A novel ECG-index for prediction of ventricular arrhythmias in patients after myocardial infarction

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Abstract

Background: Risk prediction of ventricular arrhythmias after myocardial infarction (MI) is still insufficient. Prolonged QTc is a known risk marker of mortality and ventricular arrhythmias. QTc has not achieved clinical importance in predicting arrhythmic events in patients after MI. Recent studies have displayed that the terminal part of the QT-interval, T-peak to T-end (TpTe) may be a more promising predictor of adverse outcome. Herein, we assessed whether TpTe may serve as a predictor of ventricular arrhythmias in patients with previous MI fulfilling current ICD indications.

Methods: Seventy-six patients with previous MI eligible for ICD therapy were prospectively enrolled. ECG measurements at baseline were recorded using a 12 lead ECG with 50 mm/s paper speed. TpTe was measured from peak of the T wave to end of T wave. Events during follow up were defined as ventricular arrhythmias requiring appropriate ICD therapy, including anti tachycardia pacing and shock.

Results: During 23 ± 19 months, arrhythmic events occurred in 36 (47 %) patients. TpTe was longer in ICD patients with recorded ventricular arrhythmias compared with those without (116 ± 26 ms vs. 102 ± 20 ms, p=0.01), while EF at baseline did not differ (35 ± 9 % vs. 35 ± 11 %, p=0.87). TpTe was an independent predictor of ventricular arrhythmias when adjusted for age, EF and QRS duration (HR 1.16; 95% CI 1.03-1.31, p=0.02).

Conclusions: TpTe predicted malignant arrhythmias in patients after MI independently of EF. TpTe may contribute in the risk stratification of patients to identify post-MI patients disposed to malignant arrhythmias and their need of ICD-therapy.

Key words: ECG, ventricular arrhythmias, myocardial infarction

Abbreviations:

TpTe = T-peak to T-end

 MI = myocardial infarction

ICD = implantable cardioverter-defibrillator

EF = ejection fraction

VF = ventricular fibrillation

VT = ventricular tachycardia

LV = left ventricular

ROC = receiver-operating characteristic

AUC = area under the curve

Ventricular arrhythmias are the major cause of sudden cardiac death in patients after myocardial infarction (MI). Despite improved treatment of patients with MI by coronary revascularization, a substantial proportion of patients still suffer from sudden cardiac death. ICD therapy is the leading therapy available to avert sudden death in high-risk patients [1-3]. However, ICD is not an inert therapy and carries risk of complications. Therefore, effective selection of patients for this therapy is needed. Left ventricular (LV) ejection fraction (EF) is currently the main parameter applied to select patients for implantable cardioverter-defibrillator (ICD) therapy [3-5]. EF is an excellent predictor for prognosis of heart failure and heart failure death, but has limitations in accurate prediction of sudden death. Less than 50 % of patients with prior infarction, who die suddenly, have EF below 30 % [1,6-8]. There is a growing awareness of the limitations of EF as the only risk stratification tool for ICD therapy [1,5,9,10]. A variety of different parameters have been reported to improve prediction of ventricular arrhythmias, but no single parameter has so far shown sufficient sensitivity and specificity for this devastating event. A combination of several risk markers, including reduced EF, will most likely provide the most reliable risk stratification for sudden cardiac death [1,11,12].

However, QTc has not achieved clinical importance in predicting arrhythmic events in patients after MI. Previous studies have shown that the ECG measurement of T-peak to T-end (TpTe) is a predictor of mortality during the first year after MI [13-16]. TpTe is defined as the time interval between the peak amplitude of the T wave and the end of the T-wave. TpTe is suggested as an index of total spatial dispersion of cardiac repolarization [17]. Increased dispersion of repolarization contributes to the development of malignant ventricular arrhythmias and may be the mechanism of why prolonged TpTe may be a marker of increased risk of ventricular arrhythmias [13,18]. We hypothesized that TpTe may be a marker of

ventricular arrhythmias by reflecting the mechanisms of arrhythmogenesis. The purpose of

the present study was to evaluate if TpTe can serve as an additional risk marker for the

occurrence of malignant ventricular arrhythmias in patients with implanted ICD after MI.

