

Impact of myocardial blush grade on Tpe interval and Tpe/QT ratio after successful primary percutaneous coronary intervention in patients with ST elevation myocardial infarction

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Abstract. – **INTRODUCTION:** Myocardial perfusion, when assessed by myocardial blush grade (MBG) is an independent predictor of major adverse cardiac outcomes. The terminal part of repolarization, measured as the interval from the peak to the end of the T wave (Tpe), is a relatively novel indicator of ventricular arrhythmias. The relations between MBG and Tpe interval have not been examined before. We aimed to evaluate the relationship between MBG and Tpe and Tpe/QT ratio after successful primary percutaneous coronary intervention (PCI) in acute ST-segment elevation myocardial infarction (STEMI).

PATIENTS AND METHODS: In this study, 149 consecutive patients with STEMI and underwent primary PCI were included. The Tpe interval was defined as the interval from the peak of T wave to end of T wave, and measurements were performed from precordial leads on ECGs at admission and 90 minutes after revascularization. Patients with no myocardial blush were graded as MBG 0, those with minimal myocardial blush were graded as MBG 1, those with moderate myocardial blush were graded as MBG 2 and patients with normal myocardial blush were graded as MBG 3.

RESULTS: Comparisons were made between the MBG 0-1, MBG 2 and MBG 3 groups. In all groups, post-procedural Tpe interval were significantly shorter than pre-procedural Tpe intervals (for all groups $p < 0.001$). Post-procedural Tpe interval in MBG 3 group was significantly shorter than MBG 0-1 and MBG 2 groups (Tpe=81±11 ms in MBG 0-1 group, 81±11 ms in MBG 2 group and 72±10 ms in MBG 3 group; $p < 0.001$, for all groups). Post-procedural Tpe/QT ratios decreased in all three MBG groups ($p < 0.001$, for all groups). Tpe/QT ratios were smaller with the increasing MBG ($p < 0.001$).

CONCLUSIONS: Tpe interval and Tpe/QT ratio are closely associated with MBG after successful primary percutaneous coronary intervention in STEMI.

Key Words

Myocardial blush grade, Repolarization, T peak to end, Arrhythmia.

Introduction

Rapid reperfusion of infarct-related artery in acute ST-segment elevation myocardial infarction (STEMI) is associated with substantial improvement in prognosis; however, providing epicardial flow, doesn't always mean a normal tissue perfusion. Myocardial perfusion, when assessed by myocardial blush grade (MBG) is an independent predictor of both short and long-term major adverse cardiac outcomes^{1,2}. Previous studies^{3,4} have demonstrated that higher MBG, representing microvascular circulation, was consistently related to ST-segment resolution and improved left ventricular systolic function.

In this patient population, arrhythmias are also a major cause of mortality and morbidity. Repolarization heterogeneities on surface electrocardiograms (ECG) are considered as predictors of malignant ventricular arrhythmias and sudden cardiac death in patients with STEMI^{5,6}. The terminal part of repolarization, measured as the interval from the peak to the end of the T wave (Tpe), is a relatively novel indicator of risk of ventricular arrhythmias, and accumulating data suggest that T peak-to-end interval and Tpe/QT ratio are more sensitive arrhythmia markers than the older index QT dispersion^{7,8}. Fukushima et al⁹ found that increased myocardial blush grade was associated with reduced QT dispersion; however, the relations between myocardial blush grade and Tpe interval or Tpe/QT ratio have not been examined before. In the present study we evaluate

the relationship between myocardial blush grade and the new indices of transmural dispersion of repolarization, Tpe interval and Tpe/QT ratio, after successful primary percutaneous coronary intervention (PCI) in STEMI patients.

