Effects of Slow Coronary Artery Flow on QT Interval Duration and Dispersion

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Background: The coronary slow-flow phenomenon is an angiographic phenomenon characterized by delayed opacification of vessels in the absence of any evidence of obstructive epicardial coronary disease. Several studies have demonstrated myocardial ischemia in patients with slow coronary artery flow. In the present study, we aimed at evaluating the effects of slow coronary artery flow on QT interval duration and QT dispersion as a possible indicator of increased risk for ventricular arrhythmias and sudden cardiac death.

Methods: The study population included 49 patients with angiographically proven normal coronary arteries and slow coronary flow in all three coronary vessels (group I, 33 males, 16 females, mean age = 48 ± 9 years), and 71 patients with angiographically proven normal coronary arteries without associated slow coronary flow (group II, 47 males, 24 females, mean age = 50 ± 8 years). Coronary flow rates of all subjects were documented by thrombolysis in myocardial infarction frame count (TIMI frame count). QT interval duration and QT dispersion of all subjects were measured on the standard 12-lead electrocardiogram.

Results: There was no statistically significant difference between the two groups in respect to age, gender, presence of hypertension, and diabetes mellitus. There was a significant difference between the two groups in respect to the presence of cigarette smoking, typical angina, and positive exercise test results. TIMI frame counts of group I patients were significantly higher than those of group II patients for all three coronary arteries ($P < 0.001$). Maximum corrected QT interval (QTcmax) of group I did not differ from the QTcmax of group II ($P > 0.05$). However, minimum corrected QT interval (QTcmin) of group I was significantly lower than that for group II ($P = 0.008$). Consequently, corrected QT dispersion (QTcd) in group I was found to be significantly higher than in group II ($P < 0.001$).

Conclusion: QTcd, indicating increased risk for ventricular arrhythmias and cardiovascular mortality, was found to be significantly higher in patients with slow coronary artery flow. However, further long-term prospective studies should be carried out to establish the significance of QTcd as a risk factor for ventricular arrhythmias and subsequent sudden cardiac death in patients with slow coronary artery flow.

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Angiographically normal coronary arteries are found in as many as 10–30% of patients being evaluated for typical angina or angina-like pain and suspected coronary artery disease.^{1–3} The etiology of angina pectoris in patients with normal coronary anatomy on angiography is not precisely known.^{4,5} The coronary slow-flow phenomenon

is an angiographic phenomenon characterized by delayed opacification of vessels in the absence of any evidence of obstructive epicardial coronary disease. Tambe et al.⁶ first reported cases of angina pectoris in patients with decreased coronary blood flow rates though no atherosclerotic disease was present. Several studies have demonstrated

myocardial ischemia in patients with slow coronary artery flow.⁶⁻⁸ Increased QT dispersion (QTd) on the surface electrocardiogram has been linked to increased heterogeneity of ventricular repolarization, implicated in the genesis of ventricular arrhythmias and has been associated with an adverse prognosis in a variety of patient populations.^{9,10}

In the present study, we aimed at evaluating the effects of slow coronary artery flow on the QT interval duration and QTd as a possible indicator of increased risk for ventricular arrhythmias and sudden cardiac death. To the best of our knowledge, this study is the first to evaluate QTd in patients with slow coronary artery flow.

METHODS

Study Population

The study population included 49 patients with angiographically proven normal coronary arteries and slow coronary flow in all three coronary vessels (group I, 33 males, 16 females, mean age = 48 ± 9 years), and 71 patients with angiographically proven normal coronary arteries without associated slow coronary flow (group II, 47 males, 24 females, mean age = 50 ± 8 years). Patients with left ventricular dysfunction, echocardiographically proven left ventricular hypertrophy, atrial fibrillation, bundle branch block, evidence of any other intraventricular conduction defect, or electrolyte abnormalities were excluded from the study. No subjects were taking agents that could affect the QT interval or autonomic tone, especially antiarrhythmic agents, digitalis, beta-blockers, or calcium antagonists.

