

Original Article

Comparisons of QTd and QTcD and Arrhythmia Prevalence Between Fibrinolytic Therapy and Primary Percutaneous Coronary Intervention

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ABSTRACT

Background: The inter-lead variations in the measurements of the QT interval reflect regional variations in ventricular repolarization. This increased dispersion results in susceptibility to ventricular arrhythmias.

Methods: We reviewed the medical records of 60 patients with ST-segment-elevation myocardial infarction (STEMI) over the last 6 years who received thrombolytic therapy (30 cases) or underwent primary percutaneous coronary intervention (PCI) (30 cases) in Ghaem Hospital and Emam Reza Hospital in Mashhad, Iran. The patients' demographic characteristics, risk factors, treatment success, QTd and QTcD before and 24 hours after treatment, arrhythmias, and echocardiographic information were analyzed. Statistical analysis was conducted using the SPSS software, version 22, and a *P* value of less than 0.05 was considered statistically significant.

Results: The success rates (50% reduction in ST-segment elevation) of primary PCI and thrombolytic therapy were 66.66% and 33.33%, respectively. In addition, QTd and QTcD were significantly decreased in both successful procedures (*P* = 0.04 and 0.03, respectively). However, no significant difference in the variations of QTd and QTcD was seen between the 2 successful procedures (*P* = 0.91 and *P* = 0.87, respectively). Further, ventricular arrhythmias were evident in 36.6% of the patients with thrombolytic therapy, but no ventricular arrhythmia was observed in those who underwent primary PCI.

Conclusions: QTd and QTcD were identified as useful predictors of ventricular arrhythmias. A significant reduction in QTd and QTcD in both successful procedures was evident, leading to a decrease in ventricular arrhythmias. Moreover, the success rate of primary PCI was higher than that of thrombolytic therapy. Therefore, primary PCI was identified as a more appropriate procedure for STEMI. (*Iranian Heart Journal 2020; 21(3): 15-24*)

KEYWORDS: QTcD, QTd, Myocardial Infarction, Primary PCI

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Received: April 15, 2019

Accepted: June 2, 2019

Despite advances in diagnosis and management, ST-segment-elevation myocardial infarction (STEMI) remains a major public health concern in the industrialized world and developing countries. Each year in the United States alone, more than 1 million patients are hospitalized for MI or coronary artery disease. The rate of MI rises sharply in both men and women with increasing age, and racial differences exist, with MI occurring more frequently in black men and women than in white people, regardless of age.

Between 1999 and 2008, the proportion of patients with acute coronary syndrome and STEMI declined by almost 50% (47.0% to 22.9%).

The overall number of deaths from STEMI has declined steadily over the past 30 years, but it has stabilized over the past decade. Both a decreased incidence of STEMI and a decline in the case-fatality rate after STEMI have contributed to this trend.¹⁻³

The care of patients with STEMI has transformed in conjunction with major shifts in the approach to reperfusion therapy from primarily pharmacologic to catheter-based strategies.

The presence of ST-segment elevation on the electrocardiogram (ECG) in a patient with ischemic discomfort highly suggests thrombotic occlusion in an epicardial coronary artery and should trigger a rapid assessment of the patient for the initiation of a reperfusion strategy. The critical factors that weigh into the selection of a reperfusion strategy include the time elapsed from the onset of symptoms, the risk associated with STEMI, the risk related to the administration of a fibrinolytic, and the time required to initiate an invasive strategy.⁴⁻⁶

Although late spontaneous reperfusion occurs in some patients, thrombotic occlusion persists in most patients with STEMI. Timely reperfusion of jeopardized myocardium is the

most effective way of restoring the balance between myocardial oxygen supply and demand. Myocardial salvage is dependent on the time elapsed until treatment with either fibrinolysis or percutaneous coronary intervention (PCI).⁷

Heterogeneity in refractoriness and conduction velocity is a hallmark of reentrant arrhythmias. One index of the heterogeneity of ventricular conduction is derived from the QRS complex duration on surface ECG leads, while the heterogeneity of ventricular refractoriness can be found in differences in the length of the QT interval. Dispersion indices usually measure the maximum difference (shortest to longest) in intervals between the leads, which may be adjusted for heart rate and the number of leads sampled (eg, when the T wave is flat in some leads for the QT dispersion). Abnormally high QRS and QT dispersion have been correlated with the risk for overall mortality and arrhythmic death in patients with various disorders, although the results are not consistent.

