Original Article

Association of Increased $T_{peak\text{-}to\text{-}end}$/QT ratio with Malignant Ventricular Arrhythmias in Acute Anterior ST-Segment Elevation Myocardial Infarction

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Abstract::

Background: **Increased $T_{peak\text{-}to\text{-}end}$/QT ratio on 12 lead surface electrocardiogram (ECG) has been shown to be the predictor of arrhythmogenesis in various cardiac disorders. There is limited data regarding association of these two parameters with malignant ventricular arrhythmias (MVA) in acute ST-segment elevation myocardial infarction (STEMI) patients.** ***Objectives:*** **This study was conducted to evaluate association of increased $T_{peak\text{-}to\text{-}end}$/QT ratio with MVAs in acute anterior STEMI.** ***Methods:*** **178 patients with acute anterior STEMI admitted within 12 hours of onset of chest pain into the Coronary Care Unit, Department of Cardiology, National Institute of Cardiovascular Diseases, Dhaka, were enrolled from November 2015 to October 2016. $T_{peak\text{-}to\text{-}end}$/QT ratio was calculated from surface ECG at the time of admission. The patients were divided into two groups, group I and II according to normal (≤0.25) and increased $T_{peak\text{-}to\text{-}end}$/QT ratio (>0.25). Each group was monitored for development of MVAs for the first 48 hours of myocardial infarction.** ***Results:*** **MVAs were significantly higher in group II than group I (19.5% vs 3.1%, p<0.001). Multivariate regression analysis showed significant association (p=0.002) of increased $T_{peak\text{-}to\text{-}end}$/QT ratio with MVAs (Odds Ratio, 3.845).Receiver operating characteristic (ROC) curve analysis showed that $T_{peak\text{-}to\text{-}end}$/QT ratio <0.25 had a negative predictive value of 96.88% for the prediction of MVAs.** ***Conclusion:*** **The study demonstrated that there was significant association of increased $T_{peak\text{-}to\text{-}end}$/QT ratio with malignant ventricular arrhythmias in acute anterior STEMI patients. Thus analysis of 12 lead surface ECG on admission may help predict malignant ventricular arrhythmias in the first 48 hours of acute anterior myocardial infarction and close monitoring with prompt management may be ensured in high risk patients.**

Key words:Acute anterior ST-segment elevation myocardial infarction, malignant ventricular arrhythmia, $T_{peak\text{-}to\text{-}end}$/QT ratio.

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Introduction:

Sudden cardiac death (SCD) causes approximately 800,000 deaths each year in the world[1]. It is often the first manifestation and responsible for 50% of the mortality of cardiovascular disease[2]. It is often caused by malignant ventricular arrhythmias (MVA). Among patients admitted with acute ST-segment elevation myocardial infarction (STEMI), 2-20% suffer from MVAs during first few hours of a sustaining myocardial infarction (MI) [3, 4]. In most cases, MVAsconsist of ventricular fibrillation (VF), or less frequently, by monomorphic or polymorphic ventricular tachycardia (VT) and Torsades de Pointes[5].

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Anterior myocardial infarction (MI) carries the worst prognosis of all infarct locations, mostly due to larger infarct size. A study comparing outcomes from anterior and inferior MI found that on average, patients with anterior MI had higher incidences of in-hospital mortality (11.9 vs 2.8%), total mortality (27 vs 11%), heart failure (41 vs 15%) and significant ventricular ectopics (70 vs 59%) compared to patients with inferior MI[6].

Various electrocardiographic(ECG) indices have been proposed as risk predictors in patients with MI e.g. T wave alternans[7], heart rate (HR) turbulence[8], decreased HR variability[9], prolonged QT interval (QT), increased QT dispersion[10]. But these ECG markers have prognostic values usually 6-8 weeks after acute MI.

$T_{peak\text{-}to\text{-}end}$/QT ratio ($T_{p\text{-}e}$ /QT ratio) has been suggested as more accurate measure for the dispersion of ventricular repolarization compared to other parameters and is independent from heart rate alterations[11, 12]. This ratio is a novel index to predict cardiac arrhythmias[13]. It includes the values of transmural dispersion ($T_{p\text{-}e}$) and spatial dispersion (QT) of ventricular repolarization. $T_{p\text{-}e}$ /QT ratio measured in healthy population in precordial lead V6 which best reflects the trasmural axis of left ventricle has a mean value of 0.21 ±0.03 and a range of value from 0.15 to 0.25[11].