Methods

Study population

A total of 76 post-MI patients fulfilling indications for ICD therapy were prospectively

included. Regional Committee for Medical Research Ethics approved the study. Written

informed consent was obtained from all patients.

The inclusion criteria were patients implanted with ICD after MI on primary or

secondary prevention criteria according to current guidelines [3,4,19]. Primary prevention criteria

included patients with EF < 35% at least 40 days after MI or EF < 40% and non-sustained

ventricular tachycardia (nsVT) and sustained arrhythmia inducible by an electrophysiology

study. Secondary prevention criteria included patients with prior MI who had survived a

cardiac arrest or sustained ventricular tachycardia (VT). The exclusion criteria were prior

coronary artery bypass graft surgery, severe valvular dysfunction, atrial fibrillation and bundle

branch block on ECG.

All the participants underwent coronary angiography before implantation of ICD.

Revascularization therapy and medical treatment were documented. The time from ICD

implantation to the first arrhythmic event during follow-up was documented. Arrhythmic

events were defined as appropriate anti-tachycardia pacing or shock from the defibrillator.

Follow-up time after ICD implantation was a minimum of 300 days.

TpTe measurements

ECG measurements prior to ICD implantation were recorded using a 12 lead ECG

with 50 mm/s paper speed. TpTe was measured using two methods. The "tail method"

(TpTeTail) was defined as the time in milliseconds from the peak of the T-wave (Tp) (or

nadir if the T-wave was negative or biphasic) to the point where the T-wave returns to the iso electric line (end of the T-wave, Te) [13,20] (Figure 1). The "tangent method" (TpTeTangent) was defined as time from Tp (or nadir) and the intersection between the tangent at the steepest point of the T-wave downslide and the isoelectric line [13,21]. In contrast to the tail method, the tangent method did not include the terminal phase of the T-wave. TpTe were measured from all 12 ECG leads and the longest TpTe was recorded. All TpTe measurements were corrected for heart rate using a modified Bazett's formula, TpTeC= TpTe / square root of RR interval. The data described of TpTe in this paper were derived from the tail method if not contrarily specified. TpTeC was measured by one author blinded to the clinical outcomes. A random selection of ECGs was re-measured by the same observer to assess intraobserver variability. TpTeC was re-measured by a cardiologist blinded to the first measurements to assess interobserver reproducibility. QRS interval and QT interval were measured according to current standards and QT-interval was rate corrected (QTc) by Bazett's formula.

Echocardiographic examination was performed prior to the ICD implantation at the same day as the ECG recording. EF was assessed by the modified Simpson method.

The use of beta blockers, ACE inhibitors and amiodarone at ICD implantation was recorded.

Statistical analyses

Data were presented as mean ± standard deviation (SD), numbers (percentages) and median (interquartile range). Comparisons of means were analyzed using unpaired t tests (SPSS version 19; SPSS, Inc., Chicago, IL). Cox regression analysis was performed to identify predictors of ventricular arrhythmias requiring appropriate ICD treatment. Significant predictors ($p<0.05$) from univariable analyses were included in multivariable regression analyses. Receiver operating characteristics (ROC) curves were utilized to determine specificity and sensitivity of TpTeC to detect those with ventricular arrhythmias. The value

closest to the upper left corner of the ROC curve was defined as the cut off value for optimal sensitivity and specificity for TpTeC to identify arrhythmic events. Kaplan-Meier analysis was used to create freedom-from-arrhythmia curves. P-values were two-tailed and values <0.05 were considered significant.

Results

Mean age was 63.1 ± 9.8 years in all patients and 65 (86 %) were male. Age and gender were similar in patients with arrhythmic events and in those without (Table 1). Thirty-eight were included on ICD primary prevention criteria and 38 on secondary prevention criteria. Time since MI was median 6 months (range 0-36 months). PCI was performed in 46 (61 %) patients, while 30 (39 %) were considered ineligible for revascularization.

During 23 ± 19 months of follow-up, 36 (47 %) of the 76 included ICD patients experienced one or more events with ventricular arrhythmias in need for ICD therapy (anti-tachycardia pacing or shock). TpTeTailC and QRS-interval were significantly longer in ICD patients with arrhythmic events compared to those without arrhythmic events (p = 0.01 and p= 0.05, respectively) (Table 1). There was no difference in TpTeTangentC, EF, QTc and medications between the two groups. In multivariable Cox regression analysis, TpTeTailC was a strong predictor of ventricular arrhythmias during follow up and predicted arrhythmic events independently of age and EF (Table 2). ROC analyses identified TpTeTailC > 100 ms as the optimal cut off value with a sensitivity of 75 % and specificity of 48 %. AUC was 0.67 (95% CI, 0.55-0.79). Kaplan-Meier analyses showed that patients with TpTeTailC > 100 ms had more frequent arrhythmic events than patients with TpTeTailC < 100 ms (p=0.05) (Figure 2).

There was no difference in TpTeTailC between patients with ICD on primary (111 $\pm$ 26 ms) versus patients with ICD on secondary (106 $\pm$ 21 ms) prevention criteria (p=0.37).

Patients with EF > 35%

Thirty-eight patients were implanted with ICD on secondary prevention criteria and had EF > 35 % and were analyzed separately. Event rate of ventricular arrhythmias requiring appropriate ICD therapy among these patients with relatively preserved EF was 20 (53 %) (Table 3). TpTeTailC was prolonged in those with arrhythmic events during follow up compared to those without arrhythmic events. QRS-interval, QTc duration, LV volumes, EF and medications were similar in these two groups. Cox regression analysis in patients with EF > 35% showed that TpTeTailC was a significant predictor of arrhythmic events and predicted events independently of age and EF. ROC analyses identified a TpTeTailC of > 100 ms as the optimal cut off value with AUC 0.70 (95% CI 0.54-0.87) with a sensitivity of 71 % and specificity of 61 %. Kaplan Meier plot showed significantly better arrhythmia free survival in those with a TpTeTailC < 100 ms (p=0.03) (Figure 3).

Reproducibility

The intra observer interclass correlation coefficient for TpTe measurements was 0.95 (95 % CI, 0.90 - 0.98) and the inter observer intraclass correlation coefficient was 0.86 (95 % CI, 0.73 - 0.92).

Discussion

This study demonstrated that TpTeTailC was a marker of risk for ventricular arrhythmias in patients after MI. Recent studies have shown that TpTeTailC was a marker of mortality in patients after MI [13]. Importantly, TpTeTailC predicted ventricular arrhythmias also in those with relatively preserved ventricular function. These findings indicate that the specific mechanisms for occurrence of ventricular arrhythmias may be assessed by TpTeTailC and that it may be used as an additional risk stratification tool for ICD treatment in patients after MI.

Current risk stratification for ventricular arrhythmias in patients after MI

Selection of patients after MI for ICD therapy remains challenging. Current guidelines recommend primary prevention by ICD implantation when EF is < 35 % and New York Heart Association class is II or III [3,22]. Nevertheless, a considerable percentage of those who die from ventricular arrhythmias have EF > 35 % [22,23] and thereby, the current guidelines fail to address a large number of patients. Thus, supplementary risk stratification tools are needed. EF is a volume based measure for LV function and is an excellent marker of contractile dysfunction and heart failure, but cannot predict electrophysiological dysfunction when contractile function is preserved. It is obvious that EF does not directly assess the electrophysiological substrates responsible for triggering ventricular arrhythmias [24]. An ideal risk marker should provide reliable information with adequate specificity and sensitivity. Furthermore, a marker should also be economically affordable, safe to obtain, simple to interpret and easily accessible in healthcare [24]. Currently, no single marker for predicting arrhythmias exists and a combination of markers seems to be the most promising approach.