Different techniques exist for determining dispersion (including automated algorithms), and the results of one study are often difficult to compare with those of another; in addition, the tests are sensitive to a variety of factors including age, the time of day, the season of the year, and even body position. More recently, the T-wave morphology and the assessment of the interval from the T-wave peak to end in lead V₅ have been correlated with increased sudden death risk.

Overall, assessments of these indices have not gained popularity as useful clinical tools. Other details of the QRS complex such as the fragmentation of the conducted complex (multiple notches in the QRS) and the simple width of premature ventricular contractions have been associated with an increased cardiovascular risk.⁸⁻¹⁰

There is some controversy concerning the behavior of the heart rate-corrected QT

interval (QTc) after STEMI. While some studies have reported an increase in QTc in the acute phase followed by a decrease after reperfusion, others have reported increased QTc, associated with non-reperfusion.^{11, 12} The QTc dispersion (QTcD) is reduced in patients with successful fibrinolytic therapy and decreased in non-revascularized patients. A reduction in QTcD after fibrinolysis is predictive of coronary reperfusion.¹³

METHODS

Sixty patients in the educational hospitals of Emam Reza and Ghaem (2016–2018) with STEMI based on the STEMI criteria (Table 1 & Table 2) were divided into 2 groups and candidated for reperfusion therapy: primary PCI or fibrinolytic therapy

All the patients' demographic characteristics and cardiac risk factors such as a family history of cardiovascular disease, diabetes mellitus, hypertension, smoking, and dyslipidemia were recorded.

In the fibrinolytic group, all contraindication criteria were checked based on Table 2-2.

Table 1: Electrocardiographic manifestations of myocardial infarction

Electrocardiographic Manifestations of Acute Myocardial Ischemia (in the Absence of Left Bundle Branch Block)	
ST-Elevation	
New ST-elevation at the J point in 2 contiguous leads with the following cut points:	
<ul style="list-style-type: none"> • ≥ 0.1 mV in all leads (except V_2-V_3) • In leads V_2-V_3 the following cut points apply: <ul style="list-style-type: none"> • ≥ 0.2 mV in men ≥ 40 y • ≥ 0.25 mV in men < 40 y • ≥ 0.15 mV in women 	
ST Depression and T-Wave Changes	
New horizontal or downsloping ST depression ≥ 0.05 mV in 2 contiguous leads	
<ul style="list-style-type: none"> • T-wave inversion ≥ 0.1 mV in 2 contiguous leads with a prominent R wave or R/S ratio > 1 	
Electrocardiographic Manifestations of Ischemia in the Setting of Left Bundle Branch Block	
Electrocardiographic Criteria	Points
ST-segment elevation ≥ 1 mm and concordant with the QRS complex	5
ST-segment depression ≥ 1 mm in lead V_1 , V_2 , or V_3	3
ST-segment elevation ≥ 5 mm and discordant with the QRS complex	2
A score of ≥ 3 has a specificity of 98% for acute myocardial infarction	
Electrocardiographic Changes Associated With Previous Myocardial Infarction (in the Absence of Left Ventricular Hypertrophy and Left Bundle Branch Block)	
Any Q wave in leads V_2 - V_3 ≥ 0.02 s or a QS complex in leads V_2 and V_3	
Q wave ≥ 0.03 s and ≥ 0.1 -mV deep or QS complex in leads I, II, aVL, aVF, or V_4 - V_6 in any 2 leads of a contiguous lead grouping (I, aVL; V_1 - V_6 ; II, III, and aVF)	
R wave ≥ 0.04 s in V_1 - V_2 and R/S ≥ 1 with a concordant positive T wave in the absence of a conduction defect	