Patients and Methods

Study Population

In this observational study we included 149 consecutive patients with STEMI who were admitted within 12 hours from symptom onset, and underwent primary PCI between 2014 and 2015. Mean age was 58.7 ± 12.3 , and 42 were females. Each patient gave informed consent before coronary angiography. The inclusion criteria were both: 1) typical ongoing ischemic chest pain for >30 minutes; 2) ST elevation ≥ 1 mm in ≥ 2 contiguous leads (2 mm for leads V1 to V3). Exclusion criteria were: 1) previous myocardial infarction; 2) bundle branch block; 3) cardiogenic shock or cardiac arrest; 4) chronic kidney disease; 5) severe primary valvular heart disease; 6) ECGs that were not analyzed properly; 7) permanent pacemaker treatment. Only patients with Thrombolysis in Myocardial Infarction (TIMI) 3 flow after primary PCI were included to avoid the possible effect of TIMI flow on electrocardiographic parameters. Clinical characteristics and current cardiovascular medication use were recorded at the time of clinical evaluation. Patients were considered as diabetics, if there was a previous diagnosis of diabetes or presence of any anti-diabetic drug use or a fasting venous blood glucose level of ≥ 7.0 mmol/l on two occasions in previously untreated patients. Hypertension was defined as the use of antihypertensive medications, a systolic pressure higher than 140 mm Hg or a diastolic pressure higher than 90 mmHg. The study protocol was approved by Ethics Committee of Ankara Numune Education and Research Hospital.

Electrocardiogram Analysis

At admission and 90 minutes after the primary percutaneous coronary revascularization procedure, a 12-channel ECG was obtained with paper speed 25 mm/s and 10 mm/mV gain. Heart rates were recorded. ECG intervals were measured by the same cardiologist using a ruler and magnifying glass. QT interval was measured from the onset of QRS complex to the end of T wave. The end of the T wave was defined as an intersecting point of a tangent line on the terminal T wave and

the T-P baseline, see Figure 1. QT intervals were corrected for heart rate using Bazett's formula¹⁰: $QTc = QT \text{ interval} / (RR \text{ interval})^{1/2}$. The Tpe interval was defined as the interval from the peak of T wave to the end of T wave and measurements were performed from all six precordial leads¹¹. All measurements (Tpe and QT intervals) were the mean value of three consecutive beats of each lead and the value reported was the maximum value obtained in all precordial leads. From these measurements Tpe/QT ratios were calculated.

Echocardiography

Transthoracic echocardiography was performed by cardiologists blinded to the study within the first 24 hours after primary PCI according to current practice guidelines using a commercially available device (Vivid 7 Pro, GE Vingmed, Horten, Norway). The left ventricular ejection fraction (EF) was obtained by the modified Simpson's rule¹².

Coronary Angiography

Coronary angiography was performed to determine the infarct-related artery (IRA) and the degree of revascularization. All patients received 300 mg of acetyl salicylic acid and 600 mg of clopidogrel. After insertion of the femoral sheath, a heparin bolus of 100 IU/kg was administered. Intracoronary nitroglycerin was given if the patient was not hypotensive, and glycoprotein IIb/IIIa inhibitor administration was left to the choice of the operator. Primary angioplasty and stenting

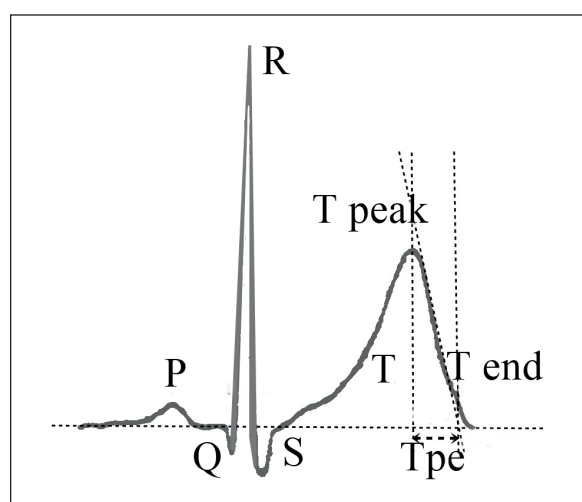


Figure 1. The end of the T wave was defined as the intersecting point of a tangent on the terminal T wave and the T-P baseline. Tpe: T peak to end.

procedures were completed according to standard techniques. Primary PCI procedure was accepted as successful if the residual stenosis was less than 20% in the infarct-related artery (IRA) by visual evaluation. Coronary angiography recordings were obtained by a Siemens Axiom Artis Zee[®] device (Siemens Healthcare GmbH, Erlangen, Germany).

