

The QT prolongation and clinical features in patients with takotsubo cardiomyopathy: Experiences of two tertiary cardiovascular centers

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ABSTRACT

Objective: There are few data regarding clinical characteristics, laboratory parameters, electrocardiographic and echocardiographic findings in takotsubo cardiomyopathy patients presenting with QT prolongation. Aim of this study was to investigate the differences in these parameters between takotsubo cardiomyopathy patients presenting with and those without QT prolongation.

Methods: We performed an observational retrospective study. One hundred five patients were enrolled from the takotsubo cardiomyopathy registry database and divided according to the presence of QT prolongation. Fifty patients presented with QT prolongation (QT group) and 55 did not (NQT group). Statistical analysis was performed using Student's t-test or Mann-Whitney U test and chi-square test.

Results: QT group had higher prevalence of dyspnea (66 versus 40%, $p=0.008$) and cardiogenic shock (46 versus 24%, $p=0.016$) than NQT group. QT group had higher prevalence of ST elevation (82 versus 64%, $p=0.036$), T wave inversion (96 versus 58%, $p=0.001$), ventricular tachycardia/ventricular fibrillation (8 versus 0%, $p=0.032$) and classic ballooning pattern (92 versus 66%, $p=0.003$), but lower left ventricular ejection fraction (mean, 39.2 versus 43.5%, $p=0.005$). In addition, QT group had significant higher hs-C-reactive protein (median, 6.6 versus 1.7 mg/L, $p=0.023$), creatine kinase-MB (median, 18.6 versus 7.6 ng/mL, $p=0.032$) and NT-pro-brain natriuretic peptide levels (median, 3637 versus 2145 pg/mL, $p=0.044$). QT group required more frequent use of inotropics (46 versus 24%, $p=0.016$) and diuretics (58 versus 38%, $p=0.042$) than NQT group.

Conclusion: The clinical features of takotsubo cardiomyopathy are different according to the presence of QT prolongation. The QT group was lesser likely to have preserved cardiovascular reserve and more likely to require hemodynamic support than the NQT group despite the entire prognosis of takotsubo cardiomyopathy is excellent regardless of QT prolongation. (*Anadolu Kardiyol Derg 2014; 14: 162-9*)

Key words: Takotsubo cardiomyopathy, stress-induced cardiomyopathy, transient left ventricular ballooning syndrome, QT prolongation, long QT syndrome

Introduction

Takotsubo cardiomyopathy (TTC), also known as transient left ventricular (LV) ballooning syndrome, stress-induced cardiomyopathy, is characterized by transients LV dysfunction in the apical and/or mid-ventricular segments, in the absence of significant angiographic coronary stenosis, usually provoked by an episode of emotional or physical stress (1-4).

Although the association between TTC and QT prolongation has been reported (4-8), there are few data regarding the clinical characteristics in TTC patients presenting with QT prolongation in detail. Moreover, there remains very little emphasis on arrhythmic risk in contemporary reviews despite the increasing

numbers of life-threatening arrhythmias reported in the setting of TTC with QT prolongation (5).

In this study, we investigated the clinical characteristics, laboratory parameters, electrocardiographic and echocardiographic findings of TTC patients presenting with QT prolongation and compared the differences in these parameters between those presenting with and without QT prolongation as initial presentation.

Methods

Study design

This is an observational retrospective study



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Study population

We approached 105 consecutive patients enrolled from the TTC registry database from January 2004 to January 2010. From 5177 consecutive patients with a diagnosis of an acute coronary syndrome, including ST- and non-ST-elevation myocardial infarction, who had an urgent coronary angiography (CAG), 105 (2%) patients were diagnosed with TTC. The criteria for inclusion were as follows: (1) transient akinesia /dyskinesia beyond a single major coronary artery vascular distribution, (2) absence of significant coronary artery disease on coronary angiograms (diameter stenosis <50% by visual estimation) or absence of angiographic evidence of acute plaque rupture, and (3) new electrocardiographic changes (ECG) (ST-segment changes, T-wave inversion, or Q-wave) (9). The enrolled 105 patients with TTC were divided into two groups: Fifty patients (48%) presenting with QT prolongation were grouped into QT group, and 55 presenting without QT prolongation were grouped into NQT group.