Based on the criteria from O'Gara PT, Kushner FG, Ascheim DD, et al 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e78

Table 2: Contraindications to and cautions in the use of fibrinolytics for treating ST-elevation myocardial infarction

Absolute Contraindications
Any previous intracranial hemorrhage
Known structural cerebral vascular lesions (eg, arteriovenous malformation)
Known malignant intracranial neoplasms (primary or metastatic)
Ischemic stroke within 3 months except for acute ischemic stroke within 4.5 hours
Suspected aortic dissection
Active bleeding or bleeding diathesis (excluding menses)
Significant closed-head or facial trauma within 3 months
Intracranial or intraspinal surgery within 2 months
Severe uncontrolled hypertension (unresponsive to emergency therapy)
For streptokinase, previous treatment within the previous 6 months
Relative Contraindications
History of chronic, severe, poorly controlled hypertension
Significant hypertension at initial evaluation (systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg)†
History of previous ischemic stroke > 3 mon
Dementia
Known intracranial pathology not covered in Absolute Contraindications
Traumatic or prolonged (>10 min) cardiopulmonary resuscitation
Major surgery (< 3 wk)
Recent (within 2–4 wk) internal bleeding
Noncompressible vascular punctures
Pregnancy
Active peptic ulcer
Oral anticoagulant therapy

Both Ghaem Hospital and Emam Reza Hospital in Mashhad, Iran, are tertiary and primary PCI-capable centers. The patients in the fibrinolytic group were chosen from admitted patients before this time, and this part of the study was retrospective. Accordingly, data were collected from the patients' recorded files in the archives of these hospitals.

ECG was recorded for the patients before and after any type of intervention until 24 hours after the procedure. QTc was calculated using the Bazett formula $QTc = QT / \sqrt{RR}$, with an upper limit of 460 ms. The QTc dispersion was calculated with this formula until 24 hours after any kind of intervention.

Patients were excluded if they met one of the following criteria: a previous history of known arrhythmia, bundle branch block, noncompliance in follow-up, previous MI, previous coronary artery disease, pacing rhythm, pre-excitation in basic ECG, severe

valvular heart disease, ventricular hypertrophy, electrolyte disturbance, and a history of antiarrhythmic drug consumption. All the recorded data were analyzed using the SPSS software, version 22, via the χ^2 test, the Fisher exact test, and the paired sample *t*-test. A *P* value of smaller than 0.05 was considered statistically significant.

RESULTS

The study population was comprised of 60 patients (9 women and 51 men). The demographic characteristics of all the patients are listed in Table 3-1. Additionally, MI localization in both groups is illustrated in Table 3-2.

Among 30 patients in the fibrinolytic group, echocardiographic data were available for 19 patients. A comparison of the echocardiographic ejection fractions is presented in Table 3-3.

The success rate based on an ST-elevation reduction of more than 50% in ECG and a reduction in chest pain was 66.66% in the primary PCI group and 33.33% in the fibrinolytic group. A comparison of the ECG data before and after the treatment between the 2 groups is presented in Table 3-4.

A comparison of the differences in QTd and QTcD between the successful and

unsuccessful interventions is presented in Table 3-5.

The differences in QTd and QTcD based on the ejection fraction are summed in Table 3-6.

A comparison of the effects of cardiac risk factors on QTd and QTcD between the 2 groups is presented in Table 3-7.

A comparison of QTd and QTcD based on MI localization is presented in Table 3-8.

Table 3-1: Prevalence of risk factors in the primary PCI and fibrinolytic groups

	Primary PCI Group	Fibrinolytic Group	P value
Sex	female: 5(16.78%)	female: 4(13.3%)	0.99
	male: 25(83.3%)	male: 26(86.7%)	
Age	60.97±12.93	54.76±12.39	0.65
Smoking	43.3%	43.3%	0.99
Dyslipidemia	23.3%	16.7%	0.52
Hypertension	33.7%	30%	0.78
Diabetes mellitus	20%	16.7%	0.74