Post-procedural myocardial perfusion was evaluated with the previously described MBG method¹³. The contrast density in the distal myocardial region of the IRA was graded in comparison with the blush of non-IRA myocardial regions on cine film at 25 frames per second on the best projection along at least 3 cardiac cycles duration to ensure washout. Patients with no myocardial blush were graded as MBG 0, those with minimal myocardial blush were graded as MBG 1, those with moderate myocardial blush were graded as MBG 2 and patients with normal myocardial blush were graded as MBG 3.

Statistical Analysis

Statistical analysis were performed by IBM SPSS for Windows Version 22.0 statistical package (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean \pm standard deviation or median [minimum-maximum]. Categorical variables are summarized as frequencies and percentages. Normality of the continuous variables was evaluated by Shapiro-Wilks test. Differences between the groups according to continuous variables were determined by one-way ANOVA or Kruskal-Wallis test as appropriate. Pairwise comparisons were done by Tukey HSD test or Siegel Castellan test. Categorical variables were compared by Pearson χ^2 -test. Within and between group differences were analyzed by repeated measures ANOVA. A two-sided p -value less than 0.05 was considered significant.

Results

Baseline characteristics of the patients are summarized in Table I. Patients were divided into three groups according to their post-procedural myocardial blush grade: MBG 0-1 ($n=53$), MBG 2 ($n=30$) and MBG 3 ($n=66$) groups. The mean age of patients with MBG 3 was significantly lower than the other patients (64 ± 12 years MBG 0-1 group, 58 ± 14 years in MBG 2 and 55 ± 10 years in MBG 3 group; $p<0.001$). Median time from onset of symptoms to revascularization was 4 [1-12] hours, slightly lower in MBG 3 compa-

red MBG 0-1 ($p=0.022$). The rate of ST segment resolution more than 50% at the 90th minute after revascularization was higher in the group with MBG 3 than MBG 0-1 and MBG 2 (40% in MBG 0-1 group, 93% in MBG 2 group and 99% in MBG 3 group; $p<0.001$). Hypertension was lower with increasing MBG ($p=0.027$), and left ventricular ejection fraction was higher with increasing MBG (41 ± 10 % in MBG 0-1 group, 48 ± 11 % in MBG 2 group and 50 ± 9 % in MBG 3 group; $p<0.001$). Diabetes mellitus and smoking frequencies did not differ significantly between the groups, although there was numerically fewer diabetic patients in MBG 3 group ($p=0.076$).

Table II shows the pre-procedural and post-procedural QTc durations, Tpe interval and Tpe/QT ratios according to the MBG groups. Pre-procedural intervals did not differ significantly between groups. MBG 0-1, MBG2 and MBG 3 groups had similar post-procedural QT durations (367 ± 32 , 374 ± 46 and 375 ± 30 ms, respectively; $p=0.438$). In group pre and post-procedural QT durations did not differ significantly (MBG 0-1 group 363 ± 36 ms vs. 367 ± 32 ms; $p=0.336$, MBG 2 group 366 ± 45 ms vs. 374 ± 46 ms; $p=0.173$, MBG 3 group 371 ± 32 ms vs. 375 ± 30 ms; $p=0.316$). Post-procedural QTc durations were similar ($p=0.080$) but post-procedural QTc durations were significantly longer than pre-procedural QTc durations (MBG 0-1 group 402 ± 27 ms vs. 412 ± 29 ms; $p=0.013$, MBG 2 group 415 ± 24 ms vs. 427 ± 36 ms; $p=0.022$, MBG 3 group 404 ± 27 ms vs. 414 ± 27 ms; $p=0.005$) see Figure 2. Also, the procedure-related change in QT duration and QTc did not differ significantly between patients in different MBG groups (interaction $p=0.836$ and $p=0.937$, respectively).

In all groups, post-procedural Tpe interval were significantly shorter than pre-procedural Tpe intervals (MBG 0-1 group 85 ± 11 ms vs. 81 ± 11 ms, MBG 2 group 86 ± 11 ms vs. 81 ± 11 ms, MBG 3 group 86 ± 9 ms vs. 72 ± 10 ms; $p<0.001$). Post-procedural Tpe interval in MBG 3 group was significantly shorter than in MBG 0-1 and MBG 2 groups ($p<0.001$). Likewise, post-procedural Tpe/QT ratios decreased in all three MBG groups (MBG 0-1 group 0.235 ± 0.035 vs. 0.222 ± 0.038 , MBG 2 0.237 ± 0.040 ms vs. 0.219 ± 0.036 , MBG 3 group 0.233 ± 0.027 vs. 0.192 ± 0.031 ms; for all groups $p<0.001$). Post-procedural Tpe/QT ratios were smaller with the increasing MBG ($p<0.001$). Additionally, the procedure-related change in Tpe interval and Tpe/QT ratios differ significantly between patients in different MBG groups (interaction $p=0.001$).

Table 1. Patient demographics, clinical, and angiographic data

	Myocardial blush grade 0-1 (n=53)	Myocardial blush grade 2 (n=30)	Myocardial blush grade 3 (n=66)	All group (n=149)	<i>p</i>
Age, years	64±12	58±14	55±10	59±12	<0.001*
Gender, female	17 (32%)	10 (33%)	15 (22%)	42 (28%)	0.415
Diabetes mellitus	18 (34 %)	6 (20 %)	11 (17 %)	35 (23 %)	0.076
Hypertension	29 (55 %)	12 (40 %)	20 (30 %)	61 (41 %)	0.027
Smoking	26 (49%)	13 (43 %)	40 (61 %)	79 (53 %)	0.224
Ejection fraction, %	41±10	48±11	50±9	46±11	<0.001*°
Fasting blood glucose, mmol/L	7.7 [4.3-22.3]	6.7 [5.0-17.5]	6.6 [3-20.3]	6.7 [3-22.3]	0.015*
Creatinine, µmol/L	92±57	74±23	70±25	79±40	0.009*
eGFR, mL/min/1.73m ²	61 [13-105]	61 [44-100]	61 [54-110]	61 [13-110]	0.130
Acetylsalicylic acid use	11 (21 %)	2 (7 %)	4 (6 %)	17 (11 %)	0.029
ACE-i or ARB use	9 (17 %)	-	5 (8 %)	14 (9%)	0.010
Beta blocker use	3 (6%)	2 (7 %)	2 (3 %)	7 (5%)	0.670
Statin use	1 (2 %)	-	3 (5 %)	4 (3%)	0.286
Triglyceride, mmol/L	1.53±0.97	1.63±0.68	1.63±1.09	1.59±0.97	0.810
LDL, mmol/L	2.95±0.92	3.06±1.07	3.12±0.88	3.05±0.93	0.628
HDL, mmol/L	1.02±0.28	1.04±0.26	1.06±0.33	1.04±0.30	0.728
Total cholesterol, mmol/L	4.69±1.18	4.85±1.17	4.89±1.07	4.81±1.13	0.643
Symtom to baloon time, hours	4 [1-13]	3 [1-14]	3 [1-10]	4 [1-14]	0.022*
Infarct related artery	LAD 34 (64 %)	LAD 19 (63 %)	LAD 30 (46 %)	LAD 83 (56 %)	115
	RCA 12 (23%)	RCA 8 (27 %)	RCA 25 (38 %)	RCA 45 (30 %)	
	LCX 5 (9 %)	LCX 3 (10 %)	LCX 11 (17 %)	LCX 19 (13 %)	
	Saphenous 2 (4%)	Saphenous -	Saphenous -	Saphenous 2 (1 %)	
ST segment resolution > 50 %	21 (40 %)	28 (93 %)	65 (99%)	114 (77%)	<0.001
Admission heart rate, bpm	76±16	80±17.8	72.0±10.1	74.9±14.5	0.039**

ACE-i : angiotensin-converting-enzyme inhibitor, ARB: Angiotensin II Receptor Blockers, eGFR: estimated glomerular filtration rate, HDL: High density lipoprotein, LCX: left circumflex artery, LDL: low density lipoprotein.

*Myocardial blush grade 0-1 and Myocardial blush grade 3 differ

°Myocardial blush grade 0-1and Myocardial blush grade 2 differ

**Myocardial blush grade 2 and Myocardial blush grade 3 differ

Discussion

This study shows that Tpe interval and Tpe/QT ratios are considerably shortened with revascularization of the infarct-related artery in patients with STEMI. This shortening is more pronounced with increasing MBG. However, QT and QTc durations are longer post-procedurally.

Prompt reperfusion of the infarct-related artery by primary PCI is the most beneficial treatment for decreasing myocardial infarct size, preserving left ventricular functions, and reducing electrical instability and death. Although restoration of the epicardial coronary flow is a prerequisite for reperfusion of myocardium and TIMI 3 flow is restored in more than 90 percent of patients in

experienced centers, myocardial recovery is not always optimal, and infarct complications are still noticeable¹⁴. During infarction, microvascular circulation is also compromised by edema, inflammation, neurohormonal responses, vasoactivity, and spontaneous or PCI-induced embolization¹⁵. Evaluation of angiographical MBG is a simple and reproducible marker of microcirculation, closely related to infarct size, left ventricular function and long-term mortality^{13,16}. Previous studies^{9,17-19} also demonstrated that MBG is closely related with electrical stability, depolarization and repolarization abnormalities and arrhythmias.

Heterogeneity of ventricular repolarization is determined mainly by three predominant cell types (endocardial, endocardial and mid-myocardial M

Table II. T peak to end interval, QTc interval and T peak to end / QT ratio at admission and after revascularization.

	Myocardial blush grade 0-1 (n=53)	Myocardial blush grade 2 (n=30)	Myocardial blush grade 3 (n=66)	All group (n=149)	p
Tpe, ms admission	85±11	86±11	86±9	86±10	0.751
post-revascularization	81±11	81±11	72±10	77±11	<0.001*°
In group interaction p	<0.001	<0.001	<0.001		
QTc, ms admission	402±27	415±24	404±27	405±27	0.101
post-revascularization	412±29	427±36	414±27	416±30	0.080
In group interaction p	0.013	0.022	0.005		
Tpe/QT admission	0.235±0.035	0.237±0.040	0.233±0.027	0.235±0.033	0.880
post-revascularization	0.222±0.038	0.219±0.036	0.192±0.031	0.208±0.037	<0.001 *°
In group interaction p	<0.001	<0.001	<0.001		

QTc: corrected QT interval, Tpe: T peak to end interval, Tpe/QT : T peak to end /QT ratio

*Myocardial blush grade 0-1 and Myocardial blush grade 3 differ

°Myocardial blush grade 0-1and Myocardial blush grade 2 differ

cells). Full repolarization of epicardial cells is earliest, corresponding to the peak of the T wave on the surface ECG. Mid-ventricular M cells repolarize the latest and represent the end of the T wave. During acute myocardial infarction, dispersion of ventricular repolarization is more pronounced across the ischemic border zone contributing the formation of the substrate for arrhythmias. The Tpe interval and Tpe/QT ratio are indices of transmural dispersion of repolarization, and increased in several arrhythmic conditions such as long QT syndromes, left ventricular hypertrophy and myocardial infarction with lethal ventricular arrhythmia²⁰⁻²³. Additionally, Haamark et al⁶ demonstrated that pre-PCI Tpe interval may predict all-cause mortality after STEMI regardless of infarct-related artery (left anterior descending, right coronary artery, circumflex artery or other coronary arteries larger than 2-mm diameter). In their study, post-

PCI Tpe interval was evaluated immediately after PCI, and pre and post-PCI Tpe intervals did not differ significantly. This result may be seemingly discordant with our result; however, in our study we re-measured Tpe interval and Tpe/QT ratio 90 minutes after revascularization. The difference in the timing of re-assessment of ECG may be the reason for the divergence of the findings. In this context, our findings are consistent with another study aiming to evaluate the 24 h course of QTc and Tpe interval after PCI in acute myocardial infarction, in which Bonnemeier et al²⁴ showed that QTc interval slightly lengthens in the first hour and then shortens, and Tpe interval shortens in the first hours of acute myocardial infarction and stabilize after 3-4 hours of revascularization. Authors also showed that Tpe interval may increase post revascularization in a patient with major arrhythmic events. In both studies epicardial revascularization

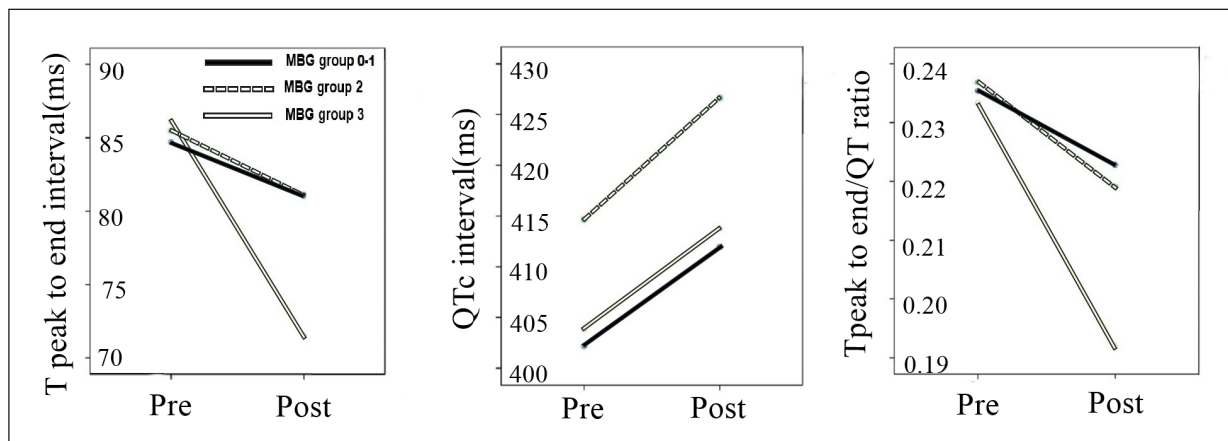


Figure 2. Comparison of admission and post-revascularization T peak to end interval, QTc interval and Tpe/QT ratios.

was achieved, on the other hand, the degree of myocardial perfusion was not indicated.

Compared to older index, QT dispersion, newer indices of transmural dispersion of repolarization, Tpe interval and Tpe/QT ratios have been found to be more sensitive predictors of arrhythmias⁷. Although the relationship between QT dispersion and MBG after successful transluminal recanalization in STEMI setting was evaluated previously by Fukushima et al⁹, they did not assess the impact of myocardial perfusion status on Tpe interval and Tpe/QT ratio, and the decrease in QT dispersion was found only in patients with MBG 3 perfusion. In our study, we evaluated the association between MBG and newer indices and then the decreases in these indices were more remarkable with the increasing MBG. This result may also be considered as a clue for Tpe interval and Tpe/QT ratio to be more sensitive indicators of arrhythmia compared to QT dispersion.

QT interval depends on both ventricular conduction and ventricular repolarization whereas Tpe interval is solely related with ventricular repolarization and is not affected by heart rate or autonomic nervous system. Imbalance in sympathetic innervation is associated with QTc prolongation and may be still dominant in the early hours of myocardial infarction despite the achievement of reperfusion, while the Tpe interval is depending on reperfusion and moreover the grade of reperfusion. These specific properties of cardiac electrical activity may be the explanation of QTc prolongation after successful revascularization in STEMI patients.

Impaired myocardial perfusion is complicated with ongoing ischemia, microvascular edema, scar formation, local metabolic abnormalities and alterations in the expression of myocyte membrane ion channels, facilitating the formation of arrhythmic milieu²⁵. Restoration of epicardial blood flow with adequate microvascular reperfusion may promote the electrical integrity of myocardial cells in the infarcted zone. In our study, we showed that not only providing the successful revascularization, but also the degree of myocardial reperfusion, is closely associated with surrogates of arrhythmia following STEMI. This study also contributes to the explanation of the prognostic value of MBG in STEMI, at least partially as a predictor of arrhythmia.

This study has some limitations. It was carried out on a relatively small number of patients. We evaluated myocardial perfusion only by conventional angiography, and validation of myocardial perfusion grade with other quantitative modalities might have

additional value. The incidence of ventricular arrhythmias and the long-term cardiovascular mortality of the study population were not recorded.

Conclusions

Tpe interval and Tpe/QT ratio, characterizing the repolarization of myocardial cells, was found to be closely associated with myocardial blush grade, as an indicator of myocardial microvascular perfusion after successful primary percutaneous coronary intervention in STEMI.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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