was recommended that TpTe/QRS and TpTe/(QRS \(\times QT\)) parameters may be used, since the TpTe interval has been shown to be more precise in predicting arrhythmic risk rather than the QT interval.\(^\text{[20]}\) In the present study, we evaluated Tpec/QRS and Tpec/(QTc \(\times QRS\)) as well as aforementioned novel markers. To the best of our knowledge, this was not previously evaluated in CRT patients.

The LV pacing polarity has also a substantial role in the pathophysiology of arrhythmogenesis other than TDR. Asvestas et al.,\(^\text{[21]}\) in a patient who presented with a monomorphic electrical storm two years after CRT, completely terminated the storm by changing the LV pacing configuration from the true bipolar to the extended bipolar (unipolar). The authors suggested that the bipolar configuration (D1-M2) caused the initiation of the one-way block and re-entry circuit due to its proximity to the critical isthmus in the scar tissue, and they prevented the onset of the re-entry circuit by pacing from extended bipolar. Considering the novel arrhythmia markers along with depolarization and TDR in our study, we observed that, in the bipolar group, where electrical storm and sustained VTAs were predominantly observed, the TpTe/QRS, Tpec/QRS, Tpec/QRS \(\times QTc\), TpTe/QRS \(\times QTc\) values increased more than the unipolar group. We persuaded that these markers may be used to predict arrhythmia, if supported by larger studies.

The main limitation of the present study is its relatively small sample size. The second limitation is the relatively high ischemic etiology (44.4%). The presence of ischemic scar tissues, as well as the heterogeneity of myocardium may have influenced the transmural activation sequence and VTAs. However, it should be kept in mind that the CRT patient population in daily practice is quite heterogeneous, as in this study. Bias in choosing the LV pacing configuration can be also considered a limiting factor; many factors, such as the branch of the existing CS, the risk of phrenic nerve stimulation, avoiding anodal capture, and optimization of LV pacing thresholds are taken into consideration in the decision-making process. Furthermore, given the nature of the study, we cannot ignore the impact of extrinsic and intrinsic variables, such as use of antiarrhythmic agents, coronary anatomy, and LV lead position on the outcomes.

In conclusion, left ventricular pacing polarity significantly affects Tpec/QTc, but not other ventricular repolarization parameters. Novel arrhythmia predictors (TpTe/QRS, Tpec/QRS, TpTe/(QRS \(\times QTc\)) and Tpec/(QRS \(\times QTc\)) are more influenced in bipolar pacing associated with more frequent ventricular tachyarrhythmias.

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