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Original Article

Role of QT dispersion and Tp-e interval after biventricular pacing in the incidence of sustained ventricular arrhythmias in patients with implanted cardiac resynchronization therapy device

Fariborz Akbarzadeh*[1], Sepideh Ataeyeh[1], Babak Kazemi[1], Amirhossein Akbarzadeh[2], Naser Safaei[3]

[1] *Department of Cardiology, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran*
[2] *School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran*
[3] *Department of Cardiothoracic Surgery, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran*

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Abstract

Introduction: QT dispersion (QTd) and Tp-e interval show controversial results in incidence of sustained ventricular arrhythmias (SVA) in patients with heart failure (HF). In patients with implanted cardiac resynchronization therapy (CRT) device, there is a unique opportunity to record SVAs. The aim of this study was to evaluate the effects of QTd and Tp-e interval on the incidence of SVAs after simultaneous biventricular (Biv) pacing.

Methods: In the present study, 31 consecutive patients with advanced HF and implanted CRT device were evaluated one year for possible SVAs, corrected QT (QTc), QTd, and Tp-e interval. Patients were divided into two groups; with (group 1) and without (group 2) SVAs.

Results: Among the studied patients, 5 (16%) experienced SVAs. The intrinsic and Biv pacing QTd were 70.74 ± 18.00 and 89.26 ± 28.00 msec, and 95.09 ± 44 and 88.09 ± 33 msec in group 1 and group 2, respectively (P = 0.18 and P = 0.16, respectively). Tp-e was not different between the two groups. In group 1, QTc increased from 438.83 ± 64 msec to 488.24 ± 48 msec (P = 0.13), and in group 2, it decreased from 499.70 ± 65.00 msec to 480.00 ± 31.00 msec after simultaneous Biv pacing (P = 0.13).

Conclusion: QTd, Tp-e, and QTc did not differ significantly after Biv pacing to show any positive effect on the incidence of SVAs in part due to the severity of changes which already occur in patients with advanced HF. QTc, QTd, and Tp-e showed little changes after Biv pacing and probably do not have a significant role in the incidence of SVAs.

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Introduction

Cardiac resynchronization therapy (CRT) is one of the effective treatments for advanced heart failure (HF).[1] It has been shown that CRT can reduce the possibility of sudden cardiac death probably due to its induction of left ventricular remodeling; however, some proarrhythmic effects have been attributed to CRT in the literature.[2] Electrophysiological alterations which occur during biventricular (Biv) pacing such as increased QT dispersion (QTd)[3] and alterations in Tp-e interval[4] may be precursors of cardiac arrhythmias. On the other hand, patients with HF have intrinsically increased QTd which may make them prone to cardiac arrhythmia.[5] Some studies have reported the strong correlation of increased QTd[3] and increased Tp-e[6] with sudden cardiac death and major cardiac arrhythmias after implantation of CRT device. On the other hand, some studies have questioned the strong effect of QTd on the genesis of cardiac

* **Corresponding Author:** Fariborz Akbarzadeh, Email: akbarzadehf@tbzmed.ac.ir

arrhythmias.[7] Furthermore, a study on the prognostic effect of Tp-e on cardiovascular mortality showed conflicting results;[8] thus, the role of these electrophysiological factors on arrhythmogenesis in patients with HF requires greater attention.

The memory of CRT combined with defibrillator (CRT-D) device provides the unique opportunity to record lifelong arrhythmias in patients with HF. Therefore, due to discrepancies in results of studies regarding the arrhythmogenic effects of QTd and Tp-e interval, this study was conducted to evaluate the effects of these variables on the incidence of cardiac arrhythmias in patients who have undergone CRT-D device implantation.

The primary aim of this study was to evaluate the effects of QTd and Tp-e interval on the incidence of sustained ventricular arrhythmias after CRT-D device implantation in patients with advanced HF. The secondary aim of this study was to evaluate the effects of different pacing modes on QTd and Tp-e interval.