The protocol was approved by the Institutional Research Ethics Committee. The recommendations of the revised version of the Declaration of Helsinki were met.

Definitions

QT prolongation was defined as corrected QT interval (QTc) more than 430 milliseconds for male patients and QTc more than 450 milliseconds for female patients according to the formula by Bazett (10). Ballooning pattern was divided into 4 subgroups: classic pattern (showing apical and/or midventricular akinesia or hypokinesia with normal contractility or hyper contractility in basal segments), reverse pattern (showing basal akinesia or hyperkinesias with preserved contractility of apical and midventricular segments), midventricular pattern (showing mid-ventricular akinesia or hypokinesia sparing the base and the apex), and localized pattern (affecting a segment of the left ventricular wall) (11).

Cardiogenic shock was defined as a systolic blood pressure (SBP) <90 mm Hg for ≥ 30 minutes that was not responsive to fluid administration alone, accompanied by evidence of tissue hypo-perfusion in the setting of clinically adequate or elevated LV filling pressures (12). Pulmonary edema was defined as the presence of rales at pulmonary examination or a radiographic report of pulmonary alveolar/interstitial congestion at initial chest roentgenogram (12). Hypertension was defined as repeated measurements of SBP and diastolic blood pressure (DBP), or previous antihypertensive drug treatment. Diabetes mellitus was defined as serum glucose level of 125 mg/dL or higher, a history of diabetes mellitus, or current use of anti-diabetic therapy. Current smoking was defined as having smoked cigarettes less than 1 year before patients presented with TTC.

Study protocol

The medical history and coronary risk factors were obtained from medical records combined with a patient questionnaire. Any physical or emotional stresses prior to the onset of this syndrome were specifically investigated. Electrocardiography

(ECG) and laboratory data including cardiac enzymes [creatinine kinase (CK), creatine kinase MB fraction (CK-MB), and troponin-I] were recorded during the acute phase and were followed until the abnormalities disappeared.

All patients underwent coronary angiography concomitant with left ventricular angiography at the time of presentation. To exclude vasospastic angina, a spasm provocation test was performed in 71 (68%) patients by intracoronary ergonovine infusion as described previously (13).

Electrocardiogram

Daily standard 12-lead ECGs during hospitalization were recorded at a paper speed of 25 mm/s and amplification of 10 mm/mV in all patients. More ECGs were recorded, especially in the acute phase, according to patients' clinical conditions. Patients with malignant ventricular arrhythmias [ventricular tachycardia /ventricular fibrillation, (VT/VF)] captured on 12-lead ECG or on telemetry were identified. Tracings were analyzed manually using a ruler without magnification. ST-segment elevation (millivolts) was measured at the J point. Inverted T-wave amplitude was also measured from the T-wave trough to the baseline determined using the PR segment. T-wave inversion was defined as > 0.05 mV of the negative component. In the case of biphasic T waves, the most inverted deflection was measured from the baseline. QT interval was measured manually over 3 consecutive RR intervals, and results were averaged. Corrected QTc was calculated according to Bazett's formula. All components of ECGs were analyzed by 2 experienced cardiologists blinded to patients' clinical data.

Echocardiography

Transthoracic echocardiographic examinations were performed in all patients with a 2.5 MHz transducer attached to a commercially available Doppler echocardiography machine (Acuson 512, Siemens Medical Solutions, Mountain View, CA, USA), on the first hospital day or within 24 hours of CAG and follow-up. LV end-diastolic (LVEDD) and end-systolic diameters (LVESD), along with septal and posterior wall thickness at end-diastole were measured in the para-sternal long axis view, using 2D-guided M-mode echocardiography according to the recommendations of chamber quantification (14). The LV ejection fraction (EF) was calculated by modified Simpson's method. The valvular regurgitation (VR) was assessed by color Doppler flow mapping of spatial distribution of the regurgitant jet in accordance with the ASE recommendation (15). In our study, significant VR was defined as regurgitation of more than a mild degree. In our study, we assessed the presence of systolic anterior motion (SAM) of the mitral leaflet using 2-dimensional imaging (9). The early diastolic mitral inflow velocity (E) was recording using pulse wave Doppler echocardiogram, with sample volume placing at the tip of the mitral valve leaflets as they opened. The early diastolic tissue Doppler velocity (E') of the mitral annulus was obtained from 4-chamber apical view in the septal position. Left atrial (LA) volume was determined by the prolate ellipse method and indexed by body surface area (LAVI).