Increased $T_{p\text{-}e}$ /QT ratio represents a period of potential vulnerability to reentrant ventricular arrhythmias[14]. Underlying mechanisms to explain modification ofthis indicators in acute myocardial ischemia include an expression of cardiac M cells properties. Activation of Mcells determines an increase in the action potentialin the heart and subsequently QT interval and $T_{p\text{-}e}$ prolongation[15, 16, 17].Other proposed mechanisms arethe reduction in epicardial temperature[18], acidosis[19] and changes in sodium and potassium currents[20].

In the past years, some studies have shown $T_{p\text{-}e}$ /QT ratio as predictors of malignant ventricular arrhythmias in patients with ST-segment elevation myocardial infarction (STEMI)[21,22,23].

There is no data in our country regarding association of this ECG parameter with malignant arrhythmia in acute anterior STEMI setting till date.

Methods:

178 patients with acute anterior ST-segment elevation myocardial infarction (STEMI) admitted within 12 hours of onset of chest pain into the coronary care unit (CCU) of National Institute of Cardiovascular Diseases (NICVD), Dhaka and receiving thrombolyticswere studied from November 2015 to October 2016. Patients with prior MI, acute left ventricular failure and cardiogenic shock; valvular heart disease, congenital heart disease and cardiomyopathy; prior pacemaker implantation; previous

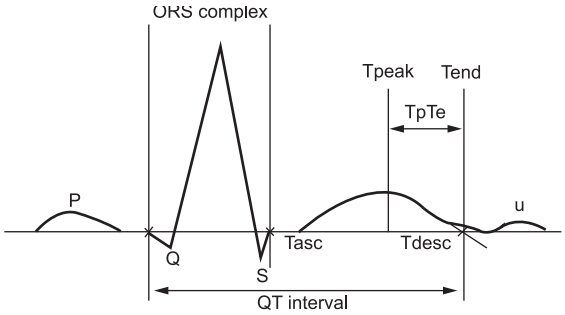


Fig.-1: *Electrocardiographic parameters measured when assessing the QT interval and $T_{p\text{-}e}$ interval*

history of any arrhythmias, abnormal electrolyte values, bundle branch block, patients on medications affecting QT and $T_{p\text{-}e}$ intervals such as antibiotics, tricyclic antidepressants, antihistaminics, antipsychotics and antiarrhythmics; family history of sudden cardiac death and ECGs without clearly analyzable $T_{p\text{-}e}$ interval and QT segment were excluded from the study. Study population were divided into two groups on the basis of $T_{p\text{-}e}$ /QT ratio: Group I: Normal $T_{p\text{-}e}$ /QT ratio &Group II: Increased $T_{p\text{-}e}$ /QT ratio. In the study, group I consisted of 96 subjects and group II consisted of 82 subjects.

Informed written consent and meticulous history were taken and detailed clinical examination was done and recorded in pre designed data collection sheet. Demographic data profile was recorded: age, sex. Cardiovascular risk factors were determined e.g. smoking, hypertension (HTN), diabetes mellitus (DM), dyslipidemia and family history of premature CAD. Clinical profile: pulse, blood pressure, respiratory rate, precordial examination findings were recorded. Baseline investigations like blood sugar, serum creatinine and serum electrolytes were done.

12 lead resting ECG was done at a paper speed of 25 mm/s and 10mm standardization on admission with subject in supine position by Fukuda Denshi Cardimax FX-2111 Electrocardiograph, Fukuda Denshi Co., Ltd., Japan.The resting heart rate was measured from the ECG data. ECG measurements of QT and $T_{p\text{-}e}$ intervals were performed manually by the investigator, using slide calipers and a magnifying glass to decrease measurement errors. In case of a difference of >20 ms in each measurement, an agreement was obtained after consulting an electrophysiologist who was blinded to the patients.The average value of three examinations was calculated.The QT interval was measured from the earliest onset of the QRS complex to the point at which the tangent of the maximal downslope of the descending limb of the T wave crossed the isoelectric baseline.

The QT interval was corrected for heart rate using Bazett's formula. The QT_{peak} (QT_p) interval was measured from the onset of the QRS complex until the maximal deflection

of the T wave. The T_{p-e} interval was calculated as the difference between the corresponding lead QT interval and the QT_p interval. The T_{p-e} /QT ratio was calculated as the ratio of T_{p-e} in that lead to the corrected QT interval.