TpTeTailC as an additional risk marker of ventricular arrhythmias and mechanisms of prolonged TpTe interval

We have recently demonstrated that TpTeTailC is a predictor of first year mortality in patients after MI and that TpTeTailC provided additional prognostic information in these patients compared to traditional risk factors [13]. The study by Erikssen et al also indicated that TpTeTailC may be a specific predictor of sudden, probably arrhythmic, death. Importantly, the present study adds further to the knowledge of TpTeTailC as a prognostic marker, by showing more directly that TpTeTailC is a marker of ventricular arrhythmias and may reflect underlying electrical mechanisms for ventricular arrhythmias.

Dispersion of ventricular repolarization has been recognized as a mechanism for ventricular arrhythmias and may be indicative for the patient's risk of developing arrhythmias even before the threshold value is reached [25]. TpTeTailC has been correlated to transmural

electrical heterogeneity and reflects electrical dispersion in patients with long QT syndrome [25,26]. Furthermore, TpTeTailC has been associated with drug-induced QT interval prolongation and expresses total distribution of repolarization in the whole LV [27].

This study shows that TpTeTailC reflect arrhythmic risk in patients after MI. It is well known that myocardial scars after MI give rise to malignant arrhythmias [5,28]. Ventricular arrhythmias after MI can arise from the heterogeneity in the scar tissue and border zones which establishes areas of slow conduction. A possible mechanism has been considered to be reexcitation of fibers with short action potentials by adjacent fibers with longer action potentials [18]. Spatial dispersion of repolarization is known to prolong the QT interval, QTc and the QT dispersion. However, QTc include depolarization in homogeneity and conduction abnormalities such as bundle branch block and is therefore unspecifically prolonged in a variety of conditions. TpTeTailC is a more specific marker of repolarization by including only the phase 3 and 4 of the action potential and may therefore more specifically assess mechanisms for ventricular arrhythmias.

QT dispersion, assessed as the difference between longest and shortest QT interval in a 12 lead ECG, was presented as a promising marker of arrhythmic risk some decades ago [29]. However, difficulties in assessing end of the T-wave made reproducibility challenging and the QT dispersion did not gain the clinical relevance as initially expected. The challenges of determining the end of the T-wave remain in the TpTeTail method described in this study. However, the TpTeTail method does not require measurements of difference as in QT dispersion and excludes the differences in the QRS duration as a possible confounder in measures of QT dispersion.

TpTe tail versus TpTe tangent

TpTe measured by the tail method, was a significant multivariable predictor of malignant ventricular arrhythmias in patients after MI. When measured with the tangent

method, TpTe became non-significant (p = 0.14), thereby suggesting that the tail method adds a greater prognostic potential than the tangent method [13].

Clinical implications

TpTeTailC is easy to obtain and an inexpensive measurement from 12 lead ECG. Furthermore, it is simple to interpret and is a swift examination, thereby making TpTeTailC a potential important supplement to EF in determining which patients to select for ICD-therapy. Particularly, TpTeTailC may add information in patients with EF > 35 % who contribute to a substantial proportion of sudden deaths, but in whom EF is inadequate for prediction of sudden death.

Limitations

The study is limited by the small sample size, but has a relatively high event rate. The study can be regarded as a pilot study which may be confirmed by larger prospective trials.

Measuring the end of the T-wave may be challenging, e.g. in presence of horizontal T-waves. Still, we found an excellent inter- and intra-observer agreement in our study.

Conclusions

TpTeTailC predicted malignant arrhythmias in patients after MI independently of EF. TpTeTailC was an excellent predictor of arrhythmias also in those with relatively preserved EF. Measurement of TpTeTailC might be a supplemental parameter to help identify patients after MI predisposed to malignant arrhythmias and help the selection of patients for ICD therapy.

