Original Article

Acute and Chronic Changes and Predictive Value of Tpeak-Tend for Ventricular Arrhythmia Risk in Cardiac Resynchronization Therapy Patients

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Abstract

Background: Prolongation of the Tpeak-Tend (TpTe) interval as a measurement of transmural dispersion of repolarization (TDR) is an independent risk factor for chronic heart failure mortality. However, the cardiac resynchronization therapy's (CRT) effect on TDR is controversial. Therefore, this study aimed to evaluate CRTs acute and chronic effects on repolarization dispersion. Furthermore, we aimed to investigate the relationship between TpTe changes and ventricular arrhythmia.

Methods: The study group consisted of 101 patients treated with CRT-defibrillator (CRT-D). According to whether TpTe was shortened, patients were grouped at immediate and 1-year follow-up after CRT, respectively. The echocardiogram index and ventricular arrhythmia were observed and compared in these subgroups.

Results: For all patients, TpTe slightly increased immediately after CRT-D implantation, and then decreased at the 1-year follow-up (from 107 ± 23 to 110 ± 21 ms within 24 h, to 94 ± 24 ms at 1-year follow-up, $F = 19.366$, $P < 0.001$). No significant difference in the left ventricular reverse remodeling and ventricular tachycardia/ventricular fibrillation (VT/VF) episodes between the TpTe immediately shortened and TpTe immediately nonshortened groups. However, patients in the TpTe at 1-year shorten had a higher rate of the left ventricular (LV) reverse remodeling (65% vs. 44%, $\chi^2 = 4.495$, $P = 0.038$) and less VT/VF episodes (log-rank test, $\chi^2 = 10.207$, $P = 0.001$) compared with TpTe 1-year nonshortened group. TpTe immediately after CRT-D independently predicted VT/VF episodes at 1-year follow-up (hazard ratio [*HR*], 1.030; $P = 0.001$).

Conclusions: Patients with TpTe shortened at 1-year after CRT had a higher rate of LV reverse remodeling and less VT/VF episodes. The acute changes of TpTe after CRT have minimal value on mechanical reverse remodeling and ventricular arrhythmia.

Key words: Cardiac Resynchronization Therapy; Dispersion of Repolarization; Tpeak-Tend Interval

Introduction

Cardiac resynchronization therapy (CRT) decreased morbidity and overall mortality in selected patients with advanced heart failure and cardiac dyssynchrony.[1] Traditional CRT placed a left ventricular (LV) lead on the LV epicardia through a suitable vein. It was recognized that left ventricular epicardial pacing (LVEpiP) reversed the left ventricle's sequence of depolarization and repolarization, which might increase repolarization dispersion and promote ventricular arrhythmia.[2]

However, biventricular pacing's (BiVP) effect on repolarization dispersion represented by the Tpeak-Tend interval (TpTe) is controversial. Some experimental and small-sample clinical studies have suggested that both repolarization dispersion and ventricular arrhythmia increased after CRT implantation.[2-4] Conversely, other studies have demonstrated decreased TpTe and reduced ventricular arrhythmia.[5,6] Itoh *et al*.[7] showed a CRTs time-dependent effect on transmural dispersion of repolarization (TDR). However, the relationship of TpTe's

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acute and chronic changes after CRT with ventricular arrhythmia is not well established. Therefore, this study aimed to evaluate the CRTs acute and chronic effects on repolarization dispersion. In addition, we aimed to identify the relationship between TpTe changes and ventricular arrhythmia.

Methods

Patients

Data were collected from 101 consecutive patients with successful placement of CRT-defibrillator (CRT-D) devices between January 2010 and December 2013 at Fuwai Hospital, Beijing, China. Criteria for selecting the subjects were as follows: Adult patients (>18 years old) receiving optimal medical therapy who were clinically indicated for resynchronization therapy (i.e., those with a New York Heart Association Class III–IV), sinus rhythm, QRS duration ≥130 ms, and an LV ejection fraction ≤35%. In addition, only those undergoing pacemaker implantation for the first time were included.

All the patients signed informed consent forms, and the study complied with the *Declaration of Helsinki* and was approved by the Research Ethics Board of our center.

Device implantation

All patients underwent CRT-D implantation using a transvenous approach. In all cases, the LV lead was preferably positioned in the lateral or posterolateral vein. If these veins were not accessible, then the lead was implanted in the other branch of the coronary sinus, closer to the lateral LV wall. The right ventricular lead was implanted in the right ventricular apex, right atrial lead in the right auricle. The atrioventricular and ventricular-ventricular intervals were optimized with echocardiography after CRT implantation. The pulse generators were implanted in the left subclavicular region and programmed to DDD(R) mode.

Electrocardiography assessment

Electrocardiogram (ECG) recordings were conducted at baseline, within 24 h (immediate), and 1 year after CRT-D implantation using a standard digital recorder with 12 simultaneous leads at a paper speed of 25 mm/s.

The TpTe was averaged for all 12 leads and defined as the interval from the peak of a positive T-wave or the nadir of a negative T-wave to the end of the T-wave. The first peak in the bimodal T-wave was selected. At the different time, TpTe was measured and indicated by $TpTe_{baseline}$ and $TpTe_{immediate}$, as well as $TpTe_{at\ one\ year}$, respectively. All ECG measurements were independently performed by two physicians in a blinded fashion. The mean values were calculated when the measurements were not identical. The measurements were adjudicated by a third reviewer when the values differed by >10 ms.

Echocardiography analysis

Echocardiography using a commercially available system (Vivid 7, GE Medical Systems-Americas, Waukesha, WI, USA) was performed at baseline and 6 months for all patients. Images were obtained using a 2.5-MHz broadband transducer in the parasternal or apical view at a depth of 16 cm. The left atrium's diameter and LV end-diastolic dimension were measured from the parasternal long axis view according to the recommendations of the American Society of Echocardiography.[8] The left ventricle ejection fraction was assessed using the biplane Simpson's method with 2- and 4-chamber apical views. Patients were classified as CRT responders in terms of LV reverse remodeling that the left ventricular end-diastolic dimension (LVEDd) decreased by at least 10%.

Assessment of appropriate implantable cardioverter defibrillator therapy

Ventricular arrhythmia episodes were classified as sustained VT or VF that required anti-tachycardia pacing (ATP) or shock therapy. The implantable cardioverter defibrillator (ICD) shocks or ATP occurrences after CRT-D implantation were confirmed in all patients by device interrogation at the pacemaker follow-up center. Two electrophysiologists who were blinded on patient follow-up data reviewed all ICD therapy events and identified appropriate ICD therapy. Inappropriate therapy was excluded from the analysis.

Definition of groups

For the TpTe, acute changes after CRT were calculated as the $TpTe_{immediate}$ minus $TpTe_{baseline}$ and were indicated by $\Delta TpTe_{(immediate\text{-}baseline)}$, while chronic changes after CRT were calculated as the TpTe 1 year after CRT minus TpTe immediately after CRT and was indicated by $\Delta TpTe_{(1\ year\text{-}immediate)}$.

Patients were divided into groups according to whether TpTe shortened after CRT within 24 h and 1 year, respectively (acute change groups: ΔTpTe[immediate-baseline] <0 and ΔTpTe[immediate-baseline] ≥0); chronic change groups: ΔTpTe (1 year-immediate) <0 and ΔTpTe (1 year-immediate) ≥0.

Statistical analyses

Continuous variables were expressed as the mean ± standard deviation (SD), and statistical significance was assessed using the Mann-Whitney test. Categorical variables were presented as numbers and/or percentages and were analyzed using the Chi-square test or Fisher's exact test. Differences between the baseline and postimplantation values were tested using the Wilcoxon signed-rank test for continuous variables. Cumulative event rates (appropriate ICD therapy) were evaluated with the Kaplan-Meier method and log-rank test was utilized to compare between groups. Univariate and multivariate Cox proportional hazard models were performed to determine the independent predictors of ventricular tachycardia/ventricular fibrillation (VT/VF). Variables with $P < 0.1$ on univariate analysis were retained in the multivariate model. All statistical analyses were two-tailed and a value of $P < 0.05$ was considered significant. All data were analyzed using the SPSS statistical software (version 19.0; SPSS Inc., Chicago, IL, USA).

Results

Patients

A total of 101 consecutive patients were included. The patient's baseline characteristics patients are described in Table 1. Twenty-one patients (21%) were implanted with CRT-D for secondary prevention of sudden cardiac death. Five patients had a history of VF, and 16 patients had VT. A large percentage, 90% to be exact, of the cases had the LV lead placed in the lateral or posterolateral vein, with others placed in a diagonal vein leading to the lateral wall.

Within 24 h after CRT-D implantation, 43 patients (43%) demonstrated TpTe interval shortening. At the 1-year follow-up, 65 patients (64%) had shortened TpTe interval after CRT-D implantation. The baseline characteristics of the TpTe shorten and nonshorten groups were similar [Table 2].

Effect of cardiac resynchronization therapy-defibrillator on Tpeak-Tend

Figure 1 shows the TpTe evolution after CRT implantation in overall patients and responders, as well as nonresponders.

In the overall patients, a slight TpTe increment was detected immediately after CRT-D implantation, while decurtated significantly at the 1-year follow-up (from 107 ± 23 ms at baseline to 110 ± 21 ms immediately after the operation to 94 ± 24 ms at the 1-year follow-up, $F = 19.366$, $P < 0.001$).

At the 6-month follow-up, 59 (58%) patients were classified as responders based on significant reverse LV remodeling. There was a trend for TpTe to decrease in both groups, and TpTe in responders was lower than nonresponders at 1 year (92 ± 20 ms vs. 103 ± 20 ms, $t = -11.212$, $P = 0.010$), with a mean 20 ± 22 ms reduction after CRT for responders and 5 ± 21 ms reduction after CRT for nonresponders. There was a significant reduction of TpTe at 1 year after CRT implantation (92 ± 20 ms vs. 112 ± 21 ms, $t = 20.349$, $P = 0.010$) in the responder group. However, no significant change was observed in the nonresponders.

Table 1: Baseline characteristics of all patients, $n = 101$

Variables	Results
Age (years)	60.03 ± 10.71
Male, *n* (%)	70 (69)
BMI (kg/m^2)	24.85 ± 4.74
NYHA Class	2.78 ± 0.64
QRS duration (ms)	158 ± 28
LBBB, *n* (%)	81 (80)
Dilated cardiomyopathy, *n* (%)	74 (73)
Ischemic cardiomyopathy, *n* (%)	27 (27)
Hypertension, *n* (%)	36 (35)
Dyslipidemia, *n* (%)	31 (31)
Ventricular arrhythmia, *n* (%)	22 (22)
Atrial fibrillation, *n* (%)	16 (16)
LVEF (%)	28.64 ± 8.29
LVEDd (mm)	69.72 ± 10.60
Left ventricular lead position, *n* (%)	
Lateral vein/posterior vein	91 (90)
RV-to-LV interval (ms)	85.4 ± 36.7
Biventricular pacing during follow-up (%)	98.3 ± 1.5
ACEI/ARB, *n* (%)	68 (67)
Beta-blocker, *n* (%)	92 (91)
Diuretic, *n* (%)	93 (92)
Digoxin, *n* (%)	58 (57)
Statin, *n* (%)	45 (45)
Amiodarone, *n* (%)	22 (22)
VT detection zone (beats/min)	156 ± 12
VF detection zone (beats/min)	194 ± 14

Data are presented as *n* (%) or mean ± standard deviation. BMI: Body mass index; LBBB: Left bundle branch block; NYHA: New York Heart Association; LVEF: Left ventricular ejection fraction; LVEDd: Left ventricular end-diastolic dimension; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker, VT: Ventricular tachycardia, VF: Ventricular fibrillation.

Tpeak-Tend evolution in acute and chronic change groups

Tpeak-Tend immediate shorten and nonshorten groups

Compared with the TpTe immediate nonshorten group, patients in the TpTe immediate shorten group showed a significantly longer TpTe baseline and a shorter TpTe immediately after CRT (120 ± 25 ms vs. 98 ± 17 ms at baseline, $t = 22.023$, $P = 0.000$; 103 ± 17 ms vs. 117 ± 22 ms immediately after CRT, $t = -14.674$, $P = 0.003$). At the 1-year follow-up, the TpTe immediate nonshorten group had observed significant decurated TpTe (105 ± 23 ms, $t = 12.192$, $P = 0.000$), without significant difference compared with the TpTe immediate shorten group (104 ± 25 ms, $t = -1.349$, $P = 0.950$) [Figure 2a].

Tpeak-Tend at 1 year shorten and nonshorten groups

TpTe at 1 year in the shorten and nonshorten groups had no difference in TpTe at baseline and immediately after CRT-D operation (107 ± 22 ms vs. 108 ± 27 ms at baseline, $t = -1.344$, $P = 0.688$; 110 ± 21 ms vs. 112 ± 15 ms immediately after CRT, $t = 2.011$, $P = 0.000$). A huge difference occurred at the 1-year follow-up after CRT; the TpTe at 1-year shorten group showed a serious decrease in TpTe (97 ± 19 ms vs. 110 ± 21 ms immediately after CRT, $t = -13.477$, $P = 0.000$) and shorter than the nonshorten group (117 ± 26 ms, $t = -20.314$, $P = 0.000$). The TpTe at 1-year nonshorten group, however, had no such TpTe change (117 ± 26 ms vs. 112 ± 15 ms, $t = 5.322$, $P = 0.163$) [Figure 2b].

Tpeak-Tend changes and left ventricular reverse remodeling

The relationship between TpTe and echocardiographic parameters from baseline to 6 months is shown in Figure 3. At 6 months after CRT-D, all patients had a significant increase in LVEF (38% ± 11% at 1-year vs. 29% ± 8% at baseline, $t = 9.021$, $P = 0.000$) and a decrease in LVEDd (63 ± 12 mm at 1-year vs. 70 ± 11 mm at baseline, $t = -6.308$, $P = 0.000$). Fifty-nine patients (58%) experienced LV reverse remodeling. There was no significant difference in the rate of LV reverse remodeling (24 patients [56%] vs. 35 patients [60%], $\chi^2 = 0.209$, $P = 0.648$), ΔLVEF (11% ± 10% vs. 9% ± 8%, $t = 2.269$, $P = 0.540$), and ΔLVEDd (−6 ± 11 mm vs. −6 ± 9 mm, $t = 0.145$, $P = 0.200$) between the TpTe immediately shorten

Table 2: Baseline characteristics of subgroups

Variables	Acute effects				Chronic effects			
	$\Delta TpTe_{(immediate-baseline)}$ <0 (n = 43)	$\Delta TpTe_{(immediate-baseline)}$ ≥0 (n = 58)	t/χ^2	P	$\Delta TpTe_{(1\ year-immediate)}$ <0 (n = 65)	$\Delta TpTe_{(1\ year-immediate)}$ ≥0 (n = 36)	t/χ^2	P
Age (years)	61.40 ± 10.89	59.02 ± 10.55	1.105*	0.270	59.12 ± 10.73	61.67 ± 10.63	−1.145*	0.255
Male, *n* (%)	28 (65)	42 (72)	0.618†	0.432	44 (68)	26 (72)	0.223†	0.636
BMI (kg/m²)	25.54 ± 5.90	24.33 ± 3.62	1.280*	0.200	24.63 ± 4.90	25.24 ± 4.48	−0.621*	0.536
NYHA Class	2.11 ± 0.66	2.76 ± 0.62	0.430*	0.670	2.61 ± 0.58	3.10 ± 0.63	−3.954*	0.00
QRS durations (ms)	161 ± 30	156 ± 25	0.870*	0.390	159 ± 25	157 ± 31	0.369*	0.713
LBBB, *n* (%)	36 (84)	45 (78)	0.263†	0.608	56 (86)	25 (69)	3.089†	0.079
Dilated cardiomyopathy, *n* (%)	31 (72)	43 (74)	1.297†	0.255	46 (71)	28 (78)	0.278†	0.598
Ischemic cardiomyopathy, *n* (%)	12 (28)	15 (26)	1.297†	0.255	19 (29)	8 (22)	0.278†	0.598
Hypertension, *n* (%)	19 (44)	17 (29)	2.382†	0.123	23 (35)	13 (36)	0.005†	0.942
Dyslipidemia, *n* (%)	13 (30)	18 (31)	0.007†	0.931	20 (31)	11 (31)	0.000†	0.982
Ventricular arrhythmia, *n* (%)	11 (26)	11 (19)	0.336†	0.238	12 (18)	10 (28)	0.797†	0.372
Atrial fibrillation, *n* (%)	7 (16)	9 (16)	0.011†	0.917	9 (14)	7 (19)	0.206†	0.650
LVEF (%)	27.12 ± 7.78	29.78 ± 8.53	−1.607*	0.111	29.38 ± 8.73	27.31 ± 7.35	1.210*	0.229
LVEDd (mm)	70.07 ± 11.22	69.24 ± 10.12	0.388*	0.699	68.34 ± 11.62	71.86 ± 7.96	−1.619*	0.109
Left ventricular lead position, *n* (%)								
Lateral vein/posterior vein	39 (91)	52 (90)	/	1.000	59 (91)	32 (89)	/	0.741
RV-to-LV interval (ms)	85.8 ± 37.9	85.0 ± 37.8	0.831*	0.360	85.5 ± 37.8	85.2 ± 38.4	0.312*	0.380
Biventricular pacing during follow-up (%)	98.6 ± 1.2	98.0 ± 1.5	0.323*	0.520	98.5 ± 1.3	98.0 ± 1.3	0.533*	0.410
ACEI/ARB, *n* (%)	29 (67)	39 (67)	0.000†	0.983	43 (66)	25 (69)	0.114†	0.736
Beta-blocker, *n* (%)	38 (88)	54 (93)	0.681†	0.409	59 (91)	33 (92)	0.023†	0.879
Diuretic, *n* (%)	37 (86)	56 (97)	2.435†	0.119	60 (92)	33 (92)	0.013†	0.909
Digoxin, *n* (%)	25 (58)	33 (57)	0.016†	0.901	36 (55)	22 (61)	0.311†	0.577
Statin, *n* (%)	19 (44)	26 (45)	0.004†	0.949	27 (42)	18 (50)	0.671†	0.413
Amiodarone, *n* (%)	11 (26)	11 (19)	0.336†	0.238	12 (18)	10 (28)	0.797†	0.372
VT detection zone (beats/min)	158 ± 13	155 ± 11	1.384*	0.239	159 ± 11	154 ± 10	0.347*	0.729
VF detection zone (beats/min)	192 ± 8	200 ± 18	−1.379*	0.240	195 ± 13	194 ± 16	1.272*	0.207

