Importance of Morphological Changes in T-U Waves During Bepridil Therapy as a Predictor of Ventricular Arrhythmic Event

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Background: Although bepridil is a useful anti-arrhythmic agent for atrial fibrillation, the appearance of serious ventricular arrhythmia, such as torsades de pointes, might be a problem. In this study, T-U wave morphology was evaluated during bepridil therapy and was examined as a predictor of ventricular arrhythmic events.

Methods and Results: The study population consisted of 113 patients on bepridil therapy. They were divided into 2 groups with and without ventricular arrhythmic events. Morphological changes in T-U waves were analyzed in leads V₂₋₅. During bepridil treatment, the QTc interval was prolonged from 0.45±0.01 to 0.49±0.01 s^{1/2} in all patients (P<0.0001) and any type of T-U wave change (fused U, slurred, bifid, biphasic or negative) appeared in 73% of event-free and 100% of event groups. In univariate analysis, QTc interval before bepridil (P=0.028), a wide QRS complex (P=0.042) before bepridil, biphasic (P=0.027) or negative (P=0.002) T-U waves in the stable phase, and the new appearance of biphasic (P=0.004) or negative (P<0.0001) T-U waves exhibited significant differences. In multivariate analysis, only newly appeared negative T-U wave exhibited a significant difference (odds ratio 10.13, 95% confidence interval=0.031–2.302, P=0.041).

Conclusions: In patients with stable bepridil treatment, a change in T-U wave morphology might be a useful predictor of ventricular arrhythmia assisting the QT interval. (*Circ J* 2010; **74**: 876–884)

Key Words: Anti-arrhythmic agent; Atrial fibrillation; Torsades de pointes; Ventricular arrhythmia

Although bepridil was originally composed as an anti-angina pectoris therapy by focusing on its calcium channel-blocking effect, recent reports have revealed that it might be useful for anti-arrhythmic therapy, especially for persistent atrial fibrillation (AF).^{1,2} In the J-BAF study, bepridil therapy achieved a high rate of AF conversion to sinus rhythm in a patient with persistent AF, although 1 patient suffered sudden cardiac death due to ventricular tachycardia (VT), and the study emphasized the need to use caution when administering bepridil.³ Because the mechanism of the appearance of ventricular arrhythmia could be understood as bepridil-induced change in ventricular repolarization, monitoring the parameters to predict ventricular arrhythmia is extremely important. There have been several attempts to use QT interval as a predictor of ventricular events during bepridil therapy, but there was considerable overlap between patients with and without ventricular events, so the QT interval is not a perfect predictor of these events.^{4,5} Because T-U waves during bepridil therapy frequently exhibit

specific changes in their morphologies,^{6,7} such as T-U fusion or slurred prolongation at T-wave end, determination of the T-wave end becomes difficult, commonly during bepridil therapy. Additionally, torsades de pointes (TdP) would appear through not only the prolongation of refractoriness but also the imbalance or dispersion of refractoriness, which would be observed as a change in T-U wave morphology, so that a simple measurement of the QT interval cannot be considered as the ultimate index to predict ventricular events. In this study, we evaluated T-U wave morphology as well as QT-related parameters during bepridil therapy to examine them as predictors of clinical events in ventricular arrhythmias.

Methods

Study Participants

The study population consisted of 113 patients who were treated with oral bepridil (100–200 mg/day). Of 113 patients, 112 were consecutive patients who were followed-up in our

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Table 1. Clinical Characteristics of the Patients

	Total population	Event-free group	Event group	Univariate P-value
Number	113	107	6	
Age (years)	62±1	62±1	65±4	0.682
Gender (F/M)	26/87	25/82	1/5	0.705
Height (cm)	164±1	164±1	164±5	0.930
Body weight (kg)	64±1	64±1	67±8	0.963
Dose of bepridil (200 mg/100 mg)	94/19	89/18	5/1	0.992
Structural heart disease				
IHD, n (%)	16 (14)	14 (13)	2 (33)	
Dilated cardiomyopathy, n (%)	2 (2)	2 (2)	0 (0)	
Hypertrophic cardiomyopathy, n (%)	8 (7)	8 (7)	0 (0)	0.706
Valvular heart disease, n (%)	12 (11)	12 (11)	0 (0)	
Congenital heart disease, n (%)	5 (4)	5 (5)	0 (0)	
Others, n (%)	3 (3)	3 (3)	0 (0)	
Use of combined medication				
Digoxin, n (%)	37 (33)	34 (32)	3 (50)	0.355
β-blocker, n (%)	42 (37)	38 (36)	4 (67)	0.124
ACEIs, n (%)	29 (26)	27 (25)	2 (33)	0.659
ARBs, n (%)	19 (17)	17 (16)	2 (33)	0.266
Diuretics, n (%)	31 (27)	29 (27)	2 (33)	0.739
Verapamil, n (%)	11 (10)	11 (10)	0 (0)	0.408
Diltiazem, n (%)	6 (5)	6 (6)	0 (0)	0.551
Parameters of metabolic function				
Total bilirubin (mg/dl)	0.69±0.04	0.68±0.04	0.82±0.15	0.238
AST (IU/L)	34±3	34±3	32±8	0.850
ALT (IU/L)	34±4	34±4	31±7	0.953
Creatinine (mg/dl)	0.98±0.12	0.99±0.12	0.87±0.09	0.958
Serum electrolyte and BNP				
K (mmol/L)	4.27±0.03	4.27±0.04	4.28±0.14	0.844
Ca (mg/dl)	8.90±0.05	8.89±0.05	9.02±0.25	0.737
BNP (pg/ml)	224±30	214±29	419±246	0.611
Parameters in echocardiogram				
Left atrial dimension (mm)	43±1	43±1	45±3	0.469
Left ventricular diastolic dimension (mm)	50±1	50±1	54±4	0.305
Thickness of interventricular septum (mm)	10.1±0.2	10.1±0.2	9.5±0.6	0.608
Thickness of posterior wall (mm)	9.7±0.2	9.7±0.2	9.5±0.8	0.769
LVEF (%)	62±1	62±1	60±3	0.299