Methods

An interventional, before–after study was performed on 35 patients with HF who were eligible for CRT-D device implantation from August 2013 to March 2015. One year follow-up was completed in 31 patients. The inclusion criterion was eligibility for CRT based on 2013 ACCF/AHA Guideline for the Management of HF.[9] Patients who had class I and II a indications were selected for CRT-D device implantation and followed one year after the implantation. Patients with secondary prevention of sudden cardiac death (SCD), antiarrhythmic drugs and digoxin use, presence of epicardial, and high threshold (> 2.5 v/0.04 second) coronary sinus (CS) lead were excluded from the study. Baseline characteristics including age, sex, presence of cardiac risk factors, blood pressure, type of cardiomyopathy, position of CS lead were recorded. Admission and follow-up electrocardiograms (ECGs) were selected for the evaluation of QRS, QT and corrected QT (QTc) duration, QTd,[10] and Tp-e duration[11] using CardioCalipers software (version 3.3, Iconico Inc., NY, USA). The mean of measurements in three consecutive beats was used for statistical analysis. Ventricular pacing of all patients was programmed as left ventricular (LV) to rigth ventricular (RV) = 0 msec, atrioventricular (AV) delay of 130 msec, and P wave to ventricular delay of 110 msec after implantation. During follow-up, CRT-D device was interrogated in order to evaluate possible ventricular arrhythmia (VA) events. Events were analyzed by a cardiologist who was an expert in device management, and true ventricular events were included in the study. Sustained ventricular arrhythmias (SVAs), defined as true ventricular arrhythmias [including ventricular tachycardia (VT), fast VT, and ventricular fibrillation (VF) episodes] which received appropriate therapy [including antitachycardia pacing (ATP) and shocks] using a device, and non-sustained ventricular arrhythmias (NSVAs) which did not require therapy, for statistical analysis. One electrocardiograph device (Cardio Touch 6.06c.30, Bionet Co., Seoul, Korea) with 6 channels recording at a speed of 25.0 mm/sec, amplitude of 10.0 mm/mv, filtering of 0.1 Hz-40 Hz, alternating current (AC) of 50 Hz, Electromyography (EMG), and power supply of 220 v and 50 Hz was used for all patients. The following ECGs were obtained at admission and after one year follow-up: 1- admission ECG from candidates of CRT-D device implantation, 2- intrinsic ECG which was obtained by programming the CRT-D device in long AV delay in patients with good AV conduction or ventricular pace, ventricular sense, inhibit mode (VVI) mode of 30 b/m in patients with long AV conduction or AV block, and patients with the Medtronic devices R sense pacing turned off temporarily, 3- simultaneous LV to RV pacing ECG, 4- 30 milliseconds (msec) earlier LV to RV pacing ECG (LV30), and 5- 50 msec earlier LV to RV pacing ECG (LV50). Electrocardiograms

were obtained every 3 minutes after changing the mode of pacing. All measurements were obtained by one cardiologist who was an expert in electrophysiology and was blinded to the grouping of patients. The measurements of some unnamed ECGs were randomly repeated and the agreement between measurements was greater than 95%.

SPSS software (version 18, SPSS Inc., Chicago, IL, USA) was used for data entry and analysis. Mean ± standard deviation (SD) of quantitative data and frequency of qualitative data were calculated and reported. Differences between quantitative data before and after any stage of pacing were analyzed using paired sample t-test. Chi-square test was used to estimate differences between qualitative data. Differences of quantitative data between the groups with and without arrhythmia events were analyzed using student t-test. All P values ≤ 0.05 were interpreted as significant difference.

Results

In total, 35 patients entered the study, of which 4 patients were excluded (2 patients no longer wished to continue participating in the study because they were from other provinces which were very far from the studied hospital, 1 patient died during the follow-up period due to neurologic causes, and 1 patient was unavailable after being discharged from the hospital). Data on 31 patients were calculated. Of the implanted CRT-D devices, 19 were made by Medtronic and 12 by St. Jude Medical, Inc. Among the patients, 5 (16.0%) experienced SVAs during follow-up. These 5 patients experienced 32 episodes of SVAs. The most common form of VAs was VT (29 episodes) which was terminated mostly by ATP. The 3 episodes of true VF were terminated by device shocks. The frequency of NSVAs was 54.8% in all patients.