N-terminal prohormone brain natriuretic peptide (NT-proBNP) assay

We took blood samples from the antecubital vein using lithium heparin, and the blood samples were then centrifuged. The blood samples were stored at -70°C until further analysis. Plasma NT-proBNP levels were measured using an Elecsys proBNP reagent kit (Roche Diagnostics, USA) and an Elecsys 2010 (Roche Diagnostics, USA). In all cases, the time interval between blood sampling for NT-proBNP and echocardiography was within 1 day.

Statistical analysis

Statistical analyses were performed using SPSS statistical software (version 11.0, SPSS Corp, Chicago, IL, USA). Quantitative data are presented as mean \pm standard deviation. Age, QTc, high sensitivity C-reactive protein (hs-CRP), serum levels of potassium, calcium, magnesium, peak CK, peak CK-MB, peak troponin-I, duration of hospitalization, and duration of intensive care unit (ICU) stay are given in terms of the median and inter-quartile range (IQR). Qualitative data are presented as frequencies. The Student's t-test or The Mann-Whitney U test was used to compare the continuous variables and the Chi-square test was used to compare the categorical variables. All p values are two-tailed and differences were considered significant when the p value was less than 0.05.

Results

The comparison of clinical characteristics between QT and NQT group (Table 1)

QT group had higher prevalence of dyspnea (66 versus 40%, $p=0.008$) and cardiogenic shock (46 versus 24%, $p=0.016$) than NQT group. There were no significant differences in other parameters of clinical characteristics and initial presentations between two groups.

The comparison of ECG changes, laboratory, and angiographic findings between QT and NQT group (Table 2)

QT group had higher prevalence of ST elevation (82 versus 64%, $p=0.036$), T wave inversion (96 versus 58%, $p=0.001$), and VT/VF (8 versus 0%, $p=0.032$) than NQT group. In addition, QT group had significant higher hs-CRP (median, 6.6 versus 1.7 mg/L, $p=0.023$), CK-MB (median, 18.6 versus 7.6 ng/mL, $p=0.032$) and NT-proBNP levels (median, 3637 versus 2145 pg/mL, $p=0.044$). There were no significant differences in time intervals from initial presentation to initial ECG [median, 24 hours, (IQR, 12-48 hours) in QT group versus median 24 hours, (IQR, 12-24 hours) in other NQT group, $p=0.120$] and follow-up ECG after regional wall motion disappeared on echocardiogram [median, 19 days, (IQR, 8-59 days) in QT group versus median, 13 days, (IQR, 8-70 days) in NQT group, $p=0.976$] were not different between the two groups. Patients who suffered VT/VF occurred during index hospitalization had significantly longer QTc interval [488 (IQR, 487-530) versus 434 (IQR, 417-483) ms, $p=0.031$] and higher preva-

lence of subjects with QT interval prolongation (100 versus 46%, $p=0.032$) on the initial ECG than those without VT/VF. There were no significant differences in QTc interval [437 (IQR, 388-480) versus 384 (IQR, 367-433) ms, $p=0.086$] and prevalence of subjects with QT interval prolongation (25 versus 10%, $p=0.282$) on the follow-up ECG between two groups (Fig. 1).

The comparison of echocardiographic findings between QT and NQT group (Table 3)

QT group had higher prevalence of classic ballooning pattern (92 versus 66%, $p=0.003$), but lower LVEF (mean, 39.2 versus 43.5%, $p=0.005$). There were no significant differences in time intervals from initial presentation to initial echocardiography [median, 24 hours, (IQR, 12-48 hours) in QT group versus median 24 hours, (IQR, 12-24 hours) in other NQT group, $p=0.120$] and follow-up echocardiography after clinical recovery [median, 19 days, (IQR, 8-59 days) in QT group versus median, 13 days, (IQR, 8-70 days) in NQT group, $p=0.976$] were not different between the two groups. All patients showed normalized regional wall motion in their follow-up echocardiogram.

The comparison of management and clinical outcomes between QT and NQT group (Table 4)

QT group required more frequent use of inotropes (46 versus 24%, $p=0.016$) and diuretics (58 versus 38%, $p=0.042$) than NQT group. There were no significant differences in use of intra-aortic balloon pump (IABP), use of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), and use of beta blocker during hospitalization between the two groups. Also, there were no significant differences in duration of hospitalization, frequency and duration of ICU stay between the two groups.

During follow-up (median, 5.7 years, IQR, 4.9-6.8 years), 10 (7%) patients died; five (50%) patients died of malignancy, 2 of stroke, 1 of chronic renal failure with panperitonitis, 1 of liver cirrhosis with variceal bleeding, and 1 died of with pneumonia with empyema. However, cardiac deaths associated with TTC itself were not noted in both groups. Also, recurrence of the TTC was not noted in both groups.

Discussion

The purpose of this study was to explore and investigate the clinical characteristics, laboratory parameters, electrocardiographic and echocardiographic findings of TTC patients presenting with QT prolongation and compared the differences in these parameters between those presenting with and without QT prolongation as initial presentation.

The main findings of this study were as follows: First, the clinical features of TTC are different according to the presence of QT prolongation. QT group had higher prevalence of dyspnea and cardiogenic shock and VT/VF than NQT group. QT group required more frequent use of inotropes and diuretics than NQT group. Second, the QT group was lesser likely to have preserved

Table 1. The comparison of clinical characteristics between QT group and NQT group

Variables	QT group (n=50)	NQT group (n=55)	*P
Age, years [†]	64 (53-72)	64 (55-74)	0.900
Male gender, n (%)	17 (34)	12 (22)	0.163
Body surface area, m ²	1.6±0.1	1.6±0.2	0.224
Diabetes mellitus, n (%)	8 (16)	10 (18)	0.767
Hypertension, n (%)	16 (32)	14 (26)	0.458
Current smoker, n (%)	3 (6)	4 (7)	0.794
Underlying diseases			
Stroke/Transient ischemic attack, n (%)	3 (5)	0 (0)	0.065
Liver cirrhosis, n (%)	0 (0)	2 (4)	0.173
Chronic renal failure, n (%)	3 (6)	2 (4)	0.570
Malignancy, n (%)	7 (14)	10 (18)	0.561
Stress event, n (%)	38 (76)	47 (86)	0.218
Preceding physical stress, n (%)	30 (79)	41 (87)	0.306
Preceding emotional stress, n (%)	8 (21)	6 (13)	-
Clinical presentation			
Chest pain, n (%)	32 (64)	26 (47)	0.085
Dyspnea, n (%)	33 (66)	22 (40)	0.008
Nausea/vomiting, n (%)	7 (14)	4 (7)	0.261
Palpitation, n (%)	1 (2)	6 (11)	0.068
Loss of consciousness, n (%)	1 (2)	0 (0)	0.292
Cardiogenic shock, n (%)	23 (46)	13 (24)	0.016
Pulmonary edema, n (%)	21 (42)	20 (36)	0.554
†Presented as median (inter-quartile range) and number (percentage)			
*Mann-Whitney and Chi-square tests			

cardiovascular reserve and more likely to require hemodynamic support than the NQT group despite the entire prognosis of TTC is excellent regardless of QT prolongation.

Frequent ECG changes in TTC include ST segment elevation, T wave inversion, and prolongation of QT interval, the latter often being quite pronounced (1-4). It is becoming evident that TTC should be considered among the causes of acquired QT prolongation (7, 8). QT prolongation is associated with sudden cardiac death as a result of reentrant polymorphic VT, torsades de pointes (TDP), which can degenerate into VF (5, 16). More recently, VF had been previously described in the clinical presentation of TTC (2, 8, 17). However, despite these severe repolarization abnormalities seen in TTC, the pathophysiology of life-threatening arrhythmias in TTC remains incompletely understood, and the clinical features remain uncertain.