PCI, Percutaneous coronary intervention

Table 3-2: Myocardial infarction localization in both groups

	Primary PCI Group	Fibrinolytic Group
Anterior	66.7%	26.7%
Anterolateral	13.3%	13.4%
Inferior	20%	59.9%

PCI, Percutaneous coronary intervention

Table 3-3: Comparisons of the echocardiographic ejection fraction between the primary PCI and fibrinolytic groups

	Primary PCI Group	Fibrinolytic Group
≥50%	3.3%	42.1%
40-50%	46.7%	42.1%
35-40%	20%	5.3%
≤35%	30%	10.5%

Among 30 patients in the fibrinolytic group, echocardiographic data were available for 19 patients.

PCI, Percutaneous coronary intervention

Table 3-4: Comparisons of the ECG data before and after the treatment between the primary PCI and fibrinolytic groups

	Primary PCI Group	Fibrinolytic Group
QTd	Before :73.21±24.04	78.67±30.14
	After:52.86±23.86	66.0±24.71
QTcD	Before :80.0±27.87	88.59±36.56
	After:57.41±25.36	76.03±29.28

PCI, Percutaneous coronary intervention

Table 3-5: Comparisons of the differences in QTd and QTcD between successful and unsuccessful interventions

		Primary PCI Group	Fibrinolytic Group	P value
QTd	successful	20.10±24.74	20.66±24	0.91
	unsuccessful	28.48±11.11	34.45±8.89	0.78
QTcD	successful	26.75±28.44	25.49±25.1	0.87
	unsuccessful	31.8±10.89	35.83±8.71	0.75

Due to the non-normal distribution of the parameters, the Mann–Whitney nonparametric test was used. In all the patients, successful interventions (either primary PCI or fibrinolytic therapy) had significant differences in terms of QTd ($P = 0.04$) and QTcD ($P = 0.03$) from unsuccessful interventions. PCI, Percutaneous coronary intervention

Table 3-6: QTd and QTcD differences based on the ejection fraction

	Primary PCI Group		Fibrinolytic Group		P value	
	QTd	QTcD	QTd	QTcD	QTd	QTcD
EF≤35%	15±27.77	22±33.79	30±14.14	23±2.12	0.18	0.09
35≤EF≤40%	16±26.58	18.83±36.47	0	7	0.57	0.86
40≤EF≤50%	25.83±21.06	25.01±25.71	2.5±36.15	5.62±40.98	0.24	.016
EF≥50%	20	17	20±21.38	21.13±25.48	0.89	0.89

There was no statistically significant difference between the 2 groups concerning QTd and QTcD based on the patients' ejection fraction. Recurrent premature ventricular contractions and ventricular tachycardia were detected in 2 of 30 (6.7%) patients. One (3.3%) patient exhibited accelerated idioventricular rhythms in the fibrinolytic group. There was no ventricular arrhythmia in the primary PCI group ($P = 0.01$).

PCI, Percutaneous coronary intervention; EF, Ejection fraction

Table 3-7: Comparisons of the effects of cardiac risk factors on QTd and QTcD between the primary PCI and fibrinolytic groups

			Primary PCI Group		Fibrinolytic Group	
Hypertension			QTd	QTcD	QTd	QTcD
Hypertension	Before	hypertensive	75.5±25.5	85.3±30.27	88.44±47.73	94.56±59.75
		non-hypertensive	72.29±29.3	76.88±28.51	79.16±19.62	85.9±21.2
	After	hypertensive	54±18.97	62.9±22.4	64.44±27.89	77.5±25.06
		non-hypertensive	52.22±29.69	54.18±27.07	66.67±23.94	73.78±37.81
Smoking	Before	smoker	67.27±18.49	71.73±19.61	72.31±33.20	80.08±36.63
		nonsmoker	77.06±26.87	85.69±31.70	83.53±27.6	94.59±36.39
	After	smoker	54.55±20.18	60.81±23.51	63.08±28.10	71.07±21.73
		nonsmoker	51.76±26.51	55.07±27.05	68.24±22.43	79.53±30.68
Dyslipidemia	Before	dyslipidemia	72±33.47	84.2±44.17	84±45.61	100.6±65.52
		non-dyslipidemic	73.48±22.48	79.05±24.18	77.06±27.28	86.08±29.02
	After	dyslipidemia	48±22.8	56.2±26.11	68±33.47	85±45.45
		non-dyslipidemic	53.91±22.45	57.6±25.8	65.6±23.47	74.17±25.77
Diabetes mellitus	Before	diabetic	62±22.8	68±22.43	72±54.04	88.8±74.7
		nondiabetic	75.65±24.09	82.73±28.7	80±24.49	88.57±26.53
	After	diabetic	48±10.59	60±18.97	72.3347	89.8±25.14
		nondiabetic	53.91±25.89	56.82±29.83	64.8±23.3	73.17±25.3

Significant differences were found in terms of QTd and QTcD in nonsmokers between the primary PCI group and the fibrinolytic group ($P = 0.04$ and $P = 0.01$).

Significant differences were found in terms of QTd and QTcD in non-hypertensive patients between the primary PCI group and the fibrinolytic group ($P = 0.01$ and $P = 0.01$).

Significant differences were found in terms of QTd and QTcD in non-dyslipidemic patients between the primary PCI group and the fibrinolytic group ($P = 0.01$ and $P = 0.02$). Significant differences were found in terms of QTd and QTcD in nondiabetic patients between the primary PCI group and the fibrinolytic group ($P = 0.02$ and $P = 0.03$). PCI, Percutaneous coronary intervention

Table 3-8: Comparisons of QTd and QTcD based on myocardial infarction localization

Myocardial Infarction Localization		Primary PCI Group		Fibrinolytic Group	
		QTd	QTcD	QTd	QTcD
Anterior	Before	71.43±24.14	79.4±29.98	76±36.27	84.5±37.6
	After	54.29±25.41	58±29.63	66±29.89	69.08±29.5
Anteroinferior	before	80±56.44	83±68.27	100±84.85	133±114.55
	After	60±51.33	73±55.92	90±42.43	116±55.15
Inferior	Before	78.33±27.14	81.5±24.81	77.65±19.85	85.25±21.99
	After	46.67±20.66	52.83±24.65	62.35±19.85	73.63±24.86

Significant differences were found in terms of QTd and QTcD in patients with anterior and inferior myocardial infarction between the primary PCI group and the fibrinolytic group ($P = 0.01$ and $P = 0.03$).

PCI, Percutaneous coronary intervention

DISCUSSION

Nikiforos et al^{11, 14} found that QTd and QTcD were significantly increased before thrombolysis/ percutaneous transluminal coronary angioplasty (PTCA) by comparison with the controls. An angiogram performed after thrombolysis showed adequate reperfusion (thrombolysis in myocardial infarction [TIMI] grade 2/3) in 20 patients, while in the other 20 patients, only TIMI 0/1 reperfusion was achieved. Thrombolysis-TIMI flow 2/3 and PTCA significantly reduced QTd (from 68 +/- 10 to 35 +/- 8 ms; $P < 0.001$, Δ QTd = 48 +/- 11%, in the thrombolysis-TIMI flow 2/3 group, and from 79 +/- 11 to 38 +/- 9 ms; $P < 0.001$, Δ QTd = 52 +/- 9%, in the PTCA group), while in the thrombolysis-TIMI flow 0/1 group, no significant changes were recorded. A 1% QTd decrease of more than 30 seconds had 96% sensitivity, 85% specificity, and 93% positive predictive value, and 94% negative predictive value, respectively, for TIMI 2/3 flow. A significant decrease in the QT dispersion may provide an additional ECG index for successful (TIMI 2/3) reperfusion. Wahab et al¹⁵ in 2009 found that the markers of the autonomic regulation of the heart such

as heart rate variability could provide valuable information about the future course of events in a patient following acute STEMI. They concluded that this finding could be utilized to plan the future course of management in patients, especially those predisposed to adverse and catastrophic outcomes.