Table 1. Baseline characteristics of patients

Variable	VT/VF (n = 5)	No VT/VF (n = 26)	Total	P
Male [n (%)]	5 (25)	15 (75)	20	0.09
Female [n (%)]	0 (0)	11 (100)	11	
Age (year) (mean ± SD)	67.0 ± 6.6	59.0 ± 11.3	60.0 ± 11.0	0.17
ICMP [n (%)]	5 (20)	20 (80)	25	0.31
NICMP [n (%)]	0 (0)	6 (100)	6	
History of MI [n (%)]	5 (25)	15 (75)	20	0.09
LV leads position posterolateral [n (%)]	2 (12.5)	14 (85.7)	16	0.72
Posterior [n (%)]	1 (14.3)	6 (85.7)	7	
Anterolateral [n (%)]	2 (25.0)	6 (75.0)	8	
DM [n (%)]	3 (17.6)	14 (82.4)	17	0.59
HTN [n (%)]	2 (11.8)	15 (88.2)	17	0.40
Current smoker [n (%)]	1 (12.6)	7 (87.5)	8	0.60
HLP [n (%)]	0 (0)	11(100)	11	0.09
EF (mean ± SD)	27.0 ± 7.5	25.6 ± 7.4	25.8 ± 7.3	0.70
Severe MR [n (%)]	1 (25.0)	3 (75.0)	4	0.52
Sinus [n (%)]	4 (14.3)	24 (85.7)	28	0.42
LBBB [n (%)]	5 (22.7)	17 (77.3)	22	0.15
SBP (mmHg) (mean ± SD)	121.0 ± 8.9	117.2 ± 11.8	117.8 ± 11.3	0.50
DBP (mmHg) (mean ± SD)	72.0 ± 4.8	73 ± 9.6	73.0 ± 0.9	0.71
Creatinine (mg/dl) (mean ± SD)	1.1 ± 0.4	1.1 ± 0.3	1.2 ± 0.4	0.69
HB (g/dl) (mean ± SD)	11.1 ± 0.1	12.6 ± 1.1	12.6 ± 1.1	0.20
B-blocker [n (%)]	4 (15)	23 (85)	27	0.60
Diuretic spironolactone [n (%)]	5 (16)	26 (84)	31	NS
ACE-I/ARB [n (%)]	4 (18)	22 (82)	26	0.70

ICMP: Ischemic cardiomyopathy; NICMP: Nonischemic cardiomyopathy; MI: Myocardial infarction; DM: Diabetes mellitus; HTN: Hypertension; HLP: Hyperlipidemia; EF: Ejection fraction; MR: Mitral regurgitation; LBBB: Left bundle branch block; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HB: Hemoglobin; ACE-I: Angiotensin converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; LV: left ventricular; SD: Standard deviation; NS: No significant

Table 2. Difference between various forms of QRS duration before and after simultaneous biventricular pacing in the groups with and without sustained ventricular arrhythmias

Variable	Sustained VT/VF	Non-Sustained VT/VF	Total	P
Intrinsic (mean ± SD)	156.4 ± 25.0	172.9 ± 32.0	169.8 ± 31.0	0.300
Simultaneous BIV (mean ± SD)	133.6 ± 5.5	133.7 ± 24.0	133.7 ± 22.0	0.900
P	0.110	< 0.001	< 0.001	

Baseline characteristics of all patients are presented in table 1. There was no difference between baseline characteristics of patients in the two groups with and without SVAs. In 4 patients, the indication for CRT-D device implantation was complete heart block concomitant with severe LV dysfunction. In addition, 3 patients had atrial fibrillation with low ventricular response. The un-paced QRS, QTc, QTd, and Tp-e of these patients were used for statistical analysis as admission and intrinsic variables. Left bundle branch block (LBBB) was the dominant bundle branch block (71%), 2 patients had right bundle branch block (RBBB) (6.5%) and others had nonspecific intraventricular conduction delay. Mean admission QRS duration was 161.23 ± 20 msec which was significantly shorter than intrinsic QRS duration (169.84 ± 32 msec) after one year follow-up (P = 0.03). Table 2 shows the QRS duration before and after simultaneous BIV pacing. QRS duration after simultaneous BIV pacing was statistically shorter in patients without SVAs.

