

# T-Peak to T-End Improvements After Beta-Blocker Administration in Peripartum Cardiomyopathy Patients

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## Abstract

**Background:** Many studies have shown that T-peak to T-end (TPTE) interval was associated with sudden cardiac events. Peripartum cardiomyopathy (PPCM) causes reversible left ventricle systolic dysfunction which may deteriorate into sudden cardiac death. This study aimed to evaluate beta-blocker as an antiarrhythmic agent to improve TPTE interval as a prognostic value of sudden cardiac death.

**Methods:** A cohort experimental prospective study was performed. The PPCM was diagnosed from the emergency ward. A total of 54 cases were identified from 2014 to 2016. Thirty-four patients were followed up for further analysis. Electrocardiograms were conducted in all the patients, and TPTE interval was measured. After a follow-up of 6 months of beta-blocker treatment, the echocardiography and TPTE interval were measured again to obtain the repolarization heterogeneity.

**Results:** The mean age of subjects was  $32 \pm 6.4$  years. The mean left ventricular ejection fraction (LVEF) was  $32.24 \pm 6.3\%$ . The mean TPTE interval was  $123.7 \pm 28.2$  ms. After 6 months of beta-blocker administration, the mean LVEF was  $58.26 \pm 4.4\%$  and the mean TPTE was  $98.7 \pm 39.5$  ms. The paired *t*-test showed a significant difference between TPTE interval pre- and post-administration of beta-blocker (*P* value < 0.001).

**Conclusions:** There is an improvement of TPTE in PPCM patients after 6 months of beta-blocker administration. Administration of beta-blocker in PPCM patients is expected to prevent sudden cardiac death in PPCM populations.

**Keywords:** T-peak to T-end interval; Peripartum cardiomyopathy; Beta-blocker; Left ventricular ejection fraction; Repolarization heterogeneity

## Introduction

Peripartum cardiomyopathy (PPCM) is defined as pregnancy-related myocardial dysfunction, which appears during the last month of pregnancy until 6 months after delivery in women without any cardiovascular disease [1]. PPCM could cause serious complications, which may lead to death or severe and prolonged morbidity. There is a higher rate of adverse events, which occur in non-Caucasian patients, mainly related with low left ventricular ejection fraction (LVEF) (< 25%) at the time of diagnosis [2-4]. The pathophysiology of PPCM confirms that inflammation, oxidative stress, and prolactin could be inter-related in a vicious circle, which is liable for initiating PPCM [5]. Ventricular tachyarrhythmias were presumed as causes of sudden cardiac death (SCD) in at least one-fourth of deaths in PPCM [6]. However, there are limited data on arrhythmic events and the risk for SCD in PPCM. T-peak to T-end (TPTE) is defined as the interval between the peak and the end of T wave on electrocardiogram (ECG). It is recognized that TPTE interval could be used as an index of transmural dispersion of ventricular repolarization [7]. Many studies have shown that TPTE interval was associated with ventricular arrhythmia and SCD. Beta-blocker is one of the cornerstone treatments for PPCM. Beta-blocker has the effect of normalization of ventricular repolarization, particularly in the case of prolonged QT [8-13]. The purpose of this study was to investigate the effects of beta-blocker treatment on the ventricular repolarization by measuring TPTE interval on the 12-lead resting ECG. We analyzed the changes of TPTE interval before and after the initiation of beta-blocker treatment for a period of time. To the best of our knowledge, the effect of beta-blockers on TPTE interval on PPCM population has not been reported before.

## Materials and Methods

This is a prospective cohort study, and patients gave the informed consent. All patients with newly diagnosed PPCM between 2014 and 2016 were included in the study. PPCM was diagnosed based on the PPCM diagnostic criteria in European Society of Cardiology (ESC) guideline, including patients presented with: 1) heart failure (HF) secondary to LV systolic dysfunction, which develops during the end of pregnancy or 6 months following delivery; 2) no identifiable explanation for HF; 3) EF below 45% based on echocardiography examination [1].

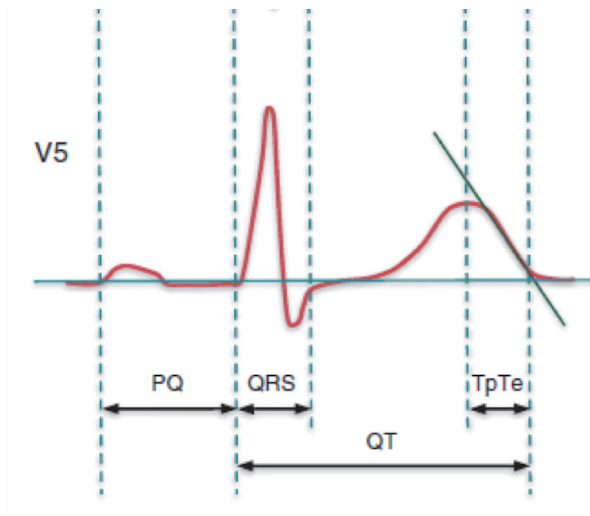
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**Figure 1.** Method of T-peak to T-end (TPTE) measurement in lead V5.

All recruited patients were categorized as New York Heart Association (NYHA) Functional Class (FC) III or IV. The treatment regimen of PPCM consists of titrated beta-blockers (bisoprolol 2.5 - 5 mg, once daily), angiotensin-converting enzyme (ACE) inhibitors, mineralocorticoid receptor antagonists, and bromocriptine as indicated. Data were collected before beta-blocker treatment was initiated; during hospitalization or outpatient clinic follow-up and after 6 months of the treatment of beta-blocker.

Electrocardiographic examinations were conducted on all patients. TPTE was calculated from two continuous beats in selected 12-lead resting ECG lead (V2 - V5). The Lepechkin's method was used to identify the endpoint of the QT segment by drawing a tangential line from the peak of the T wave to obtain the endpoint of the QT segment from the intersection with the isoelectric line (Figs. 1, 2).

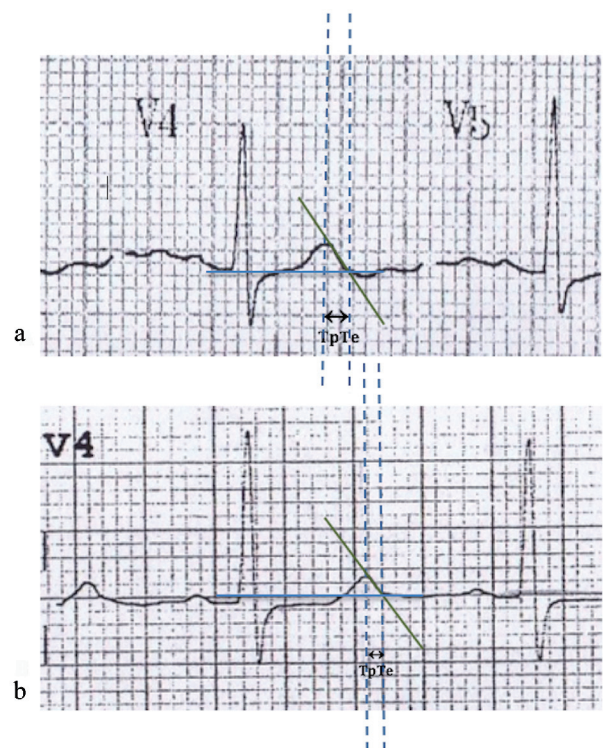
### Statistical analysis

Continuous variables are presented as mean  $\pm$  standard deviation (SD). The significance of TPTE changes before and after treatment of the PPCM patients were analysed by Student's *t*-test. A *P* value  $< 0.05$  was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics version 20 (IBM, Armonk, NY, USA).

The study protocol was reviewed and approved by Research Ethics Committee, Faculty of Medicine, Padjadjaran University, Bandung.

### Results

During a 3-year enrolment period (2014 to 2016), we diagnosed 54 women with PPCM. Thirty-four patients were followed up (mean age:  $32 \pm 6.4$  years). Baseline characteristics of subjects at the time of hospital admission are showed in Table 1. The mean of body mass index was  $24.87 \pm 3.2$  kg/m<sup>2</sup>. The mean of systolic blood pressure was  $118 \pm 11.4$  mm Hg,



**Figure 2.** Electrocardiogram example of the effect of beta-blockers on T-peak to T-end (TPTE) interval in a 31-year-old female with PPCM.

the mean of diastolic blood pressure was  $76 \pm 6.9$  mm Hg, the mean of heart rate was  $114.8 \pm 16.9$  beats/min. The mean of LVEF was  $32.24 \pm 6.3\%$ . The baseline ECGs are shown, and the mean of TPTE interval was  $123.7 \pm 28.2$  ms. Heart failure therapy administered including beta-blockers (34/34, 100%) that were up-titrated, ACE inhibitors (34/34, 100%), diuretics (34/34, 100%), and mineralocorticoid receptor antagonists (3/34, 8%). Eight patients received bromocriptine (5 mg per day for 2 weeks, followed by 2.5 mg per day for 4 weeks).