The prevalence of QT prolongation (48%) in our study was similar to the results of previously published reports in other

Table 2. The comparison of electrocardiographic changes, laboratory, and echocardiographic findings between QT group and NQT group

Variables	QT group (n=50)	NQT group (n=55)	*P
Electrocardiographic changes			
Life-threatening arrhythmia, n (%)	4 (8)	0 (0)	0.032
Torsades de pointes, n (%)	0 (0)	0 (0)	-
Complete atrioventricular block, n (%)	3 (6)	1 (2)	0.264
Sinus rhythm, n (%)	47 (94)	54 (98)	0.264
Atrial fibrillation, n (%)	3 (6)	1 (2)	-
ST-segment elevation, n (%)	41 (82)	35 (64)	0.036
Q-wave, n (%)	8 (16)	7 (13)	0.632
T-wave inversion, n (%)	48 (96)	32 (58)	0.001
Laboratory findings			
hs-CRP (mg/dL) [†]	6.6 (1.5-11.7)	1.7 (0.6-6.8)	0.023
Potassium (mmol/L) [†]	3.6 (3.6-3.9)	3.7 (3.6-4.0)	0.987
Calcium (mg/dL) [†]	9.1 (9.2-9.7)	9.2 (9.2-9.5)	0.458
Magnesium (mg/dL) [†]	1.9 (1.6-2.6)	1.9 (1.6-2.2)	0.135
Cardiac enzymes			
Peak CK (ng/mL) [†]	321 (112-632)	221 (93-412)	0.036
Peak CK-MB (ng/mL) [†]	18.6 (4.8-33.9)	7.6 (2.8-22.8)	0.032
Peak troponin-I (ng/mL) [†]	3.2 (0.2-9.4)	1.6 (0.2-10.1)	0.371
NT-proBNP (pg/mL) [†]	3637 (1932-35000)	2145 (598-17167)	0.044
†Presented as median (inter-quartile range) and number (percentage)			
*Mann-Whitney and Chi-square tests			
Life-threatening arrhythmia: ventricular tachycardia, ventricular fibrillation.			
CK - creatine kinase; hs-CRP - high sensitive C-reactive protein; NT-proBNP - N-terminal pro-brain natriuretic peptide			

areas of the world (4, 8, 17, 18). According to different case series, the prevalence of QT interval prolongation among TTC patients is high, ranging from 50% to 100% (4, 8, 17, 18). These differences of prevalence of QT interval prolongation are probably because systolic dysfunction is associated with TTC itself and QT interval prolongation (8, 19). Seth et al. (20) reported 12 cases of TTC with an average QTc interval of 478 ms. Similarly, Abe et al. (4) described 17 patients, most of whom had a prolonged QTc interval in the acute and subacute phases of the condition. As part of a report on 13 patients by Desmet et al. (21), each patient's ECG during the acute phase was described with QTc intervals ranging from 310 to 674 ms. Matsuoka et al. (18) specifically evaluated the QT interval in 10 consecutive cases of TTC. Among the possible hypotheses for the associations between these two entities, it has been proposed that mechanical and electrical dysfunctions may be caused by epinephrine-induced toxicity under stressful conditions (22-25). A similar

Table 3. The comparison of echocardiographic findings between QT group and NQT group: Initial TTE findings

Variables	QT group (n=50)	NQT group (n=55)	*P
Ballooning pattern			
Classic TTC pattern, n (%)	46 (92)	36 (66)	0.003
Reverse TTC pattern, n (%)	4 (8)	15 (27)	
Mid-ventricular pattern, n (%)	0 (0)	4 (7)	
Localized pattern, n (%)			
LVEF (%)	39.2±7.6	43.5±5.9	0.005
LVEDD, mm	53.3±6.7	53.0±6.3	0.831
LVESD, mm	37.7±8.0	37.5±5.9	0.909
LAVI, mL/m ²	25.5±8.4	27.8±16.8	0.394
E/E'	12.2±6.5	11.5±4.1	0.681
SAM, n (%)	7 (14)	3 (6)	0.136
Significant MR, n (%)	14 (28)	7 (13)	0.052
Significant AR, n (%)	2 (4)	5 (9)	0.296
Significant TR, n (%)	3 (6)	5 (9)	0.551
†Presented as mean±SD and number (percentage) *Student's t and Chi-square tests AR - aortic regurgitation; E/E' - early diastolic mitral inflow velocity/early diastolic tissue Doppler velocity; LAVI - left atrial volume index; LVEDD - left ventricular end-diastolic diameter; LVEF - left ventricular ejection fraction; LVESD - left ventricular end-systolic diameter; MR - mitral regurgitation; SAM - systolic anterior motion of anterior mitral leaflet; TR - tricuspid regurgitation, TTC - takotsubo cardiomyopathy, TTE - transthoracic echocardiography			

