

# The Effect of the Door to Needle Time of Streptokinase Administration on the QTc Interval and the Incidence of Life-Threatening Arrhythmia in Patients With Anterior Myocardial Infarction

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**Abstract-** Early administration of thrombolytic agents is standard for patients presenting with acute myocardial infarction (MI). Also, prolonged QT intervals indicate a higher risk for sudden death in patients with MI. This study was conducted to evaluate the door to needle time of streptokinase administration and the incidence of life-threatening arrhythmia in patients with anterior MI. This study was a prospective, single-center study on participants with anterior MI, who were divided into streptokinase and non-streptokinase groups. After administration of streptokinase, QTc was measured in hyper-acute, acute, and recent phases of anterior MI in the group and compared with acute and recent phases in the non-streptokinase group. The incidence of life-threatening arrhythmia was measured and compared in two groups. The data were analyzed by descriptive statistics method and variance analysis in the SPSS software, version 22. The level of significance was considered to be 0.05. Among 87 participants, there was a significant relationship between the door to needle time of 30 minutes and QTc interval in the hyperacute phase ( $P=0.005$ ). Also, QTc in the streptokinase group was significantly lower than the non-streptokinase group in the acute phase ( $P=0.003$  vs.  $P=0.205$ ) and recent phase ( $P=0.007$  vs.  $P=0.228$ ). The incidence of fatal arrhythmias in the streptokinase group was lower than in the others. The relationship between the incidence of VT/VF and TIMI flow grade was insignificant ( $P=0.089$ ). Reduction of the door to needle time after anterior MI has significant effects on QTc and incidence of threatening arrhythmia.

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**Keywords:** Anterior wall myocardial infarction; Streptokinase; Electrocardiography

## Introduction

The prevalence of cardiovascular disease (CVD) in the past century was increased. Thereby, this disease is known as the main cause of morbidity and mortality in the world (1). It is expected until 2020 ischemic heart disease will become the commonest cause of death in the world, and it is considered the first cause of mortality in middle ages people in Iran. As coronary artery disease (CAD) accounts for a high percentage of CVD, early

diagnosis and treatment will lead to a good prognosis of the patients and lower the deaths (2). In the world, most research has been done on the pathophysiologic process, risk factors, and effective treatment of this disease, which has led to the invention of alternative caring methods and using special drugs (3).

One of the drug strategies that are very frequent is using streptokinase and tissue plasminogen activators. Among them, streptokinase, due to the several years of use in Iran is better known and used more for acute ST-

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elevation myocardial infarction, results in recanalization of the infarct-related artery, save the left ventricular function, and finally, reduction of mortality (4). Early administration of streptokinase is a crucial prognostic factor in the outcome of patients with acute myocardial infarction that affected infarct size, left ventricular salvage, and survival (5). Some studies showed that streptokinase could have maximal benefit when it is administered in the first hour after symptoms appeared (5-6). The relationship between QTc interval in the electrocardiogram and cardiovascular mortality was found (7-9).

Also, the previous studies showed that QTc interval is found to be prolonged in patients with increased sympathetic tone conditions, especially acute myocardial infarction, and may help in identifying patients with a higher rate of sudden death and mortality (10-11).

Little is known about the effect of the door to needle time effect of QTc interval for predicting lethal clinical events such as ventricular tachycardia and ventricular fibrillation in patients with anterior ST-elevation myocardial infarction.

### Objectives

In this study, we evaluate the effect of the early streptokinase administration on QTc interval in different phases of anterior myocardial infarction.

### Materials and Methods

This is a prospective study; a single-center was performed among all patients with anterior myocardial infarction referred to the emergency department from January to November 2017.

Inclusion criteria were included all of the patients that diagnosed with anterior myocardial infarction based on the electrocardiographic changes (such as ST-T segment elevation or more than 1 mm in two or more consecutive ECG leads that presented anterior wall of the heart), increase in Biochemical marker (cardiac troponin greater than 0.50 ng/ml and CK-MB isoenzyme greater than 25 U/L) and minimal duration of chest pain duration equal and greater than 30 minutes after chest pain onset.

The exclusion criteria include prior myocardial infarction, history of coronary artery bypass graft (CABG) surgery, pacemaker implantation, Incidence of cardiogenic shock, Killip class 3 or 4, contraindication of streptokinase administration; except the patients that referred after 6 hours from chest pain incidence. Also, the patients with heart failure. Chronic kidney disease, baseline electrolyte abnormalities (based on electrolyte

assessment in first laboratory findings), and the patients who had drug history with impact on QTc interval on ECG. were excluded.