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Table 1. Clinical characteristics in 76 patients after myocardial infarction with ICD

	Non-arrhythmia	Arrhythmia	P-value
	N= 40	N= 36	
Age (years)	61.7 ± 9.4	64.6 ± 10.2	0.21
Female/Male (n)	8/32 (20 %)	3/33 (8 %)	0.15
Heart Rate (bpm)	68 ± 13	63 ± 14	0.12
QRS duration (ms)	104 ± 20	114 ± 26	0.05
QTc (ms)	440 ± 80	450 ± 30	0.44
TpTe-TailC (ms)	102 ± 20	116 ± 26	0.01
TpTe-TangentC (ms)	96 ± 16	102 ± 20	0.14
EDV (ml)	190 ± 69	195 ± 80	0.79
ESV (ml)	126 ± 61	129 ± 65	0.84
EF (%)	34.5 ± 11.1	34.9 ± 9.0	0.87
Amiodarone (n)	9 (23 %)	6 (17 %)	0.50
Beta-blocker (n)	37 (93 %)	33 (92 %)	0.58
ACE inhibitor (n)	34 (85 %)	30 (83 %)	0.64

Values are mean ± SD and n (%). TpTe: T-peak to T-end, EDV: End diastolic volume, ESV: End systolic volume, EF: Ejection fraction

Table 2. Predictors of ventricular arrhythmias in 76 patients after myocardial infarction with ICD by Cox Regression analyses.

	Univariate			Multivariate		
	HR	95 % CI	P-value	HR	95 % CI	P-value
Age (years)	1.01	0.98-1.05	0.40	1.02	0.98-1.05	0.34
QRS duration (per 10 ms increase)	1.14	1.00-1.29	0.05	1.11	0.98-1.26	0.12
EF (%)	1.00	0.97-1.03	0.97	1.01	0.98-1.05	0.45
TpTe-TailC (per 10 ms increase)	1.16	1.04-1.30	0.01	1.16	1.03-1.31	0.02

EF: Ejection fraction, TpTe: T-peak to T-end, Hazard ratio, 95 % CI: 95% Confidence interval.

Table 3. Clinical characteristics in 38 patients after myocardial infarction with ICD and with

EF > 35 %

	Non-arrhythmia N= 18	Arrhythmia N= 20	P-value
Age (years)	63.2 ± 10.4	65.8 ± 10.5	0.46
Female/Male (n)	2/16 (11 %)	1/19 (5 %)	0.50
Heart Rate (bpm)	63 ± 13	60 ± 13	0.47
QRS duration (ms)	101 ± 19	113 ± 28	0.13
QTc (ms)	440 ± 40	440 ± 20	0.83
TpTe-TailC (ms)	98 ± 19	111 ± 19	0.04
TpTe-TangentC (ms)	95 ± 18	99 ± 16	0.48
EDV (ml)	156 ± 39	161 ± 61	0.77
ESV (ml)	85 ± 27	92 ± 37	0.51
EF (%)	44.3 ± 8.4	41.7 ± 4.6	0.23
Amiodarone (n)	5 (28 %)	5 (25 %)	0.85
Beta-blocker (n)	18 (100 %)	18 (90 %)	0.18
ACE inhibitor (n)	15 (83 %)	16 (80 %)	0.80

Values are mean ± SD and n (%). TpTe: T-peak to T-end, EDV: End diastolic volume, ESV:

End systolic volume, EF: Ejection fraction

Table 4. Predictors of ventricular arrhythmias in 38 patients after myocardial infarction with

ICD and EF > 35 % by Cox Regression analyses.

	Univariate			Multivariate		
	HR	95 % CI	P-value	HR	95 % CI	P-value
Age (years)	1.02	0.98-1.06	0.46	1.02	0.98-1.06	0.31
QRS duration (per 10 ms increase)	1.12	0.96-1.31	0.14			
EF (%)	0.96	0.89-1.04	0.36	0.96	0.87-1.06	0.43
TpTeTailC (per 10 ms increase)	1.41	1.07-1.85	0.02	1.43	1.08-1.89	0.01

EF: Ejection fraction, TpTe: T-peak to T-end, HR: Hazard ratio, 95 % CI: 95% Confidence

interval.