Mean intrinsic QTc of all patients was 489.20 ± 68.00 msec which changed to 482.31 ± 29.00 msec after simultaneous Biv pacing. In patients with SVAs, QTc increased from 438.83 ± 64.00 msec to 488.24 ± 48.00 msec after simultaneous Biv pacing, the difference was not statistically significant (P = 0.13). In patients without SVAs, intrinsic QTc decreased from 499.70 ± 65.00 msec to 480.00 ± 31.00 msec after simultaneous Biv pacing which was not statistically significant (P = 0.17).

Abnormal QTd which is defined as QTd of longer than 50 msec[12] was found in 90.3% of patients. Table 3 shows the various forms of QTd in patients with and without SVAs. Although there was a trendeccy for significant difference between patients with and without sustained VT/VF in intrinsic limb leads QTd (P = 0.06), this finding was not observed in other forms of pacing. The calculation of the difference in QTd between intrinsic and simultaneous Biv pacing showed a tendency toward increasing QTd in patients with SVAs by the median number of 25 msec, conversely, in patients without SVAs, QTd decreased by the median number of 5 msec. Parametric and non-parametric statistical analysis showed no significant difference between the two numbers.

Mean Tp-e duration in intrinsic and simultaneous Biv pacing showed no difference between patients with and without sustained VT/VF. The difference between intrinsic and simultaneous Biv pacing in terms of mean Tp-e was not statistically significant.

In other forms of ventricular pacing modes (LV30 and LV50 pacing), there was no significant difference between intrinsic and pacing QTc, QTd, and Tp-e durations.

Table 3. Comparison of QTd (QT dispersion) between the groups with and without sustained ventricular arrhythmias in limb and precordial leads and 12 leads

Variable	Intrinsic limb leads	Simultaneous limb leads	P	Intrinsic precordial leads	Simultaneous precordial leads	P	Intrinsic 12 leads	Simultaneous 12 leads	P
Sustained VT/VF (mean ± SD)	48.0 ± 26.0	42.3 ± 21.0	0.85	45.4 ± 14.0	76.2 ± 22.0	0.11	70.7 ± 18.0	89.3 ± 28.0	0.18
Non-Sustained VT/VF (mean ± SD)	77.6 ± 24.0	61.9 ± 27.0	0.48	68.4 ± 42.0	68.5 ± 28.0	0.56	95.1 ± 44.0	88.1 ± 33.0	0.16
Total (mean ± SD)	72.0 ± 36.0	58.8 ± 21.0	0.17	64.4 ± 39.0	69.7 ± 27.0	0.53	90.9 ± 42.0	88.3 ± 32.0	0.90
P	0.06	0.15		0.24	0.24		0.24	0.94	

Discussion

This study was designed to evaluate the effects of QTd and Tp-e duration on incidence of SVAs in patients who have undergone CRT-D device implantation. Incidence of SVAs was 16% among the patients in the present study. QTd or mean Tp-e duration did not differ between patients with and without SVAs after one year of simultaneous Biv pacing.

Published data about the incidence of SVAs after implantation of CRT-D device for primary prevention purposes of sudden cardiac death are limited and often combined with data on implantable cardioverter-defibrillators (ICD). The 16% incidence of SVAs seems to be high, but is less than the 19% incidence reported by Timoteo et al. in their study on patients with CRT-D device.[13] Wilson et al. reported appropriate ICD and CRT-D therapy of about 10.2% after 32 months follow-up in elderly patients,[14] which is significantly lower than the incidence found in this study. Verma et al., in their study on "predictors of appropriate ICD therapies", reported the presence of NSVAs and lack of beta-blocker use as predictors of ICD Therapy. The incidence of appropriate therapy in their study was about 19%.[15]

The frequency of NSVAs in the present study was about 54.8% which may to some degree justify the relatively high incidence of SVAs.

The changes in QTd after simultaneous Biv pacing were not significant in all patients. Moreover, the difference in QTd between patients with and without SVAs was also not significant. Chalil et al. reported significant change in QTd after Biv pacing in patients with major arrhythmic events (MAE) and concluded that QTd is a predictor of arrhythmias after Biv pacing.[3] Although this difference was significant in their study, patients without MAE had higher QTd than patients with MAE. In the presented study, as shown in table 3, the baseline QTd was higher in patients without SVAs which decreased after Biv pacing, and QTd increased after Biv pacing in the group without SVAs. The QTd numbers in the two groups were similar after Biv pacing. This finding may clarify, at least to some degree, the importance of recovery from bad QTd intervals.

The subjects of this study had HF in the function class III or ambulatory IV, and left ventricular ejection fraction (LVEF) of about 25.83 ± 7.3%, and about 90.3% had abnormal QTd (> 50 msec) and 58.1% had high risk QTd (> 80 msec)[12] and mean QRS duration of 161.23 ± 20 msec. Based on the baseline date of patients, how is it possible for CRT-D devices to fix these arrhythmogenic substrates? Like as other studies, the results of this study questioned the sole arrhythmogenic role of QTd.[7,12]

The differences between intrinsic and simultaneous Biv pacing in terms of Tp-e interval in patients with and without SVAs were not significant. Other studies showed that Tp-e has no role in arrhythmogenesis3 or have reported the protective effects of longer Tp-e intervals,[8] which are consistent with the present study results.

In the current study, patients without SVAs had longer intrinsic QRS duration than patients with SVAs (Table 2), and during simultaneous Biv pacing, the QRS duration was nearly equal in the two groups. In other words, CRT-D was more effective in decreasing QRS duration in patients with wider intrinsic QRSs. The protective effects of shortening of QRS duration after Biv pacing may overcome other electrophysiological changes occurring after CRT-D device implantation. Widening of QRS in patients with HF is an ominous sign of mortality[16] and QRS narrowing after CRT implantation is a good sign for ventricular remodeling.[17] To our knowledge, the direct effects of post CRT narrowing of QRS on VAs have not been evaluated; however, its effects on decreasing the frequency of VAs may be related to improved LV function and reverse remodeling.

In patients with SVAs, there There was a tendency to increase in QTc and QTd after simultaneous Biv pacing and to decrease in patients without SVAs, but unfortunately the differences were not statistically significant.

After simultaneous Biv pacing, the numbers tend to be equal in groups with and without SVAs. Thus, the important predictors for major arrhythmias after CRT implantation may be the degree and direction of changes from baseline values not the numbers after Biv pacing itself.

Conclusion

Based on the findings of this small study, in patients with end stage HF and implanted CRT-D devices, QTc, QTd, and Tp-e interval had no role in the incidence of SVAs. It seems that factors like the degree and direction of changes from baseline values and degree of narrowing of QRSs are better predictors.

Limitations: A limitation of this study was its small sample volume of patients which limited many results to statistically significant. Another limitation was that the hemodynamic response of patients to CRT was not evaluated. Nevertheless, mean QRS narrowing after simultaneous Biv pacing was about 20% which may be a sign of good response. Large scale studies are needed to confirm or reject the present study findings.

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Authors' Contribution

All authors of this article participated in the designing, analysis, integration of data, drafting and critical revising of the article, and the final approval of the version to be published.

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Conflict of Interest

The authors of this manuscript announce that they have no conflict of interest regarding the publishing of this manuscript and do not have any relationship with factories providing CRT-D devices.

Ethical Approval

This study was approved by the Medical Ethics Committee of Tabriz University of Medical Sciences.

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