All data exhibited in this table were evaluated before bepridil administration. Univariate P-values indicate comparison between event-free and event groups.

IHD, ischemic heart disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; AST, serum aspartate transaminase; ALT, serum alanine transaminase; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction.

hospital. The remaining patient was transferred to our hospital due to ventricular arrhythmic episode during bepridil therapy. The purpose of bepridil was AF rhythm control in 104, AFL prevention in 5, atrial premature contractions (APC) suppression in 2 and VT/ventricular fibrillation (VF) prevention in 2 ICD patients, respectively. The clinical characteristics of the patients are summarized in **Table 1**. Among the 113 patients, 26 were female and their mean age was 62±1 years old. Structural heart disease was observed in 46/113 patients, ie, ischemic heart disease in 16 (14%), dilated cardiomyopathy in 2 (2%), hypertrophic cardiomyopathy in 8 (7%), valvular heart disease in 12 (11%), congenital heart disease in 5 (4%), and others in 3 (3%), respectively. The mean left ventricular ejection fraction (LVEF) was 62±1%, and the left atrial dimension was 43±1 mm. No AF patients

exhibited serious ventricular arrhythmias at the starting point of bepridil therapy. Clinical data, including blood chemistry and echocardiographic data, were obtained retrospectively from the routine check of each patient. On the echocardiogram (SONOS 5500; Philips, Andover, MA, USA), chamber dimensions and wall thickness were measured in the standard parasternal long-axis view, and the LVEF was calculated by the area-length method. All studies, including retrospective analysis, were performed under the approval of the Clinical Studies and Ethics Committee of Kitasato University Hospital.

Electrocardiogram (ECG) Recording and Parameters

In all patients, the body-surface 12-lead ECG was recorded (FDX-4520; Fukuda Denshi Co, Ltd, Tokyo, Japan) with

Figure 1. This figure shows representative examples of abnormal T-U wave morphologies classified in this study. Left electrocardiogram (ECG) traces in each panel indicate recordings before bepridil and right ECG traces show those after bepridil administration. Arrows indicate traces which satisfied the criteria of each category. The QT intervals evaluated in each lead are shown below. When the U-wave was present and was able to be separated from the T-wave, the T-wave end was determined as the nadir of the curve between the T- and U-waves. See text for details.

standard gain (0.1 mV/mm) and recording speed (25 mm/s) before bepridil administration and every 4–8 weeks during bepridil administration. In patients with ventricular arrhythmic events, additional ECG recordings were obtained as much as possible especially around the events. In these recordings, the following QT-related parameters were evaluated in all leads, but T-U wave morphology was evaluated only in leads V2–5. The other leads, ie, all limb leads and V1 and V6, were not employed for the latter analysis because the T-U waves in these leads were frequently low amplitude and were not suitable for reproducible analysis.⁸ Each measurement was performed by 2 blinded investigators and the mean value was employed as the data. T-U wave morphology was also determined and confirmed by 2 blinded investigators. When the decisions differed between them, the final decision was made by the third blinded investigator.

QT Interval The QT interval was measured as the interval between the onset of QRS complex and the T-wave end, which was determined as complete return of the T-wave to the T-P baseline. When the U-wave was present and was able to be separated from the T-wave, the T-wave end was determined as the nadir of the curve between the T- and U-waves.⁹ When the U-wave was fused completely into the T-wave or could not be distinguished the U-wave from the T-wave, QTU interval was measured as QT interval. When the T-wave could hardly be determined in some recording leads, it was excluded from the analysis. The representative QT interval was defined as the longest QT interval among all analyzable

leads of the 12-lead ