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Comparative study of QT, QT Dispersion, and T-Wave Peak to End Time Changes After Thrombolysis and Primary Percutaneous Coronary Intervention in Patients Presenting with Acute ST-Elevation Myocardial Infarction

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Abstract:

Background: QT dispersion (maximum QT interval minus minimum QT interval) was originallyproposed as an index of the spatial dispersion of ventricular recovery times.

Aim of the Study: To compare QTc, QTd, and TPe in thrombolytic versus percutaneous coronary intervention therapies in patients with acute STEMI and evaluate the effect on electrocardiographic QT interval, corrected QT interval, QT dispersion and TPE with implications of such assessment for prediction of ventricular arrhythmias.

Methods: The study was conducted on 100 patients presented with acute STEMI. Patients were divided into two groups. First group included 50 patients treated with thrombolytic therapy. Second group included another 50 patients treated with PCI. QT intervals of the studied patients were manually calculated at admission (before treatment) and in 24 hours (after treatment).

Results: Most patients studied were males, diabetic, hypertensive and smoker. Mean age of male patient was 57.1±8.3 years & for female was 55.6±4.6 years. Patients with anterior STEMI were more than inferior STEMI. There was a significant reduction in QTmax($p<0.02$), QTc($p<0.001$), QTd($p<.001$) and TPe($p<.001$) before and after reperfusion regardless of reperfusion strategy. There was significant reduction in QTmax($p<.001$), QTmin($p<.03$) and TPe($p<.001$) but non-significant reduction in QTc($p<0.13$) and QTd($p<.024$) before and after thrombolysis.

There was a significant reduction in QTc ($p<.02$), QTd($p<.001$) and TPe($p<.001$) before and after PCI. Our study revealed higher significant reduction in QTmax($p<.001$), QTc($p<.001$), QTd($p<.006$), TPe($p<.008$) after PCI therapies than after thrombolytic therapies.

There were non-significant differences in Intervals, QTc and dispersions before reperfusion accordingto site of infarct. There were non-significant differences in QT, QTc and dispersions after reperfusion according to site of infarct.

Conclusion: Primary PCI is associated with higher significant reduction in QT intervals, QTc and dispersion than thrombolytic therapy. Our study showed that primary PCI was effective in reducingthe degree of arrhythmogenic indices such as QTd and TPe and may be used as markers for successful reperfusion.

Keywords: QT dispersion; TPE; PCI

Introduction:

Coronary Artery Disease (CAD) is a chronic disease with symptoms that require ongoing monitoring and treatment to prevent further complications such as myocardial infarction and heart failure. [1]

The Electrocardiogram (ECG) is a necessary tool for diagnosis of myocardial infarction and cardiac arrhythmia. The QT interval reflects the duration of ventricular electrical activity determined by the phases of depolarization and repolarization. It is proposed that the different ECG leads magnify the ECG signal of different myocardial regions.

Consequently, QT dispersion (QTd), the maximum variation in the QT interval in 12-lead ECG, reflects inhomogeneity of ventricular repolarization [2] and spatial dispersion of ventricular recovery time. QTd is a crude and approximate measure of a general abnormality of repolarization. [3] This measurement was an attempt to distinguish between myocardium that is homogeneous from myocardium that displays inhomogeneity, which is accompanied by increased dispersion of the ventricular recovery times and prolongation of repolarization.

An accurate assessment of QT dispersion requires all 12 leads of the ECG to be recorded simultaneously in order to avoid the effect of heart rate changes on QT dynamics. As a result, simultaneous 12-lead recordings have been proposed as the gold standard for the measurement of QT dispersion. [4] Since rate-related changes in the QT interval develop slowly, QT dispersion measurements based upon simultaneous recording of six or even only three QRS complexes during ectopic-free sinus rhythm is acceptable for practical purposes. [5]

QTd has been shown to correlate with increased arrhythmic vulnerability in various types of cardiac diseases, such as coronary artery disease, long QT syndrome, and congestive heart failure. It is also considered a predictor of ischemic cardiac events and sudden cardiac death. [6] In addition, QTd before percutaneous coronary intervention (PCI) has been associated with an increased risk of major adverse cardiac event (MACE) and mortality in acute ST-elevation myocardial infarction (STEMI).

A T-wave on surface ECG is a representative of voltage gradient between subendocardial and sub epicardial region [7,8]. In addition to QTd, some studies used T-wave peak to end (TPE) [9] to evaluate repolarization inhomogeneity, where the peak of the T-wave coincides with the end of epicardial repolarization while the end of the T-wave indicates the end of repolarization of the whole ventricular myocardium.

Thrombolytic therapy has been a major advance in the management of acute myocardial infarction. Thrombolytic therapy works by lysing infarct artery thrombi and achieving reperfusion, thereby reducing infarct size, preserving left ventricular function, and improving survival.

Ischemia can increase QT dispersion and TPE. Percutaneous Coronary Intervention (PCI) is widely used to manage ischemia in patients with coronary artery disease. However, there is lack of information on the influence of elective PCI on ECG parameters, especially QT parameters.

Aims and Objective:

To compare QTc, QTd, and TPe in thrombolytic versus percutaneous coronary intervention therapies in patients with acute STEMI.
To evaluate the effect of thrombolytic therapy and PCI on electrocardiographic QT interval, corrected QT interval, QT dispersion and TPe and the implications of such assessment for prediction of ventricular arrhythmias.

Material and Methods:

Study design: Hospital based observational comparative analysis.
Setting: Department of cardiology, S.M.S. medical college and associated hospital.

Study population: First episode of acute STEMI who had presented within 12 hours after the onset of symptoms.

Study period: 12 months.

Inclusion criteria:

The patients enrolled were selected from those with clinical history and symptoms suggestive of a first episode of acute STEMI who had presented within 12 hours after the onset of symptoms (In all cases, acute STEMI was documented based on ECG).

Patients who underwent successful Thrombolysis defined on basis of symptom relief, ecg changes and reperfusion arrhythmia were included.

Patients who underwent successful PCI with TIMI flow grade 3 post PCI with a door-to-balloon time of <90 minutes were included.

Exclusion criteria: Patients excluded from the study for any of the following reasons:

Non ST Elevation Myocardial Infarction (NSTEMI), prior history of MI or surgical revascularization, atrial fibrillation or flutter, bundle branch block or any other intraventricular conduction abnormalities, pre-excitation on ECG, ventricular pacing rhythm, cardiogenic shock, need for urgent CABG or repeat PCI during a 24-hour period after the procedure, electrolyte disturbance, history of medications that may affect QT (anti-arrhythmic, anti-psychotic, and antidepressant drugs) and if QT interval could not be reliably measured in at least nine leads.

Sample size: - In the study 100 patients were enrolled with precision of 5% (α error =0.05) and power of study (β error) 80%.

Methods:

Acute STEMI is defined using the third universal definition of MI which signifies detection of rise and/or fall of cardiac biomarker values (preferably Troponin) with at least one value above the 99th percentile of the upper reference limit and with at least one of the following:

- Symptoms of ischemia
- New or presumably new significant STT changes (0.1mV in at least two contiguous leads)
- New LBBB
- Development of pathological Q waves in the ECG
- Imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality
- Identification of an intracoronary thrombus by angiography or autopsy

ECG localization of MI is assessed:

Anterior MI (include anterior, anteroseptal, anterolateral and extensive anterior) and inferior MI (include inferior, inferoposterior, and inferolateral).

Patients included in the study were divided into two groups depending on the reperfusion strategy. First group consists of patients reperfused by fibrinolytic therapy. Thrombolytic agent used was Streptokinase in dose 1.5 million units intravenous given over 30-60min. Coronary angiography was not done in patients who received thrombolytic therapy in the acute phase of MI. Second group consists of patients reperfused by primary PCI (aspiration device, PTCA and/or combined with stenting). Aspirin, clopidogrel, and intravenous heparin routinely given to study patients

Analysis of QT interval:

All standard 12-lead ECGs were recorded at 25 mm/s speed and 10 mm/mv gain.The QT data obtained at admission and 24 hours after Revascularization were manually measured with a ruler. QT interval was measured from the beginning of QRS to the end of the T-wave. The end of the T-wave is defined as the point of return to the isoelectric line.