Figure 1. TpTe measured by the tail method
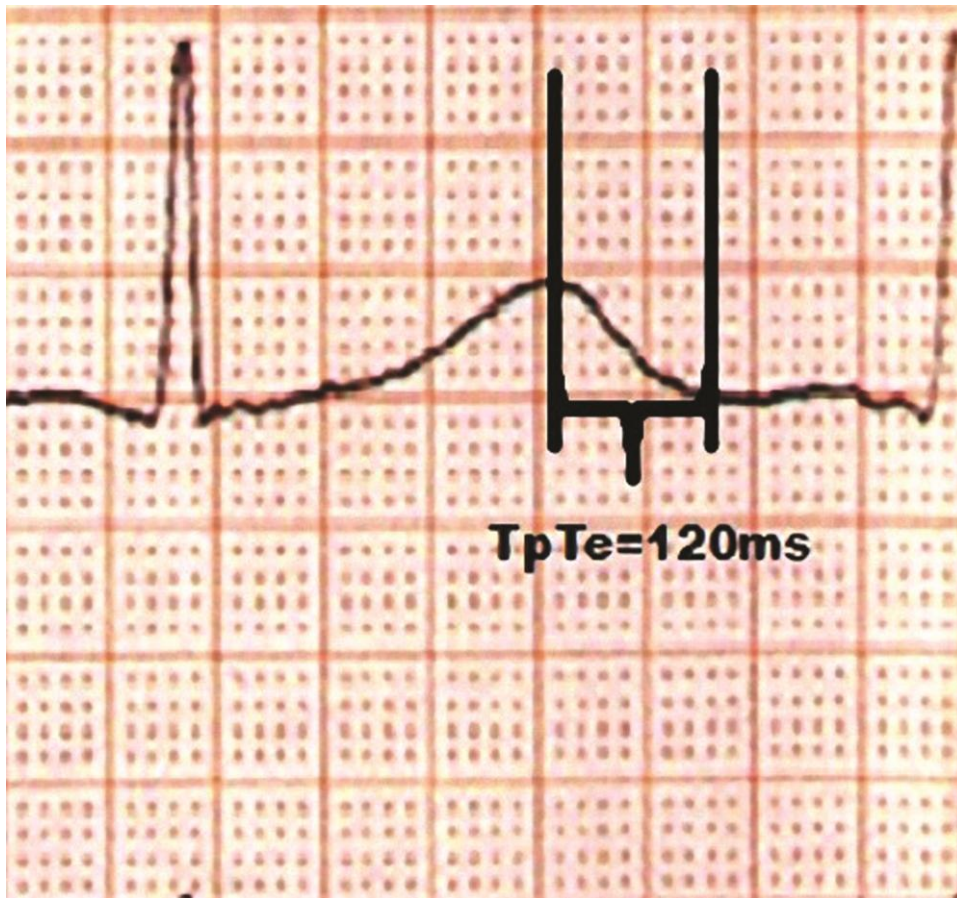
ECG from a patient with prolonged time from peak T-wave to end of T-wave by the tail method. This patient experienced ventricular arrhythmias during follow up. The left vertical line representing T wave peak and the right vertical line representing T wave end. The time between the two lines is TpTe measured by the tail method.