The sample size of the study was determined 45 patients in each group by considering means space and the hypothesis of the same study (4).

The demographic variables such as age, gender, and cardiovascular disease risk factors (Smoking, the history of diabetes mellitus, hypertension, and dyslipidemia) were recorded.

The streptokinase group encompasses those patients who passed lower than 6 hours of their chest pain onset according to electrocardiographic changes, clinical signs and symptoms, primary history, and estimated distances from the origin to the emergency department. They had chest pain when arriving at the emergency department. Since our emergency department was a non-PCI center, these patients instantly received streptokinase 1,500,000/U (Farmsya-Belgium) in 40 minutes within the antecubital vein in the left hand. For each of them, streptokinase dissolved with 50 ml of normal saline. Based on the door to needle time, the streptokinase group was categorized into 4 groups that include: group 1: 30 minutes, group2: 1 hour, group 3: 3 hours, and group 4: 6 hours.

All the patients that were referred to the emergency department more than 6 hours after the onset of chest pain were in the non-streptokinase group. This group has not taken any dose of streptokinase. These patients are closely monitored.

For each patient, according to door to needle time, standard 12-lead- electrocardiograms (ECG) (paper speed of 25 mm/s, standardization of 10 mm/1 mV) were recorded using MAC 5500 machines (GE Medical system, Milwaukee, WI, USA). After the streptokinase administration, the patients were re-categorized in hyperacute, acute, and recent phases; based on ECG characteristics. Patients in the non-streptokinase group were assessed for QTc changes in acute and recent phases of MI. For each ECG, the QT was measured in all leads from the onset of the QRS to the end of the T-wave on the isoelectric baseline. The isoelectric baseline was defined by the reference line between two P-Q intervals. The end of the T-wave was defined as the return to the isoelectric baseline. When the U-wave followed the T-wave, QT was measured to the nadir of the curve between the T and U-waves. The QTc was obtained using Bazett's formula:  $QTc = QT / \sqrt{RR}$ .

The incidence of ventricular tachycardia/ fibrillation in different phases was recorded.

The patients in streptokinase and non-streptokinase

## Door to needle time, QTc interval and the incidence of life-threatening arrhythmia

groups were transferred to the cardiac care unit and hospitalized for 5 days. During this time, they had received ASA,  $\beta$ -blockers, ACE inhibitors, statins, nitrates, and non-fractionated heparin, if they had no probability contraindications.

5 days after hospitalization, all the patients were transferred to percutaneous coronary intervention (PCI), and if angioplasty was a successful and single-vessel disease with LAD involvement, the patients remained in the study. During angiography, visual estimation of coronary artery diameter and coronary perfusion was evaluated using thrombolysis in myocardial infarction (TIMI) flow grade, and two cardiologists confirmed scoring. These cardiologists did not know about the study process. TIMI flow grade was defined as:

grade 0=no perfusion,

grade 1=penetration with minimal perfusion,

grade 2=partial perfusion

grade 3=complete perfusion. "Patent artery or normal flow" was defined as TIMI flow III.

The aim of the study was explained to the patients, and their written informed consent was obtained according to the Declaration of Helsinki. Furthermore, it was explained that the patients could withdraw from the study at any time.

Variables are expressed as mean $\pm$ SD and percentage. Differences in the frequency of characteristics were assessed by independent sample Student's t-test for continuous variables. The Chi-square test (or Fisher exact test if applicable) was used for categorical variables. The  $P < 0.05$  was considered significant. SPSS 22.0 software (SPSS Inc., Chicago, IL, USA) was used for data storage and analysis.

## Results

In the final of this study, 87 patients participated. Of these patients, the majority of them (70.1%) were males, and 26 (29.9%) were females. For all of the subjects, the mean age was  $61.98 \pm 12.80$  years. Among demographic characteristics, there was a significant relationship between the type of groups (streptokinase and non-streptokinase) and gender ( $P=0.002$ ), and age ( $P=0.043$ ).

There is no dramatic correlation between coronary artery disease risk factors such as; hypertension ( $P=0.37$ ), diabetes mellitus ( $P=0.11$ ), dyslipidemia ( $P=0.09$ ), and smoking ( $P=0.58$ ) and groups of the patients.

There is a significant correlation between the QTc prolongation greater than 450 milliseconds and the diabetes mellitus ( $P=0.009$ ), ages above 45 years old ( $P=0.01$ ) and female in gender ( $P=0.04$ ), that this patient

had a longer QTc interval than others.

Out of 87 patients, 45 (51.7%) of them were in the streptokinase group with the mean of age  $62.34 \pm 13.25$  years and received a therapeutic regimen of streptokinase. Among them, 8 (17.7%) patients were referred to the emergency department in 30 minutes after the onset of the chest pain symptoms, 9 (20%) patients in 60 minutes, 14 (31.1%) patients in 3 hours, and finally, 14 (31.1%) patients after 6 hours.

All of the patient's electrocardiograms in streptokinase and non-streptokinase groups were assessed. QT corrected (QTc) intervals of electrocardiogram showed that there is a significant relationship ( $P=0.005$ ) between the time of 30 minutes after chest pain onset with streptokinase administration and QTc interval in the hyperacute phase of anterior myocardial infarction. Other times that include; 1 hour ( $P=0.276$ ), 3 hours ( $P=0.166$ ), and 6 hours ( $P=0.686$ ) have not shown any significant relationships between the door to needle time and QTc interval in the hyper-acute phase.

The patients that were in streptokinase and non-streptokinase groups were assessed in QTc interval in acute and recent phases of anterior MI. Statistical analysis showed that the QTc interval in the streptokinase group ( $P=0.003$ ) was significantly lower than the non-streptokinase group ( $P=0.205$ ) in the acute phase (Figure 1.1) (Figure 1.2).

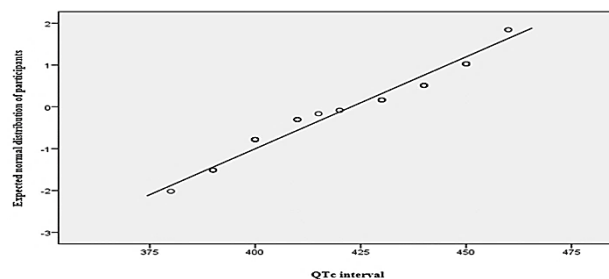


Figure 1.1. Distributions of participants in the streptokinase group relative to the QTc interval in the acute phase of anterior MI

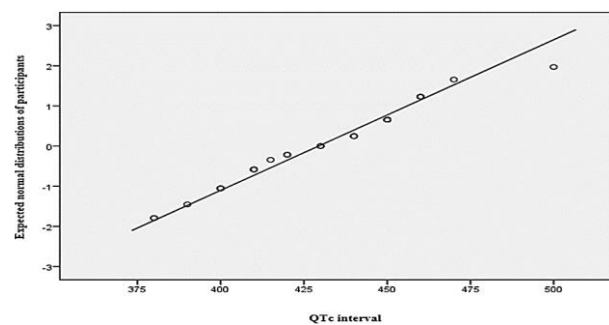
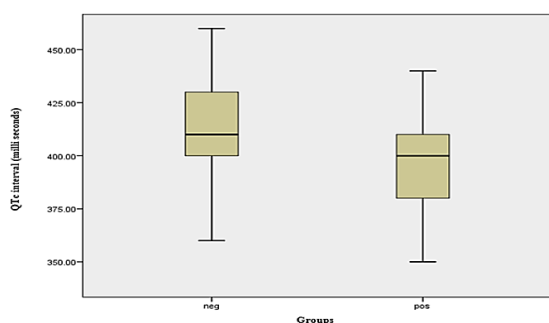


Figure 1.2. Distributions of participants in the non-streptokinase group relative to the QTc interval in the acute phase of anterior MI



**Figure 2.** Box plot demonstrated that the QTc interval in patients who received streptokinase was significantly lower than the non-streptokinase group

Also, statistical analysis showed that the QTc interval in the streptokinase group ( $P=0.007$ ) was significantly lower than in another group ( $P=0.228$ ) in the recent phase (Figure 2).

The incidence of fatal arrhythmias such as ventricular tachycardia (VT) and ventricular fibrillation (VF) in streptokinase and non-streptokinase groups showed that these arrhythmias occurred in 27 patients in the streptokinase group and involved 31 patients in another group. Pearson correlation showed that hyper-acute, acute, and recent MI, had a positive correlation with the incidence of VT and VF. Also, there is a significant relationship between the acute phase ( $P=0.001$ ) and the recent phase ( $P=0.000$ ) with the incidence of VT/VF in both groups.

The relationship between the incidence of VT/VF and TIMI flow grade was insignificant ( $P=0.089$ ), and the Pearson test showed that there is a negative correlation between them, and with increasing the TIMI flow grade, the incidence of VT/VF insignificantly decreased.

## Discussion

The endpoint of our investigation was determining the effect of the door to needle time of streptokinase administration on QTc interval in different phases of myocardial infarction (MI) and the incidence of threatening life arrhythmias following it.

The novel and most important finding of this study was the fact that there was a dramatic positive correlation between the door to needle time of streptokinase administration and QTc interval in different phases of anterior MI. This correlation showed that along with an increase in the door to needle time, the QTc interval was increased. Also, with the prolongation QTc interval in different phases of anterior MI, the incidence of VT/VF was increased.

Herein, there is various possible elucidation for this

positive association. QTc interval prolongation reflects prolonged ventricular repolarization. This event may predispose the patients to sudden death. In parallel, increasing sympathetic tone due to prolonged QTc interval can lead to increased blood pressure, atherosclerosis, and cardiovascular events (12-13).

In contrast, some studies showed that the relationship between QTc interval and the incidence of life-threatening events was a small risk and suggested that this association was not sustained (14). This contradiction may be due to the lack of precise measurement of QTc interval and a different definition of cardiovascular events following increased QTc interval.

Montanez *et al.*, (14) study showed that some risk factors such as DM and older age have not a significant correlation with QTc interval prolongation. But our study clearly showed that the patients with DM, older ages, and females had a QTc interval prolonged than others. In our study, QTc changes in patients with DM were significant. But in other studies (15-16), cardiovascular risk factors such as hypertension, DM, and smoking were not significant have not any significant correlation with the QTc. In the Chanders *et al.*, study (17) between male and female sex in terms of reduced QT dispersion after reperfusion, there was no significant difference. Although, our investigation showed that females had longer QTc intervals than others.

In our study, we showed that the patients that took streptokinase than those who did not, and also the patients that have a lower door to needle time than others, had a significantly high TIMI score in PCI. In parallel to our findings, another study (18) showed that successful fibrinolytic therapy could be reduced QT dispersion, and those had a  $TIMI \geq 2$ . But in Rahimi Darabad *et al.*, study (15), QT dispersion in patients that received streptokinase only after 1 hour of symptoms onset was dramatically decreased, but no relationship with QT interval and TIMI. One of the reasons for the difference between the results of these studies may be due to lack of precise, timely use of streptokinase in Rahimi *et al.*, study than others because in most of the previous studies and our investigation, the patients were included in the study when the interval between onset of symptoms and the fibrinolytic prescription is less than 6 hours and after fibrinolytic agent administration, the perfusion of occluded arteries was examined.

Although the pathophysiology of the effect of thrombolytic therapy on the incidence of life-threatening arrhythmia is clearly known, another novel finding of this study was determining the effect of phases of anterior MI, QTc interval, and the incidence of VT/VF. Any of the

prior studies have not shown this fact clearly. Our investigation indicated that hyperacute and acute phases of anterior MI are the most susceptible phases to fatal arrhythmia incidence.

In the Taheri *et al.*, study (3), the incidence of arrhythmia in patients who received streptokinase was more than the other group, but the incidence of fatal arrhythmia such as VT/VF in the non-streptokinase group was significantly greater than patients treated with streptokinase.

So, decreasing the door to needle time and early streptokinase administration can be diminished the VT/VF incidence. On the other hand, some studies (19,20) showed that early administration of streptokinase in patients with acute MI causes the enhancement of survival.

Also, our results showed that with early administration of streptokinase, and parallel to QTc reduction, the VT/VF incidence was decreased, and after PCI, showed that TIMI also increased, and we saw that the occluded coronary arteries had better perfusion in the patients with lower door to needle time.

Early thrombolytic therapy after anterior MI and reduction of the door to needle time have significant effects on QTc and incidence of threatening arrhythmia. So, early administration of streptokinase after confirmation of MI can be reduced mortality. It suggested that the training of first medical responders such as pre-hospital emergency medical technicians to use the streptokinase in myocardial infarction to decrease the following disability and mortality.

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