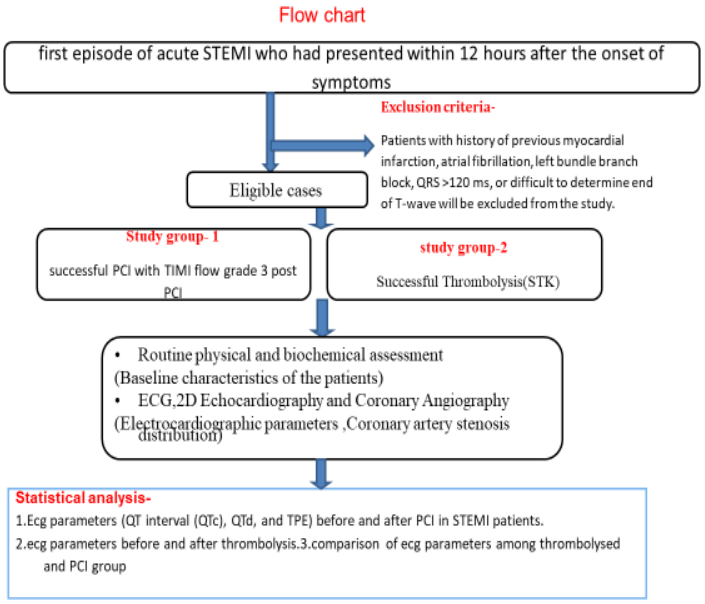
In instances where the T-wave could not be reliably determined due to extremely low voltage (<.1 mv), measurement of QT interval is not established and consequently these leads were excluded from analysis. In order to exclude the effects of heart rate (HR) on the QT interval, the QT interval is corrected according to the Bazett formula (QTc = QT/square root of RR interval).

QTd is defined as the difference between the maximum and minimum QT intervals. TPe is measured with a ruler from the peak of the T-wave to its end. The criteria to determine the endpoint of the T-wave is similar to the aforementioned criteria considered for QT measurement.
All patients have a minimum of eight ECG leads that is measurable, at least four precordial leads required for inclusion of the patient. All of the ECGs taken in sinus rhythm.

Statistical analysis:

The data was coded and entered into Microsoft Excel spreadsheet. Analysis was done using SPSS version 20 (IBM SPSS Statistics Inc., Chicago, Illinois, USA) Windows software program. Descriptive statistics included computation of percentages, means and standard deviations. The independent t -test (for quantitative data within two groups) and paired t-test (for quantitative data to compare before and after observations) were used for quantitative data comparison of all clinical indicators. Chi-square test used for qualitative data whenever two or more than two groups were used to compare. Level of significance was set at $P \leq 0.05$.

Study protocol:



Results: -

The population enrolled in this study composed of 100 CAD patients, 72 were males and 12 were females with age range between 24 and 74 years (mean age was 55.7±11.77 years in PCI group and 57.16±12.63 years in thrombolysed group), Mean age of male patient was 57.1+_8.3 years and female were 55.6+_4.6 years.

Variable	Frequency (N=100)	Percent
Age (M ± SD)	56.10±12.11	–
Gender: Male	72	72.0
Female	28	28.0
Diabetes	54	54.0
Hypertension	46	46.0
Smoking	60	60.0
Dyslipidaemia	33	33.0
Site of infarction: Anterior	63	63.0
Inferior	37	37.0

Table 1: Demographic and clinical characteristics of the studied patients.

Most of the studies patients were diabetic, hypertension and smoker. There were no significant differences between the two groups regarding demographic and clinical characteristics as studied.