After the mean 6 months of beta-blocker administration, the mean of LVEF was  $58.26 \pm 4.4\%$ , and the mean of TPTE was  $98.7 \pm 39.5$  ms. The Student's *t*-test analysis showed a significant difference between TPTE interval pre- and post-administration of beta-blocker (*P* value  $< 0.001$ ) (Table 2 and Figs. 3, 4).

### Discussion

PPCM is a pregnancy-related non-ischemic cardiomyopathy characterized by HF secondary to LV systolic dysfunction. This condition was accompanied with an LVEF  $< 45\%$  during the end of pregnancy or in the months following delivery, without any other identifiable explanation for HF [1]. The incidence of PPCM is 1 in 3,500 in USA, 1 in 1,400 in Europe, 1 in 1,000 in South Africa, and 1 in 299 in Haiti [14].

The possibility for ventricular function to have a complete recovery in PPCM patients should be contemplated. A multi-centre study which reported outcomes of 30 PPCM patients with subsequent pregnancies showed that the sustained LV

**Table 1.** Baseline Characteristics of Patients

| Variable                             | Mean ± SD      |
|--------------------------------------|----------------|
| Age (years)                          | 32 ± 6.4       |
| Body mass index (kg/m <sup>2</sup> ) | 24.87 ± 3.2    |
| Blood pressure (mm Hg)               |                |
| Systolic                             | 118 ± 11.4     |
| Diastolic                            | 76 ± 6.9       |
| ECG parameters                       | 114.85 ± 16.9  |
| Heart rate (bpm)                     | 64.42 ± 18.2   |
| QRS duration (ms)                    | 471.50 ± 440.2 |
| QTc interval (ms)                    |                |
| Heart failure medications, n (%)     |                |
| Beta-blockers                        | 34 (100)       |
| ACE inhibitor                        | 34 (100)       |
| Diuretics                            | 34 (100)       |
| MRA                                  | 3 (8.8)        |
| Echocardiographic data               |                |
| LVEF (%)                             | 32.24 ± 6.3    |
| Mitral E/A ratio                     | 1.73 ± 0.7     |
| Deceleration time                    | 147.68 ± 42.6  |

SD: standard deviation; bpm: beats per minute; QTc: QT corrected; ACE: angiotensin-converting enzyme; MRA: mineralocorticoid receptor antagonist; LVEF: left ventricular ejection fraction.

dysfunction occurred in half of subjects before the subsequent pregnancy. Sustained normal cardiac features were only presented in 56% among patients, in whom cardiac function had completely recovered before the following pregnancy. Thus, there is still a considerable chance for relapse in completely recovered LV function in PPCM patients [15].

The prevalence data of ventricular arrhythmias in PPCM patient were limited. Previous study that investigated arrhythmia in PPCM patients by performing Holter analysis in 19 subjects reported the occurrence of sinus tachycardias, premature atrial contractions and premature ventricular contractions of 89.4%, 21%, 36.8% respectively; four cases of non-sustained ventricular tachycardias (VTs), and none of the subjects had sustained ventricular arrhythmia [16]. Furthermore, severely

reduced LVEF years after the diagnosis and ventricular arrhythmias in PPCM patients were reported by some case reports [17, 18]. Several studies evaluated outcomes of patients with PPCM demonstrated mortality rates of 7.1% to 15% [2, 6, 19, 20]. Moreover, Goland et al found 38% of the deaths of PPCM patients in his cohort study were sudden deaths [2].

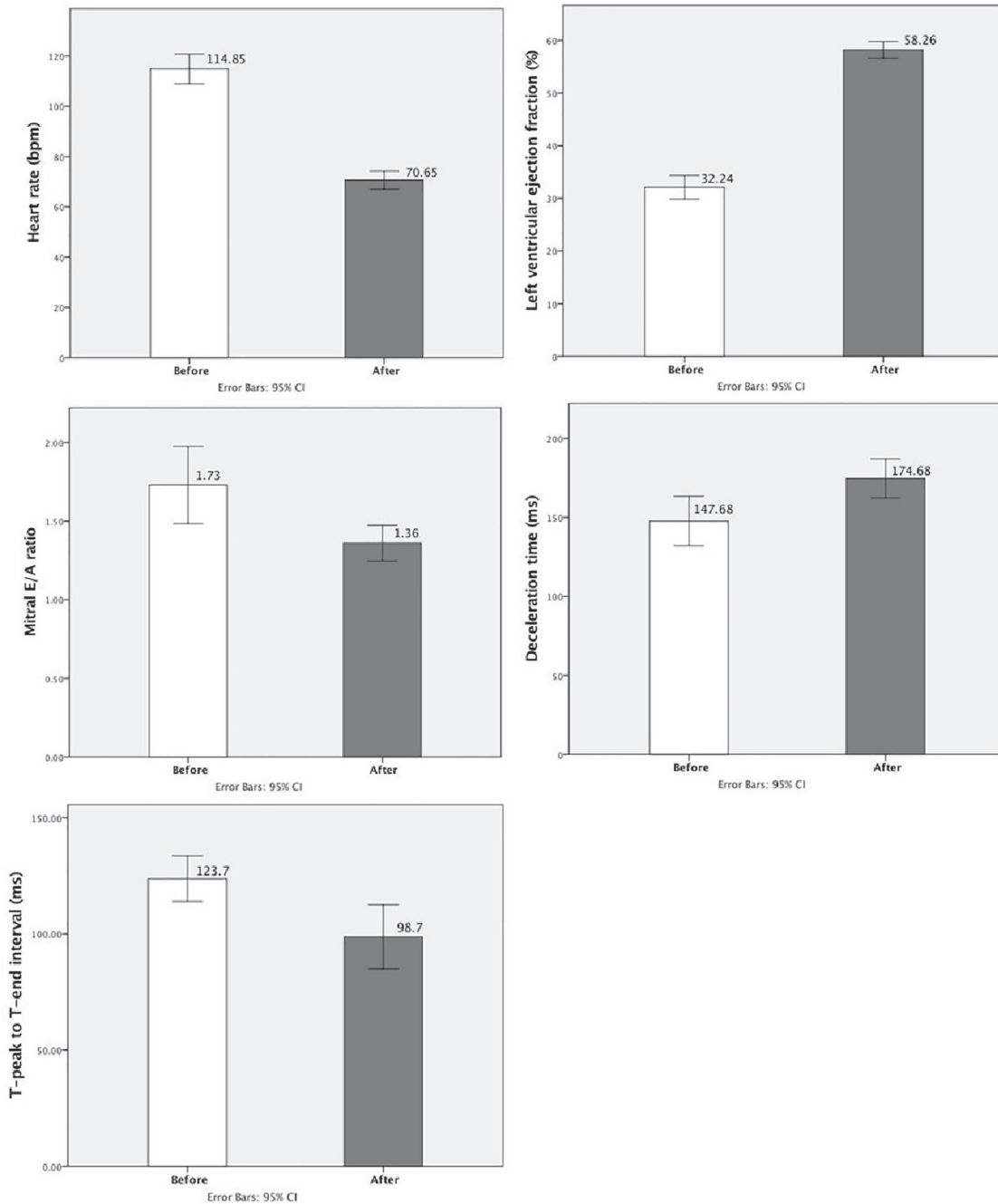
The dispersion of ventricular repolarization has been demonstrated to be associated with the TPTE interval on 12-lead resting ECG [7, 21, 22]. Originally, the dispersion was demonstrated in transmural orientation. The repolarization process was started at the epicardium, continued to endocardium, and ended at the midmyocardial “M” cells [23, 24]. Subsequent investigators showed that TPTE represents not only transmural dispersion of ventricular repolarization, but also dispersion of ventricular repolarization of entire myocardial wall [25]. Electrical re-entry requires differential repolarization, so the increased repolarization dispersion could increase arrhythmogenesis [26]. This explanation supported the hypothesis that the longer TPTE correlates with the higher risk of ventricular tachyarrhythmia and death. Hence, several studies have been conducted in various populations to evaluate the role of TPTE in predicting ventricular tachyarrhythmia and/or death [27]. Study performed by Morin et al [26] proved that the longer TPTE strongly predicts both ventricular tachyarrhythmia and death. It is also showed that TPTE correlated with the inducibility of VT/ventricular fibrillation (VF), and the longer TPTE correlated with inducibility of VT at electrophysiology study [25, 28]. Furthermore, TPTE interval on surface ECG was longer in SCD cases and was significantly associated with SCD [29].