If a U wave followed the T wave, the nadir between the T wave and the U wave was considered T-wave offset. The precordial lead V6 was selected because it best reflects the transmural axis of the left ventricle. If lead V6 was not suitable, leads V5 and V4 were measured. If the T-wave amplitude was < 1.5 mm in a particular lead, then that lead was excluded from the analysis. Increased T_{p-e} /QT ratio was defined as T_{p-e} /QT ratio ≥0.25.

The patients were followed up for the first 48 hours of MI with continuous monitoring in coronary care unit (CCU) & serial ECGs, for any development of malignant ventricular arrhythmias or symptoms. The continuous ECG monitorings of the study subjects were saved in the central monitoring system (model: Hypervisor VI, V-38108371, 2013-11, ver 1.3, Shenzhen Mindray Bio-Medical Electronics Co., Ltd., China). The recorded data was reviewed to note down any arrhythmic events. The patients were treated as per hospital protocol of treatment of acute STEMI.

The numerical data obtained from the study were analyzed and significance of differences were estimated by using statistical methods. The SPSS Statistical Software categorical (23.0 version, IBM SPSS Corporation, Armonk, New York, USA) was used for data analysis. Continuous variables were expressed in mean & standard deviation and categorical variables as frequency and percentage. Quantitative variables were analyzed by Student's t-test and Categorical variables were analyzed by Chi-square test and Fisher's exact test. Multiple logistic regression analysis was performed to establish T_{p-e} /QT ratio as the determinant of malignant ventricular arrhythmias. P value of less than 0.05 was considered as significant. Receiver operating characteristic (ROC) curve analysis was performed to assess sensitivity and specificity of T_{p-e} /QT ratio as a predictor of malignant ventricular arrhythmias.

Results:

Among 178 patients, 96 patients belonged to group-I and 82 patients belonged to group-II. The mean age of group I was 52.60±11.29 years and group II was 51.59±11.17 years. Male patients were predominant (80.2% vs 93.9%) in both groups. The highest percentage of study population had history of smoking (76% vs. 84%), followed by hypertension (47% vs. 48%), diabetes mellitus (38% vs. 28%), family history of premature CAD (29% vs 33%) and dyslipidemia (17% vs 18%) in group I and group II respectively. Among group I subjects, pulse was 86.61±12.49 beats per minute, systolic and diastolic blood pressure were 118.07±21 mmHg and 76.04±10.76 mmHg respectively. Among group II, pulse, systolic blood pressure and diastolic blood pressure were 89.26±16.99 beats per minute, 108.48±22.07 mmHg and 73.54±12 mmHg respectively.The mean T_{p-e}/QT ratio was 0.196±0.029 in group I and 0.309±0.053in group II. There was statistically significant difference between both groups regarding T_{p-e}/ QT ratio (p<0.001). Sustained VT (7.9%) occurred more than VF (2.8%) among those having malignant ventricular arrhythmias (10.7%). The mean T_{p-e}/QT ratio was 0.297±0.067 in arrhythmic patients and 0.242±0.068 in non-arrhythmic patients and difference was statistically significant between those two groups (p=0.001). Multivariate logistic regression analysis for characteristics of factors likely to cause malignant ventricular arrhythmia revealed, T_{p-e}/QT ratio was the independently significant predictors of malignant ventricular arrhythmia with odds ratio (OR) being 3.845.Receiver operating characteristic (ROC) curve for the relationship ofT_{p-e}/QT ratio with malignant ventricular arrhythmias showed, the value of the area under the curve (AUC) was 0.730 (95% confidence intervals (CI), 0.621–0.839). Sensitivity of T_{p-e}/QT ratio was high (78.95% vs 84.21%). Negative predictive value of T_{p-e}/QT ratio at value ≤0.25 was 96.88%.

Table-I

Age distribution of the study population (n=178).