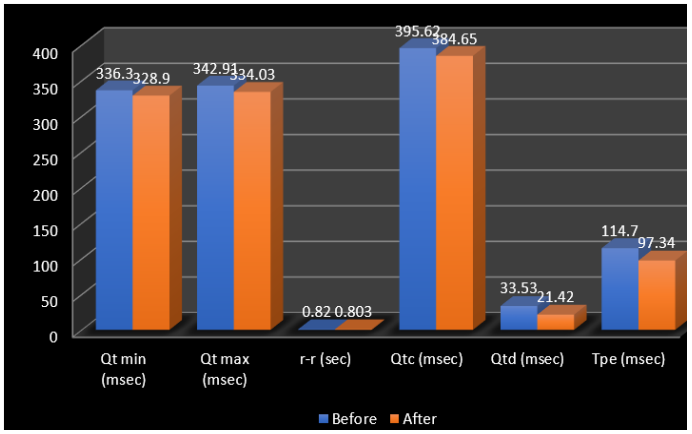


Figure 1: showing comparison of the HR and QT intervals of the studied patients before and after reperfusion therapy regardless of reperfusion strategy**.**

This figure demonstrates that there were no statistically significant differences noticed regarding HR, and QT minimum before and after reperfusion therapy (p=0.38 and 0.05, respectively). Whereas there was a significant reduction from admission to 24-hour ECGs in all studied patients treated with thrombolytic agent or primary PCI in QT dispersion, QTc maximum, QTc and TPe measurements.

variables		Mean	Std. Deviation	Mean differences	P value
Qt min (msec)	Before	337.12	56.61	12.56	0.001 (S)
	After	324.56	56.86		
Qt max (msec)	Before	376.1	51.91	14.72	0.03 (S)
	After	361.38	40.34		
r-r (sec)	Before	0.83	0.17	0.01	0.701
	After	0.82	0.14		
Qtc (msec)	Before	372.4	65.08	10.96	0.13
	After	361.44	69.24		
Qtd (msec)	Before	26.96	14.14	2.6	0.24
	After	24.36	8.78		
Tpe (msec)	Before	117.00	18.801	15.21	0.001 (S)
	After	101.88	17.409		

Table 2: Comparison of the HR and QT intervals of the studied patients before and after thrombolytic therapy.

Table (2) showed significant changes in the QT measurements from admission to 24 hour after thrombolytic therapy with significant decrease in QTmax, QTmin and TPe from baseline but no significant change in QTd.

variables		Mean	Std. Deviation	Mean differences	P value
Qt min (msec)	Before	335.48	49.29	2.24	0.73
	After	333.24	39.27		
Qt max	Before	309.72	52.23	3.04	0.4
(msec)	After	306.68	53.605		
r-r (sec)	Before	0.81	0.203	0.02	0.39
	After	0.78	0.14		
Qtc (msec)	Before	418.84	33.24	10.98	0.02 (S)
	After	407.86	25.24		
Qtd (msec)	Before	40.1	15.49	21.62	0.001 (S)
	After	18.48	11.81		
Tpe (msec)	Before	112.4	20.95	19.6	0.001 (S)
	After	92.8	16.04		

Table 3: Comparison of the HR and QT intervals of the studied patients before and after PCI therapies.

Table (3) showed significant changes in most arrhythmogenic variables like QTc, QTd and TPe measurements before and after primary PCI therapy, except HR, QT max and min.

variables		Mean	Std. Deviation	Mean differences	P value
Qt min (msec)	PCI	333.24	39.27	8.68	0.37
	Thrombolytic	324.56	56.86		
Qt max (msec)	PCI	306.68	53.605	54.7	0.001 (S)
	Thrombolytic	361.38	40.34		
r-r (sec)	PCI	0.78	0.14	0.03	0.29
	Thrombolytic	0.82	0.14		
Qtc (msec)	PCI	407.86	25.24	46.42	0.001 (S)
	Thrombolytic	361.44	69.24		
Qtd (msec)	PCI	18.48	11.81	5.88	0.006 (S)
	Thrombolytic	24.36	8.78		
TPe (msec)	PCI	92.8	16.04	9.08	0.008 (S)
	Thrombolytic	101.8	17.409		

Table 4: Comparison of the HR and QT intervals of the studied patients after reperfusion according to reperfusion strategy

Table (4) showed significant reduction in QTmax, QTc, QTd, and TPe in patients treated with primary PCI therapy when compared with those treated with thrombolytic therapy (p=0.001, p=0.001, p=0.006 and p=0.008, respectively). However, QTmin and HR measurements did not significantly vary between both groups.