Documentation of Slow Coronary Flow

All patients underwent coronary angiography for the complaints of chest pain. Coronary flow rates of all subjects were documented by thrombolysis in myocardial infarction frame count (TIMI frame count). The TIMI frame count method is a simple, reproducible, objective, and quantitative index of coronary flow velocity.¹¹ It has been suggested that a higher TIMI frame count may reflect disordered resistance vessel function.¹¹ The TIMI frame count was determined for each major coronary artery in each patient according to the method first described by Gibson et al.¹¹ Briefly, the number of cineangiographic frames, recorded at 30 frames per second, required for the leading edge of the column of radiographic contrast to reach a predetermined land-

mark, is determined. The first frame is defined as the frame in which concentrated dye occupies the full width of the proximal coronary artery lumen, touching both borders of the lumen, and in forward motion proceeds down the artery. The final frame is designated when the leading edge of the contrast column initially arrives at the distal landmark. In the left anterior descending (LAD) coronary artery, the landmark used is the most distal branch nearest the apex of the left ventricle, commonly referred to as the "pitchfork" or the "whale's tail." LAD coronary artery is usually longer than the other major coronary arteries,¹² the TIMI frame count for this vessel is often higher. To obtain a corrected TIMI frame count for LAD coronary artery, the TIMI frame count was divided by 1.7.¹¹ The right coronary artery (RCA) distal landmark is the first branch of the posteriolateral RCA after the origin of the posterior descending artery, regardless of the size of this branch. The branch of the left circumflex (LCx) artery that encompassed the greatest total distance traveled by contrast was used to define the distal landmark of the LCx artery. The TIMI frame count in the LAD and LCx arteries was assessed in a right anterior oblique projection with caudal angulation and RCA in left anterior oblique projection with cranial angulation.

Diagnostic Criteria for Slow Coronary Flow

Patients with a corrected TIMI frame count greater than two standard deviations from the normal published range for the particular vessel were considered as having a slow coronary flow while those whose corrected TIMI frame count fell within two standard deviations of the published normal range were labeled as having normal coronary flow.¹¹

Measurement of Corrected QT Dispersion

A 12-lead electrocardiogram was recorded for each subject at a paper speed of 50 mm/s. The QT interval was measured from the onset of the QRS complex to the end of the T wave, defined as its return to the T-P isoelectric baseline. The QT interval was measured to the nadir of the curve between the T and U waves when the latter was present. If the end of the T wave could not be reliably determined or when the T waves were isoelectric or of quite low amplitude, QT measurements were not

made and these leads were excluded from analysis. A lower limit of 8 or more technically adequate leads per electrocardiogram was set for inclusion in this study. QTd was defined as the difference between the maximum and minimum interval measurements occurring among any of the 12 leads on a standard electrocardiogram. QTc (heart-rate-corrected QT interval) was calculated according to Bazett's formula¹³ as follows: $QTc = QT / \text{square root of the RR interval}$. Corrected QT dispersion (QTcd) was calculated in a manner similar to QTd.

Statistical Analysis

Continuous variables were expressed as mean $\pm$ SD and categorical variables were expressed as a percentage. Comparison of categorical and continuous variables between two groups was performed using the chi-square test and unpaired *t*-test, respectively. The correlation between QTcd and TIMI frame count was assessed by the Pearson correlation test. A *P*-value of <0.05 was considered statistically significant.

RESULTS

There were no statistically significant differences between the two groups with respect to age, gender, presence of hypertension, and diabetes mellitus ($P > 0.05$, Table 1). However, there was a statistically significant difference between the two groups with respect to the presence of cigarette smoking, typical angina, and positive exercise test results ($P < 0.01$, Table 1). TIMI frame counts of group I patients were significantly higher than those of group II patients for all three coronary arteries ($P < 0.001$ for all, Table 2). Maximum corrected QT interval (QTcmax) of group I did not differ from the QTcmax of group II ($P > 0.05$, Table 3). However,

Table 2. Thrombolysis in Myocardial Infarction (TIMI) Frame Counts of Patients and Control Subjects

Vessel	Group I	Group II	P
Left anterior descending	48 $\pm$ 16	24 $\pm$ 4	<0.001
Left circumflex	51 $\pm$ 15	23 $\pm$ 4	<0.001
Right coronary artery	53 $\pm$ 14	22 $\pm$ 3	<0.001

the minimum corrected QT interval (QTcmin) of group I was significantly lower than that of group II ($P = 0.008$, Table 3). Consequently, QTcd in group I was found to be significantly higher than in group II ($P < 0.001$, Table 3). In addition, we found a significant correlation between QTcd and TIMI frame counts ($P < 0.001$, Table 4).

Table 3. Comparison of Electrocardiographic Measurements Between Patients and Control Subjects

Variables	Group I	Group II	P
QTcmin (ms)	383 $\pm$ 23	397 $\pm$ 31	0.008
QTcmax (ms)	426 $\pm$ 32	427 $\pm$ 25	>0.05
QTcd (ms)	43 $\pm$ 9	30 $\pm$ 8	<0.001

QTcmin: minimum corrected QT interval; QTcmax: maximum corrected QT interval; QTcd: corrected QT dispersion.

DISCUSSION

The main finding of this study was that QTcd is significantly higher in patients with slow coronary flow documented by TIMI frame count than those with normal coronary flow.