Age in years	Group I (n=96)		Group II (n=82)		Total(n=178)		p value
	Number	%	Number	%	Number	%	
21-30	04	4.2	03	3.7	07	7.9	
31-40	13	13.5	10	12.2	23	25.7	
41-50	31	32.3	33	40.2	64	72.5	
51-60	28	29.2	23	28.0	51	57.2	
61-70	17	17.7	12	14.6	29	32.3	
>70	03	3.1	01	1.2	04	4.3	
Mean ± SD (Range)	52.60(±11.29)		51.59(±11.17)		52.13(±11.13) (25-85)		0.71^{ns}

Group I: Acute Anterior STEMI patients with normal T_{p-e} /QT ratio
Group II: Acute Anterior STEMI patients with Increased T_{p-e} /QT ratio
ns= not significant (p>0.05)
p value reached from unpaired t-test.

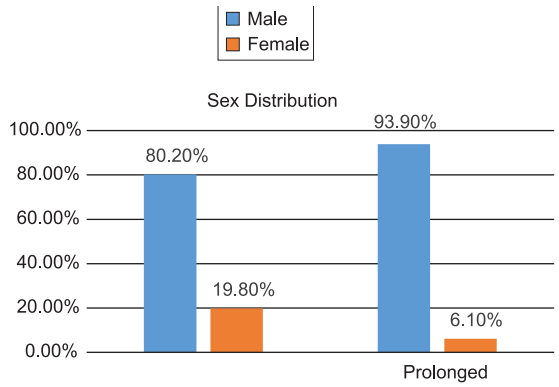


Fig.-2: *Sex distribution among the study population.*

Table-II

Distribution of risk factors of the study population (n=178).

Risk Factors		Group I(n= 96)		Group II(n=82)		Total(n=178)		p value
		Number	%	Number	%	Number	%	
Smoking								
	Yes	73	76.0	69	84.0	142	80.0	0.47^{ns}
	No	23	24.0	13	16.0	36	20.0	
Hypertension								
	Yes	45	47.0	39	48.0	84	47.0	0.92 ^{ns}
	No	51	53.0	43	52.0	94	53.0	
Diabetes mellitus								
	Yes	36	38.0	23	28.0	59	33.0	0.20^{ns}
	No	60	62.0	59	72.0	119	67.0	
Dyslipidemia								
	Yes	16	17.0	15	18.0	31	17.0	0.84 ^{ns}
	No	80	83.0	67	82.0	147	83.0	
Family H/o of premature CAD								
	Yes	28	29.0	27	33.0	55	16.0	0.62^{ns}
	No	68	71.0	55	67.0	123	84.0	

Table-III

Distribution of the study population according to clinical examination (n=178).

Parameters	Group I(n= 96)	Group II(n=82)	p value
	Mean ± SD	Mean ± SD	
Pulse/minute	86.61(±12.49)	89.26(±16.99)	0.235^{ns}
Systolic blood pressure (mmHg)	118.07 (±21)	108.48(±22.07)	0.003^{s}
Diastolic blood pressure (mmHg)	76.04 (±10.76)	73.54(±12)	0.148^{ns}

Table-IV

Distribution of ECG parameters of the study population (n=178).

ECG parameters	Group I (n= 96)	Group II (n=82)	p value
	Mean ± SD	Mean ± SD	
Heart rate (beats per minute)	91.41(±19.53)	89.09 (±20.82)	0.444
QT interval (millisecond)	444.99 (±60.52)	450.33 (±86.72)	0.631
T_{p-e}/QT Ratio	0.196(±0.029)	0.309(±0.053)	<0.001^{s}

Table-V

Distribution of occurrence of malignant ventricular arrhythmias among the study population (n=178).

Malignant Ventricular	Group I(n=96)		Group II(n=82)		Total		p value
Arrhythmia	No.	%	No.	%	No.	%	<0.001[s]
Present	03	3.1	16	19.5	19	10.7	
Absent	93	96.9	66	80.5	159	89.3	

Table-VI

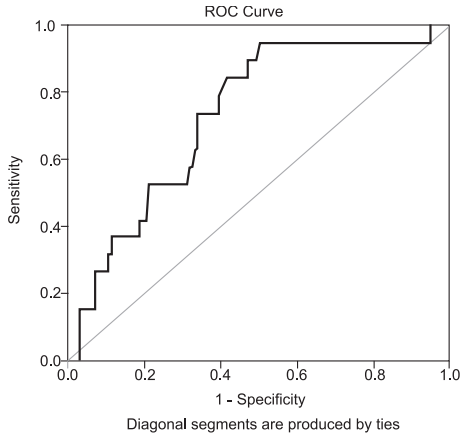
Distribution of ECG parameters of the study population depending on occurrence of malignant ventricular arrhythmias (n=178).