pattern of repolarization abnormalities, including diffuse T-wave inversions and QT prolongation have been described in other hyperadrenergic states, including pheochromocytoma and subarachnoid hemorrhage (22, 23). Catecholamines are known to increase calcium entry into cardiomyocytes, mainly by stimulating the L-type calcium current. Intracellular calcium overload has been proposed to underlie ventricular dysfunction in TTC (26, 27). The duration of the cardiac action potential determines how much calcium enters the myocytes during each contraction-relaxation cycle, so it is possible that prolonged action potential duration, as seen in long QT syndrome, exacerbates catecholamine-dependent intracellular calcium overloading and ventricular dysfunction in TTC (26-28). Therefore, it is reasonable to speculate that individuals with a reduced repolarization reserve, such as long QT syndrome or QT interval prolongation may have an increased risk for cellular calcium overload under such stressful conditions, rendering these individuals more susceptible to TTC.

Interestingly, in our study, QT group presented with severer heart failure symptoms such as dyspnea and cardiogenic shock than NQT group. Also, QT group had significantly higher levels of cardiac markers such as CK-MB, and NT-proBNP levels, but lower LVEF than NQT group. Possible hypothesis is that mechan-

Table 4. The comparison of clinical courses and management between QT group and NQT group

Variables	QT group (n=50)	NQT group (n=55)	*P
Use of inotropes, n (%)	23 (46)	13 (24)	0.016
Use of IABP, n (%)	8 (16)	5 (9)	0.283
Use of ACEI or ARB, n (%)	30 (60)	30 (55)	0.573
Use of Beta blocker, n (%)	10 (20)	9 (16)	0.516
Use of diuretic, n (%)	29 (58)	21 (38)	0.042
DC cardioversion, n (%)	4 (8)	0 (0)	0.032
Temporal pacemaker, n (%)	3 (6)	1 (2)	0.264
Permanent pacemaker, n (%)	0 (0)	0 (0)	-
Implantable cardioverter defibrillator, n (%)	0 (0)	0 (0)	-
ICU hospitalization, n (%)	33 (66)	35 (64)	0.800
ICU hospitalization (days)†	4 (1-5)	1 (0-5)	0.178
Hospitalization (days)†	19 (7-32)	14 (6-26)	0.110
In-hospital cardiac mortality, n(%)	0 (0)	0 (0)	-
Cardiac mortality during follow-up, n (%)	0 (0)	0 (0)	-
Mortality during follow-up, n (%)	7 (14)	3 (6)	0.136
Recurrence, n (%)	0 (0)	0 (0)	-
†Presented as median (inter-quartile range) and number (percentage) *Mann-Whitney U and Chi-square tests ACEI - angiotensin converting enzyme inhibitor; ARB - angiotensin receptor blocker; DC -cardioversion; direct current cardioversion; IABP - intra-aortic balloon pump; ICU - intensive care unit			

ical and electrical dysfunction in TTC may reflect the greater extent of affected myocardium in TTC patients and this extent of affected myocardium could be smaller in NQT group compared with QT group. Another possible explanation is that patients with QT group have higher prevalence of apical ballooning pattern than NQT group in our study. Classic TTC involves apical and/or mid-ventricular segments concomitant with hyper-contractility in basal segments, whereas apical and mid-ventricular segments are spared in a novel syndrome of reverse TTC (9, 11). Therefore, these findings may indicate that classic TTC has the greater extent of affected myocardium and cardiac markers such as CK-MB may reflect this extent of affected myocardium.

A remarkable finding in our study was that 4 (3.8%) among 105 enrolled patients presented VT at the index hospitalization for TTC. In addition, in our study, QT group had higher prevalence of VT/VF (8 versus 0%, p=0.032) than NQT group. Despite the increasing numbers of life-threatening arrhythmias reported in the setting of TTC, there remains very little emphasis on arrhythmic risk in contemporary reviews (5, 29, 30). Previously published study showed a 1-1.5% incidence of ventricular arrhythmias in a review of seven case series containing a total of 180 cases (29). Recently another study published by Madias et al. (5)

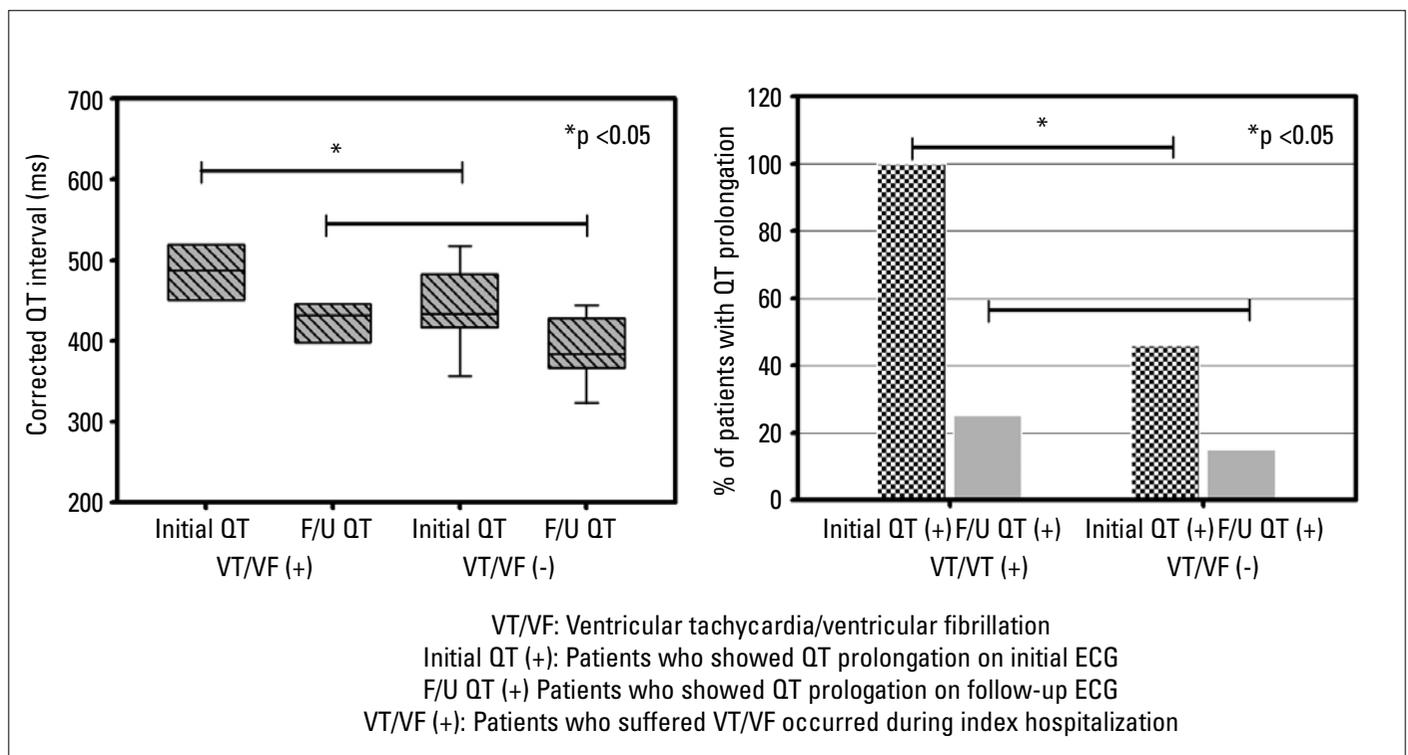


Figure 1. Comparison of QTc interval and prevalence of subjects with QT interval prolongation between subjects with VT/VF and those without. Patients who suffered VT/VF occurred during index hospitalization had significantly longer QTc interval and higher prevalence of subjects with QT interval prolongation on the initial ECG than those without VT/VF. There were no significant differences in QTc interval and prevalence of subjects with QT interval prolongation on the follow-up ECG between two groups.

ECG - electrocardiogram; VT/VF - ventricular tachycardia/ventricular fibrillation

showed 8.6% among patients with TTC had life threatening arrhythmias and TTC patients with ventricular arrhythmias had a longer QT on admission.

