

Trimetazidine: Does it Actually Reduce QT Dispersion After First Acute Myocardial Infarction?

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Abstract: We sought to explore whether trimetazidine addition reduces QT dispersion early after acute myocardial infarction. Prospectively, we randomized 60 consecutive patients with first acute ST elevation myocardial infarction to receive either trimetazidine 20 mg tid (trimetazidine group =30 patients), or placebo (placebo group =30 patients). QT dispersion and corrected QT dispersion were measured on day 3 and day 7 of admission. Patients were followed during hospitalization for the occurrence of ventricular arrhythmias (sustained ventricular tachycardia or ventricular fibrillation). QT dispersion and corrected QT dispersion were significantly lower in trimetazidine group in both days, compared to control group: day 3, 58±5 msec versus 78±6 msec, and 69±11 msec versus 91±10 msec, respectively, $p<0.001$ for both; day 7, 41±7 msec versus 60±8 msec, and 47±9 msec versus 69±6 msec, respectively, $p<0.0001$ for both. This finding was consistent in all prespecified subgroups. During hospital stay, 3 patients (10%) of the placebo group developed sustained ventricular tachycardia and 2 (6.6%) died of ventricular fibrillation, but no one in the trimetazidine group had such arrhythmias. Conclusion: In patients with first acute myocardial infarction, the addition of trimetazidine significantly reduced both QT dispersion and corrected QT dispersion and reduced the occurrence of ventricular arrhythmias throughout hospitalization.

Key Words: Trimetazidine, QT dispersion, myocardial infarction.

INTRODUCTION

There has been a growing interest in trimetazidine as the prototype of a unique class of anti-ischemic drugs that alter myocardial metabolism without affecting myocardial oxygen consumption or supply. Under conditions of hypoxia or induced ischemia, trimetazidine maintains homeostasis and cellular functions by selectively inhibiting 3-ketoacyl-CoA-thiolase [1]. As a consequence, fatty acid β -oxidation is reduced and glucose oxidation is stimulated, resulting in decreased cellular acidosis and higher ATP production [2,3].

There is evidence that trimetazidine improves left ventricular function in patients with ischemic cardiomyopathy by shifting energy substrate preference from free fatty acids to glucose oxidation [4]. Furthermore, trimetazidine facilitates restoration of systolic and diastolic left ventricular function, improves heart rate variability, and reduces late potentials in the early period after myocardial infarction [5-7].

QT dispersion (QTD) was shown to increase during episodes of myocardial ischemia [8]. Defined as the difference between the longest and the shortest QT interval on surface 12-lead ECG, it may provide an indirect measure of the underlying inhomogeneity of ventricular repolarization [9]. An increase in QTD is reported to predict the occurrence of life-threatening ventricular tachyarrhythmias and sudden cardiac death in ischemic heart disease patients [10,11]. Moreover, QTD increases during acute myocardial infarction, values being higher in the early hours and fall late after infarction with thrombolysis. Greater QTD is associated with complex ventricular arrhythmias [12].

It was suggested that trimetazidine administered early in the course of acute MI reduces QT and corrected QT (QTc) interval dispersion [13]. In a prospective randomized placebo-controlled study design, we sought to further elucidate this notion.

METHODS

Patients

Before inclusion, an informed consent was obtained from each patient and the study protocol was reviewed and approved by our local institutional human research committee as it conforms to the ethical guidelines of the 1975 Declaration of Helsinki. We enrolled 60 consecutive patients admitted to our critical care unit during the period from April 2003 to February 2004, with the diagnosis of first acute ST segment elevation myocardial infarction (STEMI) presenting within 24 hours of symptom onset.

We included patients less than 80 years, in sinus rhythm. The diagnosis of STEMI was based on 12-lead electrocardiogram showing ST segment elevation ≥ 1 mm in at least two contiguous leads plus one of the following: 1) prolonged chest discomfort typical of myocardial ischemia, 2) elevated cardiac biomarkers: CK MB and/or troponin more than twice the upper limit of normal lab reference. We excluded patients with atrial fibrillation, bundle branch block, paced rhythm, prior myocardial infarction, cardiogenic shock, and patients taking drugs known to prolong the QT interval, for example: quinidine, amiodarone, etc.