Parameters	Malignant ventricular arrhythmia		p value
	Yes(n=19) Mean ±SD	No(n=159) Mean ±SD	
Heart Rate (beats per minute)	90.32 (±28.05)	90.34 (±19.06)	0.996[ns]
QT interval (ms)	436.53 (± 77.25)	448.76 (73.27)	0.495[ns]
T_{p-e} /QT ratio	0.297 (±0.067)	0.242 (±0.068)	0.001[s]

Table-VII

Multivariate logistic regression analysis for determinants of malignant ventricular arrhythmias.

Variables of interest	Multivariate	
	OR (95% CI)	P value
Age (>45 years)	0.577 (0.218-1.526)	0.268[ns]
Sex	0.733 (0.158-3.393)	0.691 [ns]
Smoking	1.470(0.151-2.118)	0.998[ns]
Hypertension	2.086 (0.755-5.763)	0.156 [ns]
Diabetes mellitus	2.90(0.810-10.381)	0.102 [ns]
Dyslipidemia	1.896 (0.415-8.665)	0.409 [ns]
Family history of premature CAD	1.284 (0.439-3.762)	0.648 [ns]
Heart rate	0.995 (0.338-2.930)	0.993 [ns]
QT interval	0.576 (0.216-1.539)	0.271[ns]
T_{p-e}/QT ratio	3.845(1.321-11.193)	0.002[s]



Null hypothesis: true area = 0.5

Fig.-3: *Receiver operating characteristic (ROC) curve for the relationship of T_{p-e}/QT ratio with malignant ventricular arrhythmias.*

Table-VIII

Sensitivity, specificity, positive and negative predictive value and accuracy of T_{p-e}/QT ratioas predictors of malignant ventricular arrhythmias.

Performance	T_{p-e}/QT ratio(>0.25)
Sensitivity	84.21%
Specificity	58.49%
Positive predictive value	19.51%
Negative predictive value	96.88%
Accuracy	61.24%

Discussion:

An electrocardiogram (ECG) is a cost effective, easily available, non-invasive and bedside diagnostic tool that may be obtained within 10 minutes after arrival of patients with a history of chest discomfort consistent with acute

coronary syndrome[24]. Increased T_{p-e}/QT ratio have been associated with increased risk of ventricular arrhythmias in congenital as well as in acquired long-QT syndromes[25], in hypertrophic cardiomyopathy with troponin I mutations[26] and in patients with the Brugada syndrome[27].

In this study, the mean age of the study population was 52.13±11.13 years ranging from 25 to 85 years. Chowdhury et al[28] found that among 4500 cases of first MI admitted into NICVD, mean age of the patients was 53±10 years.Male patients were predominant among the study population. This was consistent with previous studies in Bangladesh by which the percentage of male patients were 85-92 %[29,30].

In the study, smoking was the most prevalent risk factor (76% vs 84%) in group I and group II study population. The second most prevalent risk factor was hypertension (47% vs 48%), followed by diabetes mellitus (38% vs 28%), positive family history of premature CAD (29% vs 33%) and dyslipidemia (17% vs 18%) between group I and II. Rahman and Zaman[31] have reported that, 79.7% cases of CAD were either current or past consumers of some form of tobacco.

Among the group I patients, the pulse, systolic blood pressure and diastolic blood pressure in mmHg were 86.61±12.49 per minute, 118.07±21mmHg and 76.04±10.76 mmHg respectively. Among group II, the pulse, systolic and diastolic blood pressure in mm of Hg were 89.26±16.99 per minute, 108.48±22.07 mmHg and 73.54±12 mmHg respectively. Abu Sayeed et al[32] have reported that mean systolic blood pressure and diastolic blood pressure in mm of Hg were 128±29 mmHg and 80±15 mmHg respectively among patients with coronary artery disease. The difference of blood pressures can be explained by the presence of an acute state in the study population.

There was no significant difference regarding heart rate (91.41±19.53 vs. 89.09±20.82 per minute) and QT interval (444.99±60.52ms vs. 450.33±86.72 ms) between group I and II. Mugnai et al[23] have found mean heart rate among anterior STEMI patient was 82 ± 18 beats per minute and mean QT interval 453 ± 39 ms, which were consistent with findings of this study.

The mean T_{p-e}/QT ratio was 0.196±0.029 in group I and 0.309±0.053 in group II. There was significant difference between the two groups regarding T_{p-e}/QT ratio (p<0.001). Malignant ventricular arrhythmias occurred in 19 patients (10.7%) out of 178. There was significant difference regarding occurrence of MVA between the groups I and II (p <0.001). MVA occurred in 03 (3.1%) subjects of group. In group II, 16 (19.5%) subjects developed MVA.

The mean T_{p-e}/QT ratio was 0.297±0.067 in arrhythmic patients and 0.242±0.068 in non-arrhythmic patients (p=0.001). Shu et al[21] have observed Tp-e/QT ratio was significantly increased (0.32±0.07 *vs.* 0.26±0.05) in those patient with STEMI having arrhythmia compared to those having no arrhythmia.Mugnai et al[23] have reported mean T_{p-e} was 149 ±41ms in subjects with MVA and 123 ± 34 msin subjects without MVA. The mean T_{p-e}/QT Ratio was 0.38 ± 0.10 in arrhythmic patients and 0.31 ± 0.08 in subjects without arrhythmia. Shenthar et al[22] have found mean T_{p-e}/QT Ratio0.41±0.09 in arrhythmic patients and 0.26±0.02 in subjects without arrhythmia.In another study, Zhao et al[33] have reported T_{p-e}/QT ≥0.29 was able to independently predict both in-hospital death (21.9% vs. 2.3%, p<0.001) and main adverse cardiac events (48.1% vs. 15.3%, p<0.005) in a population of 338 patients with STEMI treated by PCI and also after discharge. T_{p-e} /QT was significantly higher in patients with life-threatening arrhythmias compared with those without major arrhythmic events (0.38±0.10 and 0.31±0.08, p=0.02). Gupta et al[11] have found increased T_{p-e} /QT among in leads with ST elevation to be prolonged in a cohort of 32 patients with acute STEMI as compared with normal subjects. The difference of T_{p-e} and T_{p-e}/QT ratio in this study with other studies may be explained by difference in extent of myocardial injury and severity of MI in different study populations and different settings.

Multivariate logistic regression analysis revealed that after adjusting the individual risk factors, T_{p-e}/QT ratio have significant association with malignant ventricular arrhythmias (p=0.002). Odds ratio for T_{p-e}/QT was 3.845 with 95% confidence interval (1.321-11.193).

Receiver Operating Characteristic (ROC) curve showed that area under ROC curve was 0.730 (95% CI=0.621–0.839) in predicting the major arrhythmic events.

The sensitivity, specificity and negative predictive value for T_{p-e}/QT ratio at >0.25 was84.21%, 58.49% and 96.88%. Mugnai et al[23] have found T_{p-e}/QT ratio of 0.31 showed the best combined sensitivity and specificity (69.7% and 63.7%), respectively, along with negative predictive value of 92%. Shenthar et al[22] have found that T_{p-e}/QT ratio<0.3 had a negative predictive value of 100%.

Thus the results of the study suggested that there was significant association of increased T_{p-e} /QT ratio with malignant ventricular arrhythmias in acute anterior STEMI population.

Conclusion:

The study demonstrated that increased$T_{peak-to-end}$/QT ratio were associated with malignant ventricular arrhythmias in acute anterior ST-segment elevation myocardial infarction. This parameter may represent simple and useful marker in predicting increased risk of in-hospital malignant arrhythmias among patients with anteriorST-segment elevation myocardial infarction and to take prompt measures to prevent arrhythmias. But the study had limitations e.g. number of study population was limited to generalize the results, sampling method was purposive, so there was risk of selection bias.It was conducted in a single center. ECG was assessed by visual observation and despite repeated measurements, there was a few chance of intra observer variation.The study excluded patients hospitalized after 12 hours of chest pain, patients not receiving thrombolytics and patients undergoing primary PCI. Thus association of this ECG parameters with malignant ventricular arrhythmias could not be established in all patients with acute anterior STEMI.Further prospective, randomized andmulti-center studies are needed to confirm these resultsand to define optimal cut-offs of $T_{peak-end}$ and $T_{peak-end}$ /QT ratio. Other studies are also required to evaluate role of urgent revascularization in patients with prolonged $T_{peak-end}$ and increased $T_{peak-end}$ /QT ratio.

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