Data are presented as *n* (%) or mean ± standard deviation. *: *t* value. †: χ^2 value. TpTe: Tpeak-Tend; BMI: Body mass index; LBBB: Left bundle branch block; NYHA: New York Heart Association; LVEF: Left ventricular ejection fraction; LVEDd: Left ventricular end-diastolic dimension; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; VT: Ventricular tachycardia, VF: Ventricular fibrillation; RV: Right ventricular; LV: Left ventricular.

and nonshorten groups. However, compared with the TpTe at 1-year nonshorten group, the TpTe at 1-year shorten group had a higher LV reverse remodeling rate (43 patients [65%] vs. 16 patients [44%], χ^2 = 4.495, P = 0.034) and a better improvement in LVEF and LVEDd (ΔLVEF, 11% ± 9% vs. 7% ± 8%, t = 3.585, P = 0.040; ΔLVEDd, −6 ± 10 mm vs. −6 ± 10 mm, t = 0.427, P = 0.010).

Tpeak-Tend changes and ventricular arrhythmias

At the 1-year follow-up, 22 patients (22%) experienced appropriate therapy (14 ATP alone and 8 shocks) because of VT/VF episodes (VT episodes, 17 patients; VF episodes, 5 patients). Inappropriate therapy happened in eight patients (8%) including sinus tachycardia in three patients and atrial tachycardia/fibrillation/flutter in five patients. The rate of various groups' VT/VF episodes was calculated. For the acute change groups, 11 patients (26%) in the TpTe shorten group were compared with 11 patients (19%) in the TpTe immediate nonshorten group (χ^2 = 0.634, P = 0.426). For the chronic change groups, eight patients (12%) with shortened TpTe experienced VT/VF episodes, compared with 14 patients (39%) with nonshortened TpTe (χ^2 = 0.961, P = 0.002). Kaplan-Meier event-free survival analysis demonstrated that the TpTe at 1-year shorten group had a notably lower rate of VT/VF episodes compared with the TpTe at 1-year nonshorten group (log-rank test, χ^2 = 10.207, P = 0.001) [Figure 4]. The TpTe immediate shorten and nonshorten groups, however, had similar VT/VF episodes rates (log-rank test, χ^2 = 0.574, P = 0.449) [Figure 3].

On multivariate Cox regression analysis, TpTe immediately after CRT-D implantation was independently associated with the risk of VT/VF (hazard ratio [*HR*]: 1.030; P = 0.001) [Table 3].

Discussion

Major findings

The major findings of our study were as follows: (1) CRT was associated with a reduction of TpTe at 1-year immediately

after device implantation, (2) the acute changes of TpTe after CRT implantation had no effect on the response and VT/VF episode rates, (3) patients with TpTe shortened at 1-year after CRT implantation had a higher rate of LV reverse remodeling and less VT/VF episodes compared with the TpTe nonshorten group, and (4) TpTe immediately after CRT-D independently predicted VT/VF episodes at the 1-year follow-up.

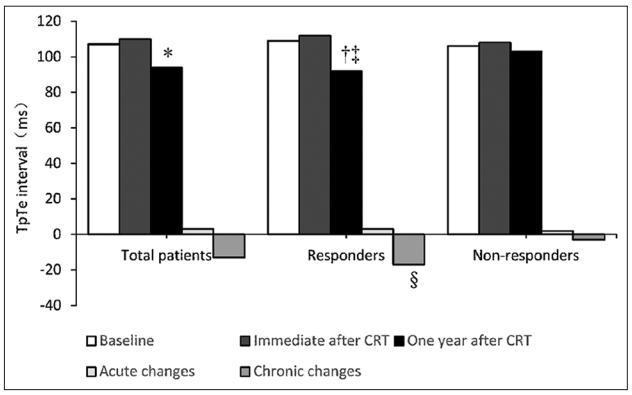

Figure 1: Evolution and changes of TpTe (mean) before, immediately, and 1 year postimplantable cardiac resynchronization (CRT) in total patients, with and without responders. Acute changes in TpTe were calculated as the difference between immediate and baseline values. Chronic changes in TpTe were calculated as the difference between 1-year and immediate postimplantable CRT. *$P < 0.05$, $TpTe_{one\text{-}year}$ versus $TpTe_{immediate}$ in total patients, †$P < 0.05$, $TpTe_{one\text{-}year}$ versus $TpTe_{immediate}$ in responders, ‡$P < 0.05$, $TpTe_{one\text{-}year}$ in responders versus nonresponders, §$P < 0.05$, chronic changes of TpTe in responders versus nonresponders. TpTe: Tpeak-Tend.