QTd, defined as the difference between maximum and minimum QT interval measured on the surface electrocardiogram, is regarded as a measure of regional ventricular repolarization abnormalities.^{9,14} Previous studies have shown that

Table 1. Baseline Clinical Characteristics of Group I and Group II Patients

Variable	Group I (n = 49)	Group II (n = 71)	P
Age (year, mean $\pm$ SD)	48 $\pm$ 9	50 $\pm$ 8	NS
Gender (male/female)	33/16	47/24	NS
Hypertension	18/49 (37%)	25/71 (35%)	NS
Diabetes mellitus	6/49 (12%)	9/71 (13%)	NS
Cigarette smoking	26/49 (53%)	25/71 (36%)	<0.01
Typical angina	32/49 (65%)	23/71 (32%)	<0.01
Positive exercise test	27/49 (55%)	16/71 (22%)	<0.01

NS: Nonsignificant.

Table 4. Correlation Between Corrected QT Dispersion and Thrombolysis in Myocardial Infarction (TIMI) Frame Count

	TIMI Frame Count					
	LAD		LCX		RCA	
	r	P	r	P	r	P
QTcd	0.686	<0.01	0.527	<0.01	0.558	<0.01

QTcd: corrected QT dispersion; LAD: left anterior descending; LCX: left circumflex; RCA: right coronary artery.

healthy subjects exhibit a small degree of QTd.^{14,15} However, increased QTd has been linked to increased heterogeneity of ventricular repolarization, implicated in the genesis of potentially lethal ventricular arrhythmias, and has been associated with an adverse prognosis in a variety of patient populations.^{9,10}

Slow runoff dye in the coronary arteries during selective coronary angiography is known as slow coronary artery flow.⁶ Since its original description in 1972 by Tambe et al.⁶ the phenomenon of slow dye progression in the coronary arteries is well known to invasive cardiologists. However, over all these years only scarce attention has been paid to this phenomenon and consequently, its clinical significance remains unclear. Some authors have suggested that an abnormal increase of small vessel resistance was the cause of the slow progression of the dye in selective coronary angiography.^{16–18} It is believed to represent coronary microvascular dysfunction. Histopathological studies have revealed the existence of fibromuscular hyperplasia, medial hypertrophy, myointimal proliferation, and endothelial degeneration in microvascular circulation from the right ventricular biopsy specimens of patients with slow coronary artery flow.¹⁸ It has been suggested that these histopathological changes lead to an abnormally increased microvascular tone.^{17,18} Most patients with slow coronary flow complain mainly of typical angina pectoris. Yaymaci et al.⁷ have documented the presence of myocardial ischemia in 83.4% of these patients with positive scintigraphic findings. Furthermore, some authors have shown exercise-induced ST-segment depression in patients with slow coronary flow without obstructive coronary artery disease.^{6,8} In our study, most of the patients (65%) with slow coronary flow had a typical angina as compared with a much smaller proportion (32%) with normal coronary flow. Also, a definitively positive exercise test was

much more commonly observed in patients with slow coronary flow than in patients with normal coronary flow (55% vs 22%, respectively). Therefore, increased QTcd in patients with slow coronary flow may be attributed to the impaired coronary blood flow, which may result from microvascular dysfunction. Coronary insufficiency caused by impaired coronary blood flow seems to be the most valuable explanation for increased left ventricular repolarization heterogeneity in patients with slow coronary flow.

In the present study, increased QTcd in patients with slow coronary artery flow is mainly due to the shortened minimum QTc interval. In other words, the decrease in minimum QTc interval caused the increase of QTcd. In patients with ischemic heart disease, an increase in QTcd has been shown in patients with both acute ischemia¹⁹ and chronic ischemic heart disease²⁰ without any accompanying significant change in the length of maximum QTc interval. Myocardial ischemia shortens the action potential duration of myocardial cells through the increase of outward potassium ions, which is caused by ischemia-enhanced adenosine triphosphate-dependent potassium channel activity.^{21,22} This results in the shortening of minimum QTc interval; subsequently QTcd increases. We have also found decreased minimum QT interval in accordance with the previous studies, which have reported increased QTd due to decrease in minimum QT interval in a patient with acute or chronic ischemic heart disease. This finding can also be attributed to myocardial ischemia caused by microvascular dysfunction or slow coronary flow.

CONCLUSION

In conclusion, we found that QTcd, indicating increased risk for ventricular arrhythmias and cardiovascular mortality, is significantly higher in

patients with slow coronary artery flow. However, further prospective studies should be carried out to establish the significance of QTcd as a risk factor for ventricular arrhythmias and subsequent sudden cardiac death in patients with slow coronary artery flow.

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