Reduction of TPTE was showed after 6-month treatment of beta-blocker administration. A study conducted on patients with type 1 long-QT (LQT1) syndrome to evaluate the effect of beta-blocker administration to TPTE interval, showed that beta-blockers could reduce the prolongations of TPTE at elevated heart rates [30]. This finding is consistent with a previous study, which investigated the effect of propranolol to TPTE interval. Propranolol was demonstrated to suppress the increasing rate-corrected TPTE interval in LQT1 patients caused by epinephrine administration [31]. Earlier experimental studies presented that beta-blocker could inhibit the transiently prolonged duration of M cell action potential induced by sympathetic, hence prevent the increase of transmural dispersion of repolarization [11, 12]. We considered the reduction of TPTE interval in our study was not caused by any other

**Table 2.** Comparisons of Variables Between Before and After Beta-Blocker Treatment

| Variable               | Before treatment | After treatment | P value |
|------------------------|------------------|-----------------|---------|
| Heart rate (bpm)       | 114.85 ± 16.9    | 70.65 ± 10.4    | < 0.001 |
| LVEF (%)               | 32.24 ± 6.3      | 58.26 ± 4.4     | < 0.001 |
| Mitral E/A             | 1.73 ± 0.7       | 1.36 ± 0.3      | 0.011   |
| Deceleration time (ms) | 147.68 ± 42.6    | 174.68 ± 33.9   | 0.001   |
| QRS duration (ms)      | 64.42 ± 18.2     | 60 ± 12.1       | 0.420   |
| QTc interval (ms)      | 471.50 ± 440.2   | 440.17 ± 24.9   | 0.082   |
| TPTE (ms)              | 123.7 ± 28.2     | 98.7 ± 39.5     | < 0.001 |

LVEF: left ventricular ejection fraction; bpm: beats per minute; QTc: QT corrected; TPTE: T-peak to T-end. P value is considered significant if P < 0.05.



**Figure 3.** Comparisons of variables between before and after beta-blocker treatment.

drugs such as ACE inhibitors, diuretics, or mineralocorticoid receptor antagonists, as we acknowledged there was no study showed TPTE interval changes related to these drugs.

**Limitations**

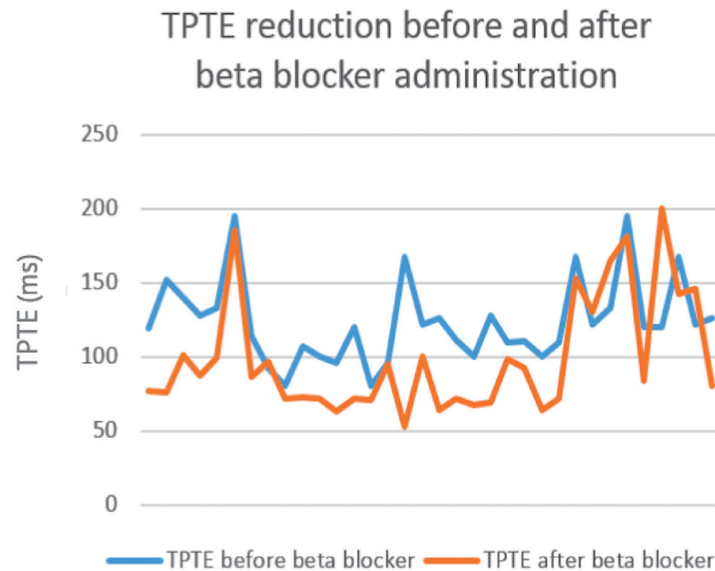
We focused this study only on the effect of beta-blocker on TPTE interval. Other ECG parameters that could be affected by beta-blocker treatment were not included in this study due

to the limitation of data. This study is the first in assessing ventricular repolarization on PPCM patients. We recommend multi-centre and randomized controlled trial (RCT) studies with larger data size for further analysis.

**Conclusions**

We observe an improvement of TPTE in PPCM patients after 6 months of beta-blocker administration. Administration of





**Figure 4.** Reduction of T-peak to T-end interval before and after administration of beta-blocker.

beta-blocker in PPCM patients is expected to prevent SCD in PPCM populations.

### Acknowledgments

None to declare.

### Financial Disclosure

None to declare.

### Conflict of Interest

All authors declare no conflict of interest related to this study.

### Informed Consent

Informed consents were obtained.

### Author Contributions

CA made conception and design of study, implemented the study, analysed and interpreted the study results, drafted the manuscript and revised it. MI, GK, HSP, and MF contributed to the design of study, analysis, and interpretation of study data.

### Data Availability

The data that support the findings of this study are available on

request from the corresponding author CA.

### Abbreviations

PPCM: peripartum cardiomyopathy; LVEF: left ventricular ejection fraction; SCD: sudden cardiac death; TPTE: T-peak to T-end; ECG: electrocardiogram; ESC: European Society of Cardiology; HF: heart failure; EF: ejection fraction; NYHA: New York Heart Association; FC: functional class; ACE: angiotensin-converting enzyme; SD: standard deviation; VT: ventricular tachycardia; VF: ventricular fibrillation

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