Effect of cardiac resynchronization therapy on Tpeak-Tend

The TpTe, a noninvasive indicator of TDR, represented the difference between the epimyocardial repolarization and mid-myocardial repolarization times.[9,10] Therefore, this ECG parameter was susceptible to LVEpiP. Studies have demonstrated that LVEpiP enhanced TpTe because of the alteration in the ventricular activation sequence.[2] However, the effect of BiVP on TpTe was controversial.[6,11] In our study, TpTe slightly increased immediately after CRT and decreased at the 1-year follow-up for all patients, especially for responders. These results were in agreement with Itoh's[7] findings, which showed a time-dependent reduction of TpTe 6 and 12 months after CRT implantation. Through analysis of the acute and chronic changes of TpTe after BiVP, respectively, we had some interesting findings.

In the two groups divided by whether TpTe immediately shortened after CRT, patients with TpTe shortened along with significantly longer $TpTe_{baseline}$ and shorter $TpTe_{immediate}$. Therefore, the acute TpTe changes might be dependent

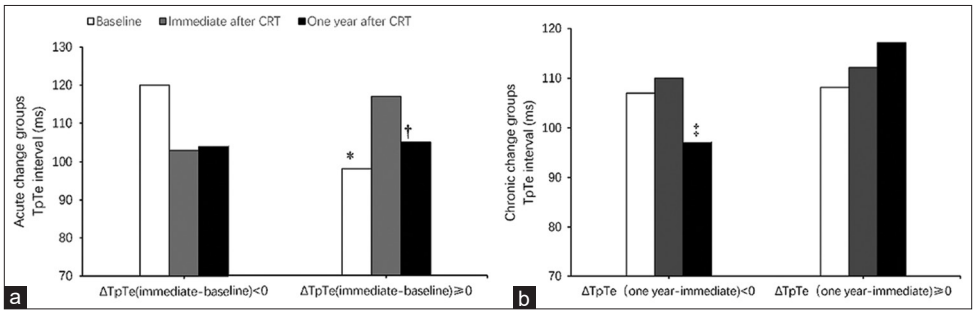

Figure 2: Evolution of TpTe (mean) before, immediately, and 1-year postimplantable cardiac resynchronization (CRT) in (a) acute change groups and (b) chronic change groups. Acute changes in TpTe were calculated as the difference between immediate and baseline values. Chronic changes in TpTe were calculated as the difference between 1-year and immediate postimplantable CRT. *P <0.05, $TpTe_{baseline}$ in $\Delta TpTe_{(immediate\text{-}baseline)}$ <0 versus $\Delta TpTe_{(immediate\text{-}baseline)}$ ≥0. †$P < 0.05$, $TpTe_{immediate}$ versus $TpTe_{one\ year}$ in $\Delta TpTe_{(immediate\text{-}baseline)}$ ≥0. ‡$P < 0.05$ $TpTe_{one\text{-}year}$ in $\Delta TpTe_{(one\ year\text{-}immediate)}$ <0 versus $\Delta TpTe_{(one\ year\text{-}immediate)}$ ≥0. TpTe: Tpeak-Tend.

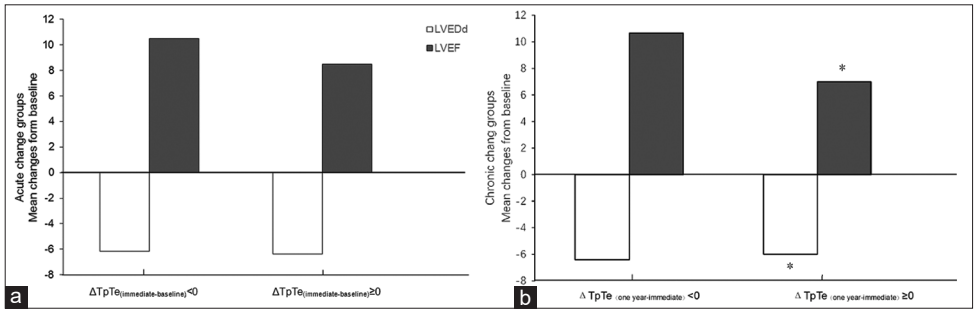

Figure 3: Comparison of absolute 6-month changes (mean) in LVEDd (mm) and LVEF (%) in (a) acute change groups and (b) chronic change groups. Acute changes in TpTe were calculated as the difference between immediate and baseline values. Chronic changes in TpTe were calculated as the difference between 1-year and immediate postimplantable cardiac resynchronization therapy. *$P < 0.05$, LVEDd and LVEF in $\Delta TpTe_{(one\ year\text{-}immediate)}$ <0 versus $\Delta TpTe_{(one\ year\text{-}immediate)}$ ≥0. TpTe: Tpeak-Tend; LVEDd: Left ventricular end-diastolic dimension; LVEF: Left ventricular ejection fraction.

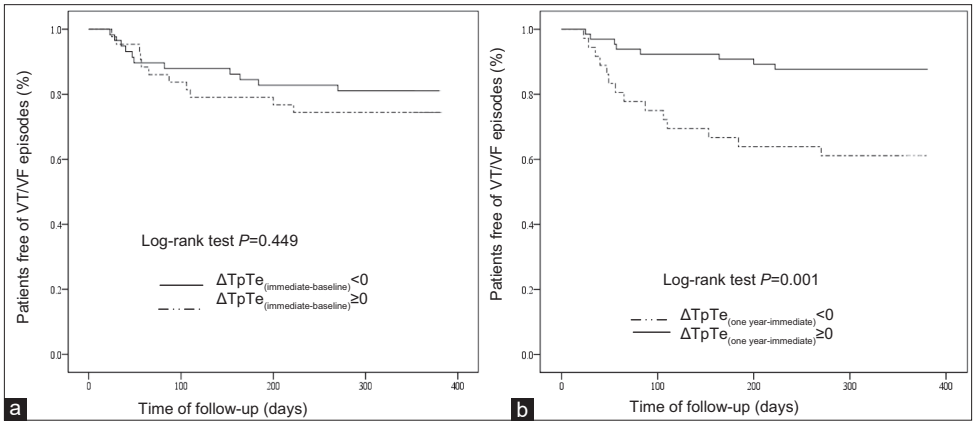

Figure 4: Kaplan-Meier estimates of cumulative incidence of ventricular tachycardia/ventricular fibrillation episodes in (a) acute change groups and in (b) chronic change groups. TpTe: Tpeak-Tend; VT/VF: Ventricular tachycardia/Ventricular fibrillation.

Table 3: Cox proportional hazards analyses of variable in relation to the occurrence of VT/VF

Items	Univariate			Multivariate		
	HR	95% *CI*	*P*	*HR*	95% *CI*	*P*
Male	2.372	0.484–11.634	0.287			
Age	1.027	0.962–1.097	0.418			
Ischemic cardiomyopathy	1.220	1.120–1.320	0.068	0.340	0.072–1.168	0.122
QRS duration	0.999	0.974–1.026	0.956			
LBBB	1.761	0.344–9.005	0.497			
Amiodarone	0.793	0.117–5.387	0.812			
LVEF	0.99	0.880–1.114	0.865			
LVEDd	1.073	0.967–1.190	0.185			
TpTe at baseline	0.971	0.919–1.026	0.291			
TpTe at immediate after CRT	1.040	1.003–1.047	0.010	1.030	1.020–1.040	0.001
TpTe at 1 year after CRT	1.010	0.969–1.052	0.646			
ΔTpTe (immediate-baseline)	1.314	0.179–9.631	0.788			
ΔTpTe (1 year-immediate)	0.480	0.270–0.870	0.017	0.196	0.026–2.310	0.184

LBBB: Left bundle branch block; LVEF: Left ventricular ejection fraction; LVEDd: Left ventricular end-diastolic dimension; *CI*: Confidence interval; *HR*: Hazard ratio; TpTe: Tpeak-Tend; CRT: Cardiac resynchronization therapy; VT: Ventricular tachycardia, VF: Ventricular fibrillation.

on the baseline TpTe level. Patients selected for CRT implantation always had deterioration of the LV myocardium structure; therefore, those patients tended to have increased intrinsic TDR (i.e., augmented the monophasic action potential duration of the mid-myocardium). Transmural repolarization heterogeneity would be more prominent for these patients. The advantage of synchronization outdistanced the disadvantage of LVEpiP after CRT implantation. The transmural repolarization heterogeneity had been ameliorated as a consequence. For this reason, patients with large intrinsic TDR would more likely benefit from CRT. However, this would be a temporary advantage as there were no differences of TpTe at 1-year between the two groups. Furthermore, it is worth mentioning that the changes of LV reverse remodeling and ejection fraction, as well as VT/VF episodes, were also not different between the acute TpTe-changed groups.

Therefore, we put forward the hypothesis that the acute changes of TpTe after CRT might have a minimal value on mechanical reverse remodeling and ventricular arrhythmia at the 1-year follow-up. However, the impact on the long-term outcome deserves further research.