Figure 2

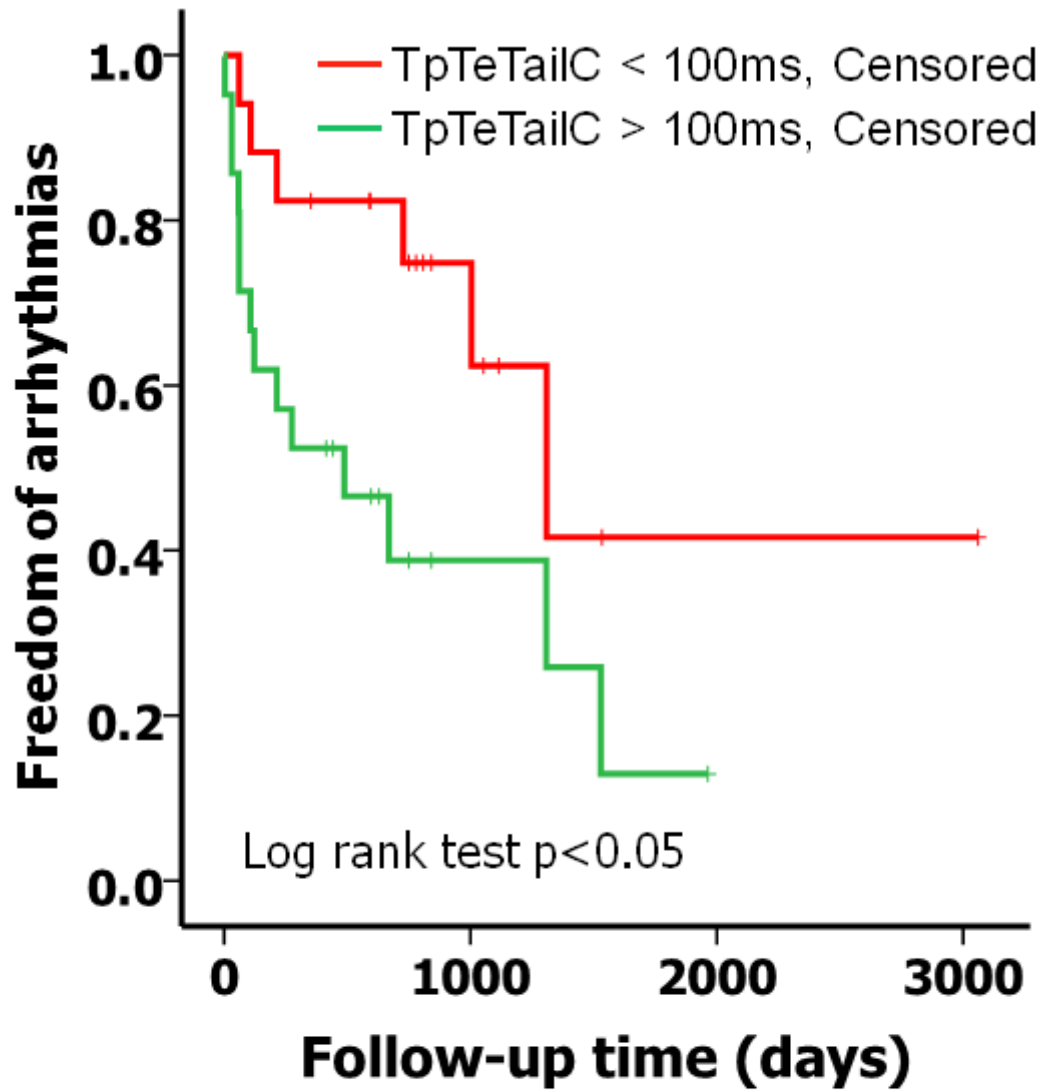Kaplan Meier analyses in 76 patients after myocardial infarction with ICD
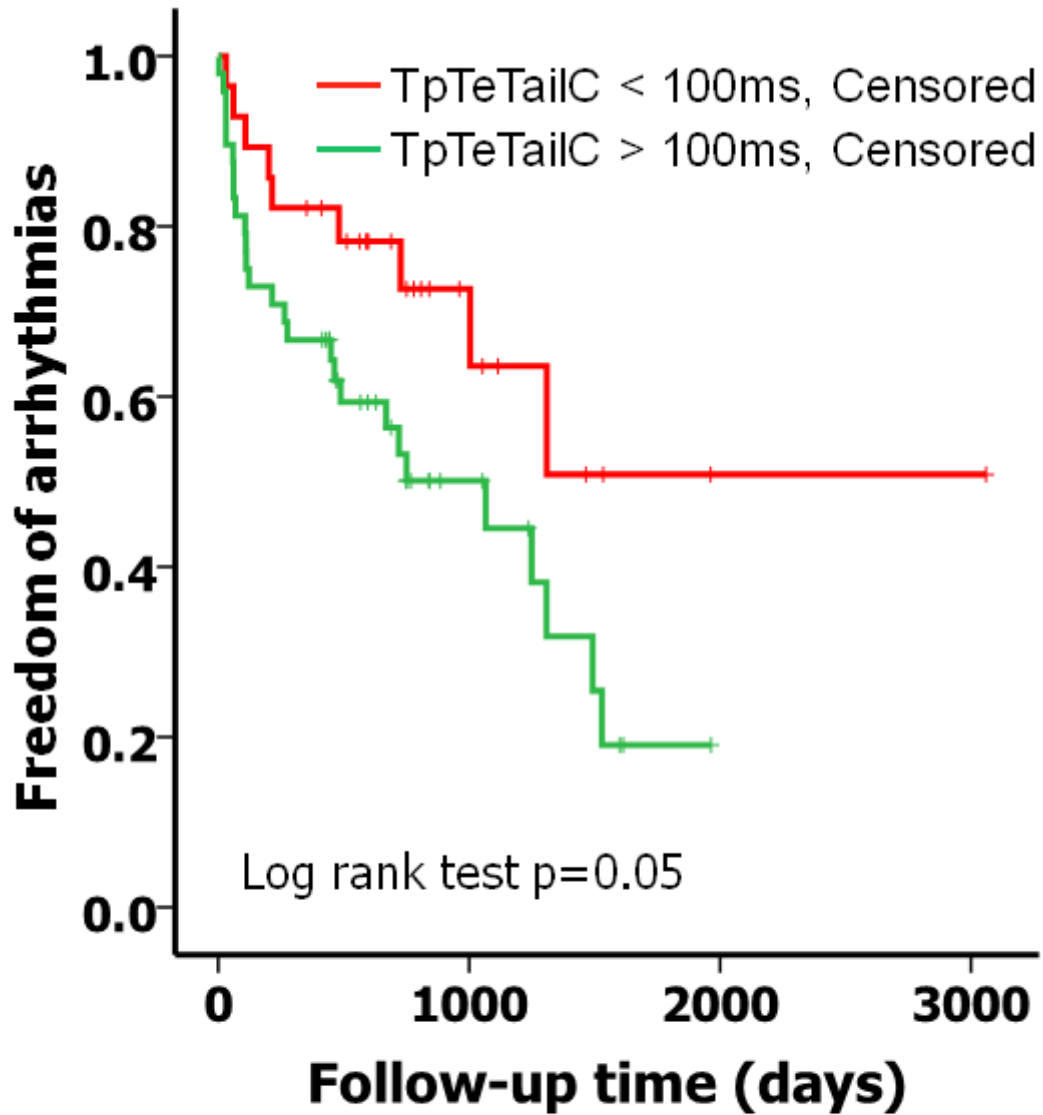
Kaplan Meier curves showing freedom of ventricular arrhythmias in patients after myocardial infarction. Patients with TpTeTailC > 100 ms (green curve) had more

arrhythmic events compared to patients TpTeTailC < 100 ms (red curve) (p=0.05) during

23±19 months of follow up.

Figure 3

Kaplan Meier analyses in 38 patients after myocardial infarction with ICD and with EF > 35 %.

No.at risk				
< 100ms	17	13	11	11
> 100ms	21	9	8	8

Kaplan Meier analyses in 38 patients after myocardial infarction and ejection fraction > 35 %. Patients with TpTeTailC > 100 ms (green curve) had more arrhythmic events compared to patients with TpTeTailC < 100 ms (red curve) ($p < 0.05$) during 23 ± 19 months of follow up.