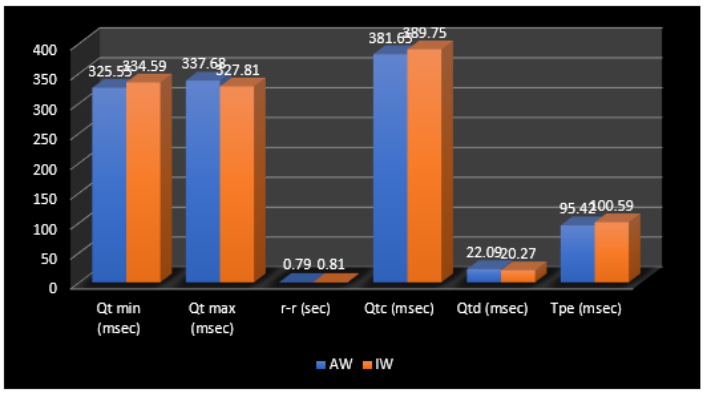
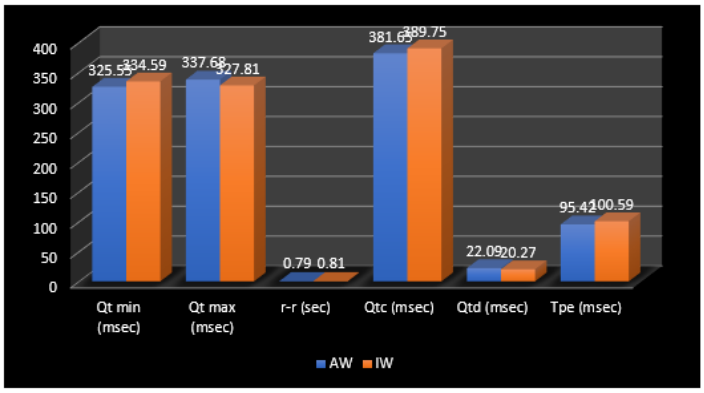


Figure 2: Comparison of some ECG data *before* reperfusion according to the site of the infarction regardless to reperfusion strategy.



According to World Health Organization most of Low and Middle exposure to self and non-self-antigens in the context of major histocompatibility complex (MHC) molecules. Antigen–MHC be studied (6) (7).

On the other hand, herpes simplex virus type 2 (HSV-2) is a DNA virus that is a part of the neurotropic herpesvirus family (12). The formulation of latent infection occurs after primary infection. However, in the presence of immunosuppression, the virus could become active and involve multiple organs (cutaneous, kidney, liver, and brain) (12) (13).

Several studies performed in severe cases of COVID-19 infections suggest that HSV-2 reactivations are frequent as the severe forms of SARS-CoV-2 are associated with acquired forms of immunosuppression biological and/or clinical signs, for instance, lymphopenia (14) (15). As a result, viral reactivations are inclined to occur due to immunodeficiency. Furthermore, SARS-CoV-2 patients suffer from septic shock with the typical biological and/or clinical pictures (15). There are variable immunological aspects of patients with SARS-CoV-2. Severe cases might present with immunosuppression and cytokine storm syndrome (16), which indicates the existence of an irregular immune response and exhaustion of cytokines by attacking T lymphocytes (CD4 cells, CD8 cells, and NK cells) (17); this unbalanced response could explain the reactivation of latent viral infection such as HSV-2 and this could explain also the sudden worsening of symptoms during the recovery (16) (17).

The prevalence of infection with HSV-2 between adults is around 25% in the United States and between 4-18% in Western Europe (18). HSV is transmitted at the sub-clinical shedding phase (19) (20). Most patients with seropositive HSV-2 report no history of genital lesions (21) (15). The acquired infection transmission of HSV-2 is high among persons with no history of genital herpes infection (22). As a result, viral shedding is frequent in seropositive patients; in spite of having a history of genital herpes or not. Additionally, women might asymptomatically shed HSV-2 “internally” (cervix and vagina), and this can explain the undergoing unnoticed reactivations of infection (15).

Case Report:

A 21-years-old female nursing student with no known co-morbidities and a recent history of HSV- 2 DNA infection and viral meningitis was presented to the Acute Covid Assessment Unit (ACAU) for COVID-19 infection with a 1-day history of frontal headache and severe photophobia, and a 1-day history of vomiting and mild myalgia. She denied any cough, shortness of breath, neck stiffness, and diarrhea. Initially, the patient was known as COVID-19 positive after one week from receiving the second dose of the ®Pfizer vaccine. Due to her illness upon presentation, COVID-19 PCR was ordered which came back positive.