Notably, in our study, despite QT group had significantly higher prevalence of cardiogenic shock than NQT group, there were no differences in beta blocker use between two groups, whereas QT group had a significantly higher proportion of patients who were treated with inotropes and diuretics than NQT group. It has been reported that the use of inotropic agents, particularly in patients with shock, may increase the LV outflow tract obstruction and worsen cardiogenic shock in patients with TTC (9, 22, 31-34). Given that the pathophysiology of TTC has been attributed to catecholamine excess (9, 22, 31), the mainstay of therapy in most series has been early beta-blockade. These findings in our study are in contrast to the aforementioned reports (32-34). It seems likely that cardiogenic shock or acute heart failure is treated with standard therapies such as inotropes, diuretics and IABP, although a cautious trial of intravenous fluids and beta blockers may help by the basal hypercontractility, thereby reducing the obstruction in the absence of shock.

In view of the potential risk of pause dependent TDP, it is possible that beta-blockers should be used more cautiously, especially in TTC patients with bradycardia or severe QT prolongation (5-8). Of course, if pause-dependent TDP occurs, beta-blocker therapy should be withheld and instituted only after bradycardia and QT intervals have normalized (5). Moreover,

whether beta-blocker therapy is effective in preventing recurrences of TTC remains unknown (5-8). Among other therapies, potassium supplementation to maintain serum potassium at high-normal levels is suggested for management of drug-induced TDP (5, 16, 19). Hypokalemia can occur in the setting of catecholamine excess via a stress-induced intracellular shift of serum potassium (5, 16, 19). Similarly, in patients with TTC complicated by TDP or VF, or those featuring severe QT prolongation, rapid and aggressive potassium supplementation should be considered (5, 16, 19). Magnesium supplementation to high-normal values is also likely indicated. QT prolonging medications should be avoided in all patients with TTC (5, 16, 19).

In our study, permanent pacemaker (PPM) or implantable cardioverter defibrillator (ICD) has not been performed on all patients during follow up duration. Although QT prolongation is prevalent among patients with TTC, PPM insertion has been performed on few patients (5, 7, 8, 26). Whether PPM or ICD therapy is required for the long-term management of patients with TTC complicated by TDP and VF is unknown (5, 7, 8, 26). In general, QT interval prolongation and ST-T changes occur during the acute or subacute phase of illness, and these ECG changes typically normalize within several weeks of improvement in LV wall motion (5-8). Mastuoka et al. (18) reported electrocardiographic morphologies observed with obvious T-wave inversion or an ST-T abnormality change persisted for more than several weeks, although all patients had normal left ventricular function within a few weeks. Moreover, no patients experienced sudden

death or malignant ventricular arrhythmias, although the sub-acute phase ECG during giant negative T wave inversion showed significantly long repolarization dispersion.

In the present study, the overall mortality (7%) was relatively higher than in previous studies (1-4). However, the overall mortality associated with TTC itself was 0%. This excellent prognosis of TTC was comparable to results of published reports in other areas of the world (1-4).

Study limitations

There are some limitations that should be considered in our study. First, this was a retrospective analysis. In all patients, thorough review of all ECGs and telemetry strips was performed. However, it is possible that short, non-sustained arrhythmic events might not have always been documented in patient charts. Data on serum electrolytes were collected around the time of the arrhythmic events. However, the exact timing of blood draw relative to the arrhythmic episode was unclear in some circumstances; therefore, electrolyte levels might have been affected by resuscitative measures, including drug infusions in some of the patients. The value of QT is dynamic according to the time of recording of the ECG in relation to symptoms onset. Because of retrospective design, we could not evaluate possible relations between dynamic QT values and other ECG findings such as negative T waves. Second, clinically, genetic testing was not thought to be warranted at the time of their hospitalizations. Thus, common variants of congenital long QT syndrome cannot be definitively ruled out in these patients. Third, the results of our study may be limited by the relatively small number of enrolled patients. Fourth, we did not perform systemic investigations such as magnetic resonance imaging, viral antibody titers, or pathology. Finally, although patients with TTC have been shown to have marked elevations in plasma catecholamines and their metabolites, such measurements were not carried out in this study. Thus, we were unable to evaluate a possible relationship between higher catecholamine levels, QT prolongation, and risk of ventricular arrhythmia in TTC.

Conclusion

The clinical features of TTC are different according to the presence of QT prolongation. The QT group was lesser likely to have preserved cardiovascular reserve and more likely to require hemodynamic support than the NQT group despite the entire prognosis of TTC is excellent regardless of QT prolongation.

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B.G.S.; Literature search- S.H.K., S.H.P.; Writing – B.G.S.; Critical review- J.H.O., S.M.C.

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