Bonakdar et al¹⁶ in 2014 reported that type 2 diabetic patients with NSTEMI might have a greater QTc max. They also posited that QTcD and these QT parameters might have a relationship with worse cardiac outcomes and poorer prognoses.

Jiménez-Candil¹⁷ in 2009 found that -R after primary PCI could occur early and that it was closely related to the restoration of reperfusion at the microvascular level and could provide additional prognostic information.

Lancellotti et al¹⁸ in 2004 reported that the analysis of pre-discharge dobutamine stress ECG was useful for predicting residual stenosis in the infarct-related artery and contractile recovery in the affected area. The changes in the QT dispersion during the test were the most accurate parameters.

Eslami et al¹⁹ in 2013 showed that primary PCI was effective in reducing the degree of arrhythmogenic indices. They concluded

that ischemia-induced arrhythmias and T-wave peak to end were important arrhythmogenic parameters responding to successful primary PCI and might be used as markers for successful reperussions.

Pan et al²⁰ in 2011 showed that according to their multivariate analysis, absolute C change was an independent predictor for the development of major adverse cardiac events, with an odds ratio of 1.498 for each 10-ms decrement in absolute QTcD change (95% CI: 1.157 to 1.939, $P = 0.002$). In conclusion, the absolute QTcD change after primary PCI was an independent predictor of the development of major adverse cardiac events in patients with single-vessel disease and acute STEMI.

Chávez-González et al²¹ in 2017 showed that an increased QRS duration and dispersion implied a greater likelihood of ventricular arrhythmias in the early stages of acute MI than an increased duration and dispersion of QTc.

Heris et al²² in 2014 concluded that thrombolytic therapy did not increase the risk of arrhythmias.

Aziz et al²³ in 2010 reported that the markers of the autonomic regulation of the heart could confer valuable information about the future course of events in patients following acute STEMI.

Dotta et al²⁴ in 2018 showed that the regional dispersion of the QT interval corrected for heart rate (regional QTcD) was 60 minutes after thrombolysis ($P = 0.06$) in anterior wall infarction in patients with TIMI flow 3 and Blush grade 3 [T3B3(+)]. When regional QTcD was added to the ECG criteria for reperfusion (ie, > 50% ST-segment resolution), the area under the curve increased to 0.87 (95% CI: 0.78 to 0.96, $P < 0.001$) in patients with coronary flow of T3B3(+). In patients with ST-segment resolution of greater than 50% and regional QTcD of greater than 13 ms, they found

93% sensitivity and 71% specificity for reperfusion in T3B3(+), and 6% of the patients with successful reperfusion were reclassified. Consequently, Dotta and colleagues suggested that regional QTcD was a promising noninvasive parameter for the detection of reperfusion in the culprit artery 60 minutes after thrombolysis.

Rahimi Darabad et al²⁵ in 2014 reported that the mean in ECG 1 hour after the administration of streptokinase was decreased compared with the preoperative value, but this decline was not statistically significant. Additionally, the mean in ECG 4 days after MI was slightly increased compared with the baseline, which was not statistically significant.

In conclusion, our results demonstrated that QTd and QTcD were useful predictors of ventricular arrhythmias. A significant reduction was evident in QTd and QTcD in both successful procedures (thrombolytic therapy and primary PCI), leading to a decrease in ventricular arrhythmias. Nevertheless, in unsuccessful procedures, no such difference could be noted. Our results also showed that the success rate of primary PCI was higher than that of thrombolytic therapy. Therefore, we identified primary PCI as a more appropriate procedure. It is worthy of note, however, that some patients undergoing primary PCI may have reperfusion arrhythmias just after revascularization in the catheterization laboratory, which may not be recorded in their hospital records: this may be the etiology of the absence of arrhythmias in our primary PCI group.

Another finding of the current study was the beneficial use of fibrinolytic therapy or primary PCI in patients without conventional cardiac risk factors such as diabetes mellitus, hypertension, dyslipidemia, and smoking, which may be due to fewer atherosclerotic changes in the

vessels of these patients. This finding indicates the possible greater significance of intervention in this group of patients.

Conflict of Interest: There is no conflict of interest to be declared.

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