QT Dispersion and Prognosis after Coronary Stent Placement in Acute Myocardial Infarction

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Summary

Background: QT dispersion is increased in acute myocardial infarction (AMI), but the relation of QT dispersion to prognosis has not yet been fully elucidated.

Hypothesis: The purpose of this study is to evaluate prospectively whether QT dispersion is associated with the risk of major adverse cardiac events (MACEs) and mortality after successful coronary stenting in AMI.

Methods: One hundred and forty-two patients with AMI and undergoing successful percutaneous coronary intervention (PCI) were enrolled in this study. Corrected QT dispersion was measured before and 24 h after PCI.

Results: During a period of 4477 person-months, we confirmed 21 cases of MACE. Univariate analysis indicated that corrected QT dispersion before and 24 h after PCI, age, number of Q waves, and Killip class ≥ 2 were related to MACE and mortality. By multivariate analysis, corrected QT dispersion before PCI was an independent predictor of MACE and mortality, but corrected QT dispersion at 24 h after PCI was not statistically associated with MACE and mortality. Multiple-adjusted

hazard ratios for a 1 standard deviation (SD) magnitude increase in corrected QT dispersion before PCI were 2.24 (95% confidence interval, 1.36–3.68, $p = 0.001$) for MACE and 2.71 (95% confidence interval, 1.50–4.89, $p = 0.001$) for mortality after adjustment for age, gender, ejection fraction, and Killip class ≥ 2 .

Conclusions: Corrected QT dispersion before PCI is associated with an increased risk of MACE and mortality after successful PCI in patients with AMI.

Key words: QT dispersion, prognosis, acute myocardial infarction

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Introduction

QT interval on 12-lead electrocardiogram (ECG) reflects ventricular repolarization; QT dispersion reflects dispersion of ventricular refractoriness.¹ Antzelevitch *et al.*² have reported that contributing to QT dispersion are heterogeneities of repolarization time in the three-dimensional structure of ventricular myocardium, which are secondary to regional differences in action potential duration and activation time. Some studies reported that QT dispersion predicts ischemic heart attack and the incidence of sudden death due to cardiac arrest.^{3,4} Therefore, the index of QT dispersion is considered to be useful for predicting cardiac events of ischemic heart disease and mortality.

Several studies have demonstrated that QT dispersion is increased in acute myocardial infarction (AMI),³ and that increased QT dispersion predicts the risk of ventricular arrhythmias in AMI.⁵ However, the relationship between QT dispersion and prognosis has not yet been fully elucidated in AMI. Therefore, we prospectively

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investigated the relation of QT dispersion to major adverse cardiac events (MACEs) and mortality after successful coronary stenting in patients with AMI.

Materials and Methods

Study Subjects

From August 1999 to May 2004, a total of 147 consecutive patients with AMI who underwent primary percutaneous coronary intervention (PCI) less than 12 h from symptom onset, were admitted to the Ishikiri-seiki Hospital, Japan. The diagnosis of AMI was based on typical ECG changes and increased serum cardiac enzymes. The enrollment criteria for this study were as follows: (i) successful coronary stenting; (ii) standard 12-lead ECGs were recorded before and 24 h after PCI; (iii) transthoracic echocardiogram was performed about 1 week after PCI; (iv) lack of intraventricular conduction disturbance and ventricular pacing. We excluded 1 patient with unsuccessful coronary stenting, 1 patient who died within 24 h after PCI, and 3 patients because of right bundle branch block, leaving 142 patients enrolled in this study. The protocol was in accordance with the authors' institutional guidelines for human research, and each patient provided a written statement of informed consent for the diagnostic and therapeutic procedures performed.

Protocol

PCI was performed according to standard techniques. Standard 12-lead ECGs were recorded before and 24 h after PCI. Transthoracic echocardiogram was performed to examine the left ventricular ejection fraction about 1 week after PCI.

ECG Analysis

Standard 12-lead ECGs were recorded at a paper speed of 25 mm/s and a gain of 10 mm/mV, and assessed at twofold enlargement. QT interval analysis was completed by the same experienced observer who was not given the clinical data and follow-up results. The QT interval was measured from the beginning of the QRS complex to the end of the T wave. When a T wave was interrupted by the U wave, the end of the T wave was defined as the nadir between the T and the U waves. If the end of the T wave could not be reliably determined due to extremely low voltage (<0.1 mV), measurements of the QT interval were not made, and these leads were excluded from the analysis. In all patients, the QT interval was measurable in at least eight ECG leads (mean 11 ± 1 leads). In order to exclude the effect of heart rates on QT intervals, QT intervals were corrected with Bazett's formula. Corrected QT dispersion

was defined as the difference between maximum and minimum corrected QT interval. Intraobserver variability was examined in 50 randomly selected ECGs. The mean of absolute difference between the first and second measurements of QT dispersion was 6.3 ± 2.0 ms (range 1.6–10.8) with a correlation coefficient of 0.93. Abnormal Q waves were defined as ≥ 40 ms in duration and/or $>25\%$ of the R wave amplitude. The ST-segment elevation at the J points in the lead with the largest deviation was measured. The percent resolution of ST-segment elevation from before PCI to 24 h after PCI was calculated.