TpTe changed again after 1-year BiVP in this study. The TpTe at 1-year shorten group showed a significant decline at 1-year. In this group, most patients experienced LV reverse remodeling and had a low rate of VT/VF episodes. However, no improvement in echocardiographic parameters was observed in the TpTe at 1-year nonshorten group. The chronic changes of TpTe after CRT implantation were probably associated with LV reverse remodeling. Prior studies have noted the relationship between electrical and mechanical remodeling in patients with CRT implantation. In those studies, responders always had positive ECG change indexes, including TpTe.[7,12] Chakir *et al*.[13] in their experimental study found that CRT reversed regional and global molecular remodeling, developing more homogeneous activation of stress kinases and reducing apoptosis. Furthermore, some studies suggested that CRT contributes to rebuilding ion channel function[14]

and amending the gene expression changes[15] caused by electromechanical dyssynchrony. All of those bring about the improvement of electrophysiological function and LV systolic and diastolic function after CRT.

Predictors of implantable cardioverter defibrillator therapy in cardiac resynchronization therapy-defibrillator

CRTs effects on ventricular arrhythmias are controversial. Some studies pointed out CRTs potential proarrhythmic effects based on their findings that TDR increased after BivP.[2,11] In our study, 19% patients experienced appropriate ICD therapy because of VT/VF. There was no significant difference in the rate of VT/VF between the TpTe acute shorten and nonshorten groups. Instead, the TpTe at 1-year shorten group showed a significant reduction in VT/VF episodes, and the TpTe at 1-year nonshorten group had a significant increase in VT/VF episodes. Therefore, CTRs chronic effect on TpTe might play an important role in ventricular arrhythmias. The TpTe, which corresponded to the TDR on intracardiac electrograms, was associated with ventricular arrhythmia. Increased TpTe was associated with an increased incidence of ventricular arrhythmias in CRT-D.[3] Therefore, patients with electrical reverse remodeling after CRT had a low rate of VT/VF episodes. In addition, the TpTe at 1-year shorten group had a higher rate of LV reverse remodeling in this study. According to recent research, CRT responders always had a low incidence of ventricular arrhythmias.[7,12] CRTs antiarrhythmic effect could benefit from contributions of LV reverse remodeling and reduce myocardial wall tension, as well as stabilize the myocyte membranes electrical activity.[16]

In the end, we explored the predictors of the VT/VF episodes after CRT. Through multivariate Cox regression analysis, we found that TpTe immediately after CRT was the only independent predictor of appropriate ICD therapy. This result was consistent with some previous research. In recent years, the application of TpTe as a marker of risk in arrhythmia syndromes has been validated in several experimental and clinical studies.[17,18] Barbhaiya *et al*.[3] and Lellouche *et al*.[4] have also demonstrated that TpTe as a marker of ventricular arrhythmia risk in patients with CRT-D increased and TpTe was associated with an increased incidence of VT/VF in CRT-D. In our study, the TpTe at 1-year shorten group had a low rate of VT/VF episodes, but $\Delta TpTe_{(1\ year\text{-}immediate)}$ was not an independent predictor of ICD therapy. Markowitz *et al*.[19] found that responder status predicted single premature ventricular contractions (PVCs) and PVC runs but did not predict VT/VF episodes. They pointed out that reverse remodeling may affect triggers (PVCs and PVC runs) but not substrate for VT/VF. The exact mechanism needs more investigation.

This study was retrospective in nature with a limited sample size; therefore, the results should be verified with larger prospective studies. Because of the limited number of cases, we analyzed patients according to acute and chronic changes of TpTe after CRT, respectively, without further grouping as TpTe nonshortened immediately but shortened after 1-year, and so on. In addition, CRT effects on ventricular arrhythmias are time dependent;[7] the duration of this study was perhaps too short to obtain the exact conclusion. It is unclear what impact TpTe acute and chronic changes had on the long-term outcome. Finally, the TpTe contained information about the global transventricular repolarization process, whereas the TDR reflected local repolarization differences in adjacent regions.[20] Therefore, the correlation between the TpTe and TDR needs to be confirmed by investigations and clinical studies of the basis mechanism.

In conclusion, CRTs effect on TpTe is time dependent, and TpTe's acute changes after CRT might have a minimal value on mechanical reverse remodeling and ventricular arrhythmia. Patients in the TpTe shorten at 1-year group after CRT implantation had a higher rate of LV reverse remodeling and less VT/VF episodes compared with the TpTe nonshorten group. Improved CRT response was the key to improving the prognosis. TpTe immediately after CRT-D was an independent predictor of VT/VF episodes at the 1-year follow-up.

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Conflicts of interest

There are no conflicts of interest.

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