Methods

After enrollment, patients were randomly assigned to receive either trimetazidine (trimetazidine dihydrochloride, Servier, France) 20 mg tid starting from the first admission day (trimetazidine group = 30 patients), and continued throughout the period of hospitalization (7 days), or placebo

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for the same period (placebo group = 30 patients). In detail, sequence generation was computerized, sequence was concealed until interventions were assigned, and implementation was performed by physicians and nurses not involved in the study design. A computer-generated randomization list was drawn up by an independent statistician and given to the critical care unit pharmacy. Each patient received one or the other treatments directly from the pharmacy. The code was revealed to the researchers once recruitment, data collection, and all analyses were completed. Both physicians involved in the study and patients were blinded and unaware of group assignment. After randomization, all anti-arrhythmic drugs were completely excluded, while standard anti-ischemic medications were allowed and remained unchanged during the study period. Patients eligible for reperfusion therapy (presenting within 12 hours after symptom onset, or presenting thereafter with persistent symptoms), received pharmacological reperfusion therapy in the form of streptokinase infusion 1 500 000 U over 30-60 minutes. All included patients underwent resting high-quality 12-lead ECG recordings, from which the QT intervals were measured, at day 3, and at day 7 of hospitalization. Patients were followed during their hospitalization period for the occurrence of complex ventricular arrhythmias (sustained ventricular tachycardia or ventricular fibrillation) documented by recorded monitor ECG strip or by 12-lead ECG recording, or sudden cardiac death.

QT Dispersion Measurement

Measurements were performed by an expert electrophysiologist blinded to group assignment. QT interval was measured with the manual technique, as the time in milliseconds (msec) between the first deflection of the QRS complex and the point of return of the T wave to the isoelectric line. The measures were obtained in 3 consecutive complexes in each lead and the mean value was used. The leads in which

the end of the T wave could not be clearly identified were excluded from analysis [8]. In leads with a U wave, the nadir between the T and U waves was considered as the end of the T wave. We recorded the maximal and minimal QT intervals, and calculated the QTD as the difference between both intervals, recorded individually for each patient [14]. We calculated then the QTc interval from the Bazett's formula as follows: QTc interval = QT interval / \sqrt{RR} [15]. Finally the QTc dispersion (QTcD) was calculated as the difference between the maximal and minimal QTc intervals. The mean values of QT and QTc intervals were calculated for each group separately, as well as the mean values of QTD and QTcD.

Statistical Analysis

All continuous variables were presented as mean \pm SD, if they were normally distributed, while categorical variables were described with absolute and relative (percentage) frequencies. Comparisons of continuous variables between the individual study groups were performed using the unpaired t-test. Categorical data analysis was performed using the Pearson's χ^2 test or Fisher's exact test (two-tailed) if the expected count in any cell was <5 . Comparisons of QT dispersion and corrected QT dispersion of the trimetazidine group between day 3 and day 7 were performed using the paired t-test. All tests were two-sided and a probability value of $P < 0.05$ was considered statistically significant. Analyses were performed with SPSS version 12.0 statistical package (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 60 patients were included in the current study, with a definite diagnosis of first acute STEMI on admission. The baseline characteristics of the overall cohort as well as the 2 individual study groups are shown in Table 1. The

Table 1. Baseline Characteristic of the Whole Study Cohort and the 2 Study Groups

	Whole Cohort (N=60)	TMZ Group (N=30)	Placebo Group (N=30)	P
Age (years)	52 \pm 8	52 \pm 9	52 \pm 7	>0.05
Males	43(72)	22(73)	21(70)	>0.05
Smoking	35(58)	17(56)	18(60)	>0.05
Diabetes	32(53)	17(56)	15(50)	>0.05
Hypertension	28(47)	15(50)	13(43)	>0.05
Dyslipidemia	25(42)	13(43)	12(40)	>0.05
Heart rate (bpm)	91 \pm 23	93 \pm 19	88 \pm 21	>0.05
Anterior MI	40(66.6)	21(70)	19(63)	>0.05
Fibrinolytic therapy	38(63)	19(63)	19(63)	>0.05
Beta Blocker	60(100)	30(100)	30(100)	>0.05
ACE Inhibitor	60(100)	30(100)	30(100)	>0.05
EF <50 %	18(30)	7(23)	11(36)	>0.05

All continuous variables are presented as mean \pm SD, while categorical variables are presented as numbers (percentage). TMZ indicates trimetazidine; bpm; beats per minute; MI: myocardial infarction; ACE: angiotensin converting enzyme; EF: ejection fraction.

Table 2. QT Interval and QT Dispersion Measurements in Day 3 in the 2 Study Groups

	TMZ Group (N=30)	Placebo Group (N=30)	P
QT max (msec)	398±29	413±49	>0.05
QTc max (msec)	471±37	480±49	>0.05
QT min (msec)	340±27	335±48	>0.05
QTc min (msec)	404±30	390±47	>0.05
QTD (msec)	58±5	78±6	<0.001
QTcD (msec)	69±11	91±10	<0.001

All variables are presented as mean ± SD. TMZ indicates trimetazidine; msec: milliseconds; QTc: corrected QT; QTD: QT dispersion; QTcD: corrected QT dispersion.

mean age was 52±8 years, 43(72%) being males. All patients received beta blockers and angiotensin converting enzyme inhibitors. Nineteen patients (63%) in either group received fibrinolytic therapy. When patients were classified into a group that received trimetazidine (trimetazidine group) and another that received placebo (placebo group), no statistically significant difference was found between the two groups regarding any of the baseline characteristics.

group (58±5 msec versus 78±6 msec, and 69±11 msec versus 91±10 msec, respectively, *p* <0.001 for both), as in Table 2 (Fig. 1). Similarly, Table 3 shows that, at day 7, both QTD and QTcD were significantly reduced in patients treated with trimetazidine as compared to those who received placebo (41±7 msec versus 60±8 msec, and 47±9 msec versus 69±6 msec, respectively, *p* <0.0001 for both) (Fig. 2). However,

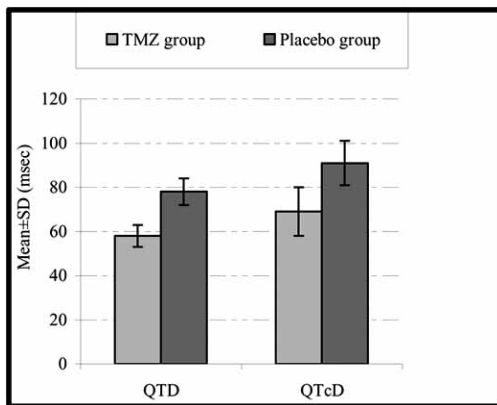


Fig. (1). QT and corrected QT interval dispersion in the individual study groups in day 3.

At day 3, both QTD and QTcD were significantly shorter in the trimetazidine group in comparison with the placebo

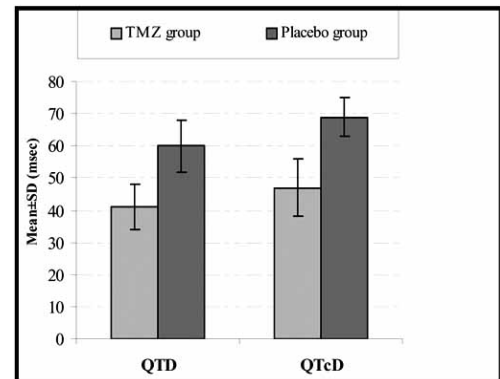


Fig. (2). QT and corrected QT interval dispersion in the individual study groups in day 7.

neither the maximal nor the minimal of either the QT or the QTc intervals, showed any statistically significant difference between the two groups at neither day 3, nor day 7.

Table 3. QT Interval and QT Dispersion Measurements in Day 7 in the 2 Study Groups

	TMZ Group (N=30)	Placebo Group (N=30)	P
QT max (msec)	385±38	390±37	>0.05
QTc max (msec)	435±28	442±38	>0.05
QT min (msec)	346±38	330±37	>0.05
QTc min (msec)	388±27	373±37	>0.05
QTD (msec)	41±7	60±8	<0.0001
QTcD (msec)	47±9	69±6	<0.0001

All variables are presented as mean ± SD. TMZ indicates trimetazidine; msec: milliseconds; QTc: corrected QT; QTD: QT dispersion; QTcD: corrected QT dispersion.

The observed statistically significant decrease of both QTD and QTcD was consistent in the subgroups of diabetics, hypertensive patients, males, females, anterior infarction, inferior infarction, those who received fibrinolytic therapy, and those who did not (Table 4). Moreover, as shown in Table 5, a further highly significant shortening of both QTD and QTcD occurred between day 3 and day 7 within the trimetazidine group (58±7 msec versus 41±7 msec, and 69±12 msec versus 47±10 msec, respectively, $p < 0.001$ for both) (Fig. 3).

On the other hand, when we studied patients within the trimetazidine group, we found no statistically significant difference regarding neither the QTD nor the QTcD, between diabetic and non-diabetic patients (42±10 msec versus 41±4 msec, and 48±12 msec versus 46±5 msec, respectively, p

>0.05 for both), between hypertensive and normotensive patients (45±12 msec versus 40±7 msec, and 49±14 msec versus 46±5 msec, respectively, $p > 0.05$ for both), nor between patients who received fibrinolytic therapy and those who did not (40±10 msec versus 43±12 msec, and 46±5 msec versus 49±15 msec, respectively, $p > 0.05$ for both).

During hospital stay, 3 patients (10%) of the placebo group developed sustained ventricular tachycardia and 2 (6.6%) died of ventricular fibrillation, but no one in the trimetazidine group had neither sustained ventricular tachycardia nor arrhythmic death.

DISCUSSION

The results of the current study demonstrate that trimetazidine significantly reduced both QTD and QTcD in

Table 4. QT Dispersion Measurements in Day 7 in All Prespecified Subgroups

Subgroup	TMZ Group (N=30)	Placebo Group (N=30)	P
Males			
QTD (msec)	40±3	59±4	<0.001
QTcD (msec)	46±5	68±7	<0.001
Females			
QTD (msec)	45±14	56±7	<0.05
QTcD (msec)	51±17	71±3	<0.005
Diabetes			
QTD (msec)	42±10	59±3	<0.001
QTcD (msec)	48±12	68±6	<0.001
Hypertension			
QTD (msec)	41±4	57±7	<0.001
QTcD (msec)	47±5	69±7	<0.001
Anterior MI			
QTD (msec)	41±9	60±11	<0.001
QTcD (msec)	48±11	71±7	<0.001
Inferior MI			
QTD (msec)	40±2	60±3	<0.001
QTcD (msec)	45±5	65±5	<0.001
Fibrinolytic therapy			
QTD (msec)	40±4	60±5	<0.001
QTcD (msec)	46±5	70±7	<0.001
No Fibrinolytic therapy			
QTD (msec)	45±15	60±1	<0.001
QTcD (msec)	52±18	68±8	<0.001

All continuous are presented as mean ± SD. TMZ indicates trimetazidine; msec: milliseconds; MI: myocardial infarction; QTD: QT dispersion; QTcD: corrected QT dispersion.

Table 5. Comparison of QT Dispersion Measurements Between Day 3 and Day 7 Among the Trimetazidine Group

	Day 3	Day 7	P
QTD (msec)	58±7	41±7	<0.001
QTcD (msec)	69±12	47±10	<0.001

All variables are presented as mean ± SD. QTD indicates QT dispersion; QTcD: corrected QT dispersion; msec: milliseconds.

patients with first acute STEMI. However, both Tables 2 and 3 showed that trimetazidine achieved an increase in minimal QT and QTc intervals, compared with placebo, at day 3 and day 7 respectively, but it was short of reaching statistical significance. In the mean time there was a comparable shortening of the maximal QT and QTc intervals, both at days 3 and 7, but again, it did not reach statistical significance. It appears that trimetazidine induces some sort of “homogenization” of QT interval among the different parts of the myocardium, in a way that overall; QTD and QTcD were reduced to an extent that meets statistical significance.

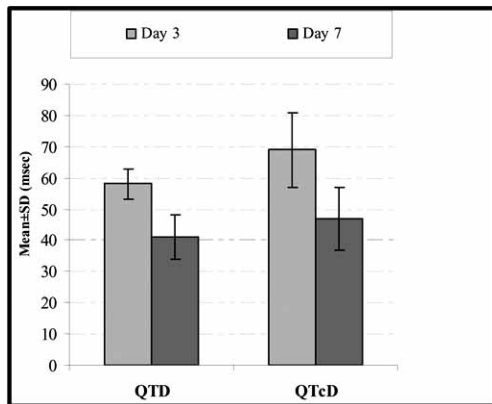


Fig. (3). Regression of QT and corrected QT interval dispersion from day 3 to day 7 in the trimetazidine group.

We excluded patients with prior myocardial infarction to avoid the effect of previous scar on QTD and on the propensity for ventricular arrhythmias. In the trimetazidine group, 7 patients (23%) had a reduced ejection fraction (below 50%) as compared to 11 patients (36%) in the placebo group. However, this difference did not meet statistical significance ($p > 0.05$). So it is not likely that the improvement in QTD and QTcD was due to better ejection fraction in the trimetazidine group.

The observed reduction of QTD and QTcD was consistent in all prespecified subgroups. With particular respect to the administration of fibrinolytic therapy, we found that both patients who received fibrinolytic therapy and those who did not, had a significant reduction of QTD and QTcD with trimetazidine, as compared to placebo, a finding that goes in accordance with previous observations [13]. On the other side, when we analyzed the trimetazidine group, we found no statistically significant difference between patients who received and those who did not receive fibrinolytic. Gligić *et al.* previously reported that QTD was significantly shorter in patients with successful reperfusion in comparison with pa-

tients who did not receive reperfusion therapy [16]. This suggests that trimetazidine had a greater influence of shortening QTD, and thence a greater benefit, in patients who did not receive fibrinolytic than in those who received it.

During follow-up, 5 patients (16.6%) in the placebo group developed complex ventricular tachyarrhythmia (sustained ventricular tachycardia or ventricular fibrillation), of whom 2 (6.6%) died, while no one in the trimetazidine developed such type of arrhythmia. This is in agreement with the observations of Di Pasquale *et al.* who found that trimetazidine administration reduces ventricular arrhythmia in the first 2 hours after reperfusion therapy [17]. This may be attributable to the antioxidant properties of trimetazidine. One study previously observed that long-term administration of trimetazidine significantly reduced superoxide anions generation and malondialdehyde (a systemic marker of oxidative stress) after ischemia-reperfusion [18]. Furthermore, Guarnieri *et al.* reported that during acute ischemia, trimetazidine reduces the loss of intracellular potassium induced by oxygen free radicals and also the membrane content of peroxidated lipids [19].

Further shortening of both QTD and QTcD occurred between day 3 and day 7 within the trimetazidine group, similar to the previous observation by Kountouris *et al.* [13]. However, when we analyzed the corresponding values within the placebo group, we found a similarly significant reduction of both QTD and QTcD between day 3 and day 7 (78±6 msec versus 60±5 msec, and 91±10 msec versus 69±6 msec, respectively, $p < 0.01$ for both). In their study of the dynamics of QTD following myocardial infarction, Glancy *et al.* previously reported that QTD increases progressively after myocardial infarction, reaching a maximum in day 3, and falling thereafter [20]. Therefore, it is likely that the progressive fall in QTD and QTcD in both study groups, between day 3 and day 7, was a reflection of the natural course of QTD after myocardial infarction, and can not be safely attributed to a cumulative effect of trimetazidine.

CONCLUSION

The results of the current study reveal that trimetazidine given to patients with first acute myocardial infarction, in addition to standard anti-ischemic therapy, reduces both QT and corrected QT interval dispersion and potentially reduces the incidence of complex ventricular arrhythmias in the immediate post-infarction period.

Study Limitations

Our findings are based on a single center study with a relatively small sample size of the cohort, a fact that makes it difficult to generalize our results to all patients with acute ST

segment elevation myocardial infarction. Multicenter studies using the same protocol and examining a larger number of patients are needed before firm conclusions can be adequately made. Moreover, the small number of arrhythmic events precludes drawing conclusions about the effect of trimetazidine on 'hard end-points'. Similarly, subgroup analysis employed comparison of small groups, and consequently, it is hard to draw final conclusions even when normal distribution is assumed. Finally, it is not known exactly how many patients achieved successful reperfusion, considering the modest reperfusion rates of streptokinase.

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