The patient was admitted for viral meningitis related to COVID-19 infection. On admission, her initial temperature was 37’8 C, respiratory rate was between 12 and 18, Oxygen saturation was 98% on Room Air, blood pressure was 130/72. She was awake, alert, and coherent. She followed commands well and was oriented to name, place, time, and situation. On examination, the patient was neurologically intact with a GCS of 15, normal cranial nerves, and no motor or sensory deficits, she had a normal tone, bulk, and strength. Additionally, negative meningeal signs Brudzinski and Kernig's and absence of meningeal rash. Her chemistry was within normal limits, as were her liver and renal function. ECG showed no acute ischemic changes and CK was within normal range. Her chest x-ray was clear. CT brain, without contrast, showed no acute intraparenchymal changes. On the other hand, lumbar puncture (LP) was done and her cerebral spinal fluid (CSF) analysis revealed 243 white blood cells with 96% mononuclear cells and 4% polymorphs. CSF red cells were 207. In addition, CSF virus screening was not detected for SARS-CoV-2; however, it was detected to HSV-2 DNA.

The patient was hospitalised for 5 days and had received supportive treatment (Paracetamol and IV fluids). Meanwhile, she showed good progress during the hospitalisation. She was symptoms-free on discharge.

Discussion

In our case, we report a case of a COVID-19 patient with reactivation of HSV-2 due to the patient’s status of immunosuppression associated with SARS-CoV-2 infection. In this case, the initial presenting symptoms seemed to be exclusive to meningitis, in spite of the patient received the second dose of the COVID-19 vaccine before she became infected with COVID-19. Meningitis is the inflammation of the coverings of the brain and spinal cord. A case of SARS-CoV-2 related meningitis /encephalitis has been reported in Japan (8), where a young patient presented with an altered level of consciousness and a single episode of seizures.

This case report draws to light the possibility of patients manifesting merely neurological symptoms without respiratory distress or severe respiratory illness. Nevertheless, the role of the COVID-19 vaccine in preventing immunosuppression in patients with latent infection and in providing immunity in complicated cases yet to be study.

In our case, the CSF showed positive results of HSV type 2 infection and negative results of SARS-CoV-2 from the same sample, which most likely indicates reactivation of latent infection with HSV-2 due to immunosuppression status post-COVID-19 vaccination. The acquired infection transmission of HSV-2 is high among persons with no history of genital herpes infection. As a result, viral shedding is frequent in seropositive patients; in spite of having a history of genital herpes or not. For people affected with SARS COV-2 infection, there is an increased risk of CNS infections due to reactivation of neurotrophic agents, which raises the question of its particular role in the brain barrier cross. As a result, this may lead to acute new infections with neurological manifestations, not associated with respiratory symptoms. However, the role of the blood-brain-barrier in averting SARS-CoV-2 from entering the brain is yet to be established.

It is important to increase awareness of these rare presentations in physicians and healthcare workers and facilitate early diagnosis and management to prevent further complications and outbreaks of the disease.

Conclusion

A literature review revealed that in addition to COVID-19 infection common presentation of fever, fatigue, and mild respiratory symptoms such as dry cough and shortness of breath, patients may also manifest a range of neurological manifestations which may include headache, anosmia, hyposmia, dysgeusia, meningitis, encephalitis, and acute cerebrovascular accidents during the course of the disease.

Finally, HSV-2 is a latent infection, the viral shedding is frequent in seropositive patients despite developing no genital lesions. Due to a deficiency in the immune system in patients with latent infection, the reactivation of the virus might occur with a range of manifestations. The infection with the new SARS CoV-2 could reactivate the latent viruses, and cause worsening of the initial symptoms, or even manifest new mild to severe symptoms. Therefore, the mechanism of how the blood-brain-barrier (BBB) is prohibiting the virus from entering the brain is yet to be studied. As a result, viral screening is highly recommended for patients with a previous history of viral infections whether the patient is symptomatic or not.

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