Cardiac Enzyme Measurements

Blood samples were obtained every 3 h after PCI for determination of the peak serum creatine phosphokinase levels.

Clinical Follow-up

The patients were followed-up with data recorded from clinic visits and/or telephone calls made after the coronary stent placement. MACE were defined as death, nonfatal myocardial infarction, life-threatening arrhythmias such as sustained ventricular tachycardia or ventricular fibrillation, and hospitalization because of congestive heart failure.

Statistical Analysis

Values were expressed as the mean $\pm$ standard deviation (SD). Categorical variables were compared using χ^2 test. Differences in the mean values between the two groups were compared using an unpaired *t*-test or a Wilcoxon rank sum test. For each patient, person-months of follow-up were counted from the data at entry (August 1999 to May 2004) to the date of diagnosis of MACE or August 2005, whichever came first. The Cox proportional hazards model was applied to verify the independent prognostic implication of QT dispersion on MACE and death. The 95% confidence interval (CI) was calculated for each hazard ratio. Values of $p < 0.05$ were considered statistically significant. Statistical analyses were performed using the SPSS 11.0 software package (SPSS, Inc., Chicago, IL).

Results

The mean duration of follow-up was 32 ± 19 months. During a period of 4477 person-months, we confirmed 21 cases of MACE: 15 deaths, 2 cases of nonfatal myocardial infarction, 1 case of ventricular fibrillation, and 3 cases of congestive heart failure. The mean age was higher in patients with MACE than those without MACE ($p < 0.01$), and was higher in patients with death than in survivors ($p < 0.01$). The proportion of Killip class ≥ 2

was higher in patients with MACE than those without MACE ($p < 0.001$) and higher in patients who died, than in survivors ($p = 0.001$). The number of infarct-related abnormal Q waves was greater in patients with MACE than those without MACE ($p < 0.05$) and greater in patients who died, than in survivors ($p < 0.05$). Corrected QT dispersion before and 24 h after PCI were significantly longer in patients with MACE than those without MACE ($p < 0.001$ and $p < 0.01$, respectively) and were longer in patients who died, than in survivors ($p < 0.001$ and $p < 0.05$, respectively) (Table 1). The proportion of previous myocardial infarction, chronic renal failure on hemodialysis, ST elevation MI, ST-segment resolution $>50\%$, left anterior descending coronary artery lesion, multivessel disease, and thrombolysis in myocardial infarction (TIMI) flow grade 0 before PCI, were not associated with MACE and mortality. There was no significant difference in maximum and minimum QT interval before and after 24 h after PCI, or heart rate before and 24 h after PCI between groups.

In univariate Cox regression analysis, corrected QT dispersion before and 24 h after PCI, age, number of abnormal Q waves, and Killip class ≥ 2 were related to MACE and mortality.

Table 2 presents the multivariate Cox regression analysis. A number of regression models were tested to assess the effects of corrected QT dispersion on MACE and mortality (Models 1–3 of Table 2). After adjusting for age, gender, ejection fraction and Killip class ≥ 2 , corrected QT dispersion before PCI was an independent

predictor of MACE and mortality. Multiple-adjusted hazard ratios for a 1 SD magnitude increase in corrected QT dispersion before PCI were 2.24 (95% CI, 1.36–3.68, $p = 0.001$) for MACE and 2.71 (95% CI, 1.50–4.89, $p = 0.001$) for mortality (Model 1 of Table 2). Model 2 of Table 2 was identical to model 1, with the exception that the number of abnormal Q waves was used in place of Killip class ≥ 2 . In this model, corrected QT dispersion before PCI was associated with MACE and mortality. Model 3 of Table 2 was identical to model 1, with the exception that corrected QT dispersion at 24 h after PCI was used in place of corrected QT dispersion before PCI. Corrected QT dispersion at 24 h after PCI was not statistically associated with MACE and mortality.

Discussion

These data demonstrated that corrected QT dispersion before PCI was associated with the incidence of MACE and mortality after successful PCI in AMI.

Although several studies have been made on the relationship between QT dispersion and mortality in AMI,^{6–9} the relation is still in controversy. Wang *et al.*⁶ showed that greater QT dispersion was related to greater mortality and sudden death rates in uremic patients. Glancy *et al.*⁷ reported that QT dispersion measured at least 4 weeks after AMI was associated with subsequent mortality, but QT dispersion measured at 48 or 72 h after

TABLE 1 Characteristics of study subjects at baseline according to MACE and survival status after follow-up

Characteristic	No MACE (n = 121)	MACE (n = 21)	p	Survivors (n = 127)	Deaths (n = 15)	p
Age (years)	61.3 $\pm$ 10.3	68.7 $\pm$ 8.9	0.002	61.5 $\pm$ 10.2	69.5 $\pm$ 9.7	0.005
Male sex	90 (74.4%)	14 (66.7%)	0.311	95 (74.8%)	9 (60.0%)	0.178
Hypertension	88 (72.7%)	18 (85.7%)	0.161	93 (73.2%)	13 (86.7%)	0.212
Type 2 diabetes	53 (43.8%)	10 (47.6%)	0.463	56 (44.1%)	7 (46.7%)	0.530
Hypercholesterolemia	82 (67.8%)	10 (47.6%)	0.064	85 (66.9%)	7 (46.7%)	0.104
Current smoker	86 (71.1%)	14 (66.7%)	0.431	92 (72.4%)	8 (53.3%)	0.111
Medications						
ACE-inhibitors and/or ARB	74 (61.2%)	9 (42.9%)	0.092	77 (60.6%)	6 (40.0%)	0.105
β -Blockers	48 (39.7%)	10 (47.6%)	0.326	52 (40.9%)	6 (40.0%)	0.587
Statins	48 (39.7%)	5 (23.8%)	0.125	49 (38.6%)	4 (26.7%)	0.272
C-reactive protein (mg/l) ^a	0.74 $\pm$ 1.53	0.91 $\pm$ 1.18	0.191	0.73 $\pm$ 1.50	1.11 $\pm$ 1.33	0.073
Peak CPK (IU/L) ^a	2478 $\pm$ 2297	3055 $\pm$ 2616	0.469	2531 $\pm$ 2281	2843 $\pm$ 2920	0.773
Time from onset to angioplasty (h)	4.9 $\pm$ 2.6	5.7 $\pm$ 3.2	0.315	4.9 $\pm$ 2.5	5.9 $\pm$ 3.6	0.297
Killip class ≥ 2	1 (0.8%)	5 (23.8%)	<0.001	2 (1.6%)	4 (26.7%)	0.001
Number of Q-waves	1.7 $\pm$ 1.7	2.6 $\pm$ 1.8	0.025	1.7 $\pm$ 1.7	2.7 $\pm$ 2.0	0.039
Corrected QT dispersion (ms)						
Before PCI	32.4 $\pm$ 17.0	49.1 $\pm$ 19.2	<0.001	32.9 $\pm$ 16.9	51.2 $\pm$ 21.7	<0.001
24 h after PCI	32.1 $\pm$ 21.2	46.0 $\pm$ 23.6	0.007	32.8 $\pm$ 21.5	45.4 $\pm$ 24.6	0.036
Ejection fraction (%)	59.3 $\pm$ 12.3	55.4 $\pm$ 15.7	0.206	58.7 $\pm$ 12.8	58.7 $\pm$ 13.9	0.990

Data are mean $\pm$ standard deviation (SD) or No. of patients.

^a Data of C-reactive protein and peak CPK were evaluated using the Wilcoxon rank sum test.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; CPK, creatine phosphokinase; PCI, percutaneous coronary intervention; Levels of C-reactive protein were determined on admission.

TABLE 2 Predictors of MACE and mortality in multivariate cox analysis

Model and variables in the model	MACE		Mortality	
	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Model 1				
Corrected QT dispersion before PCI	2.24 (1.36–3.68) ^a	0.001	2.71 (1.50–4.89) ^a	0.001
Age	1.85 (1.09–3.16) ^a	0.023	1.79 (0.97–3.31) ^a	0.064
Male	1.17 (0.41–3.34)	0.766	0.89 (0.25–3.10)	0.851
Ejection fraction	0.82 (0.54–1.26) ^a	0.365	1.08 (0.65–1.80) ^a	0.768
Killip class ≥ 2	8.44 (2.52–28.28)	0.001	9.61 (2.20–41.98)	0.003
Model 2: same variables as in model 1, except number of Q waves is substituted for Killip class ≥ 2	—	—	—	—
Corrected QT dispersion before PCI	1.93 (1.25–2.98) ^a	0.003	2.22 (1.34–3.68) ^a	0.002
Number of Q waves	1.60 (1.02–2.53) ^a	0.042	2.07 (1.19–3.62) ^a	0.010
Model 3: same variables as in model 1, except corrected QT dispersion at 24 h after PCI is substituted for corrected QT dispersion before PCI	—	—	—	—
Corrected QT dispersion at 24 h after PCI	1.36 (0.87–2.13) ^a	0.176	1.26 (0.73–2.18) ^a	0.400

PCI, percutaneous coronary intervention.

^a Hazard ratio for continuous variables reflects a 1-SD magnitude increase.

AMI was not. Zabel *et al.*⁸ suggested that QT dispersion failed to predict subsequent risk in AMI survivors. Spargias *et al.*⁹ reported that QT dispersion was an independent predictor of long-term, all-cause mortality risk in patients with AMI. In this study, corrected QT dispersion before PCI was associated with the incidence of MACE and mortality after successful PCI in AMI. Corrected QT dispersion at 24 h after PCI was inclined to be associated with the incidence of MACE and mortality, but this association was not statistically significant in multivariate analysis. There appear to be several explanations for these conflicting results about the relation between QT dispersion and mortality. One of the reasons might be that the period of examination of ECG in this study differed from that in previous studies. Another reason might be due to the differences in the therapeutic procedures for AMI. Wang *et al.*⁶ examined ECGs recorded within 24 h after the onset of AMI. Glancy *et al.*⁷ examined ECGs recorded 2 or 3 days after AMI and at least 4 weeks later. Zabel *et al.*⁸ analyzed ECGs recorded at the time of hospital discharge. Nearly half the number of patients in their studies were treated by thrombolysis and/or revascularization procedures. Spargias *et al.*⁹ examined ECGs obtained between day 0 and day 9 (median time 2 days) after AMI without revascularization procedures. Higham *et al.*^{3,10} have reported that QT dispersion increases from the very first hours and decreases with time in most cases. Spargias *et al.*⁹ discussed that early recordings might contain additional information on residual ischemia in view of the effects of acute ischemia on QT dispersion. Therefore, we examined QT dispersion before and 24 h after PCI. Further studies concerning the differences in the therapeutic procedures for AMI and the optimal timing of examination of ECG were needed.

The electrophysiological and biological mechanisms concerning the link between QT dispersion and prognosis are unclear. Fiol *et al.*¹¹ reported that QT dispersion did not predict ventricular fibrillation in AMI. On the other hand, it has been reported that increased QT dispersion predicts the risk of ventricular fibrillation in AMI.⁵ Since the number of patients with episodes of ventricular fibrillation was quite small in this study, we could not assess the relationship between QT dispersion and ventricular fibrillation. Halkin *et al.*¹² have reported that peak creatine kinase after primary PCI for AMI is a powerful predictor of mortality. Waldecker *et al.*¹³ demonstrated that poor left ventricular ejection fraction was a long-term risk factor in AMI. We examined the relation of corrected QT dispersion before PCI to peak creatine phosphokinase levels and left ventricular ejection fraction. There was a weak relationship between corrected QT dispersion before PCI and peak creatine phosphokinase levels ($r = 0.150$, $p = 0.075$) and a very weak inverse relationship between corrected QT dispersion before PCI and left ventricular ejection fraction ($r = -0.132$, $p = 0.118$). Furthermore, we examined the relationship of these factors to MACE and mortality, but there was no association. Further study is required to elucidate this mechanism.

Study Limitations

There are several important limitations to this study. First, we analyzed a limited number of patients. In addition to this, the number of observed events was quite few. Therefore, our analyses were by methods using models 1–3 of Table 2. To generalize the results of this study, studies involving a large number of patients would

help to increase the accuracy of the results. Second, we measured QT intervals manually in this study. Goldenberg *et al.*¹⁴ suggested that the accuracy of automatic measurements of QT interval was questionable in many cases. Furthermore, they suggested that standard 12-lead ECGs, tracing at 25 mm/s paper speed and a gain of 10 mm/mV, were generally adequate for accurate measurements of QT interval. The accuracy and reproducibility of QT interval measurement have been limited.

Conclusions

Corrected QT dispersion before PCI is associated with an increased risk of MACE and mortality after successful PCI in patients with AMI. Our analysis is considered to be useful for predicting prognosis after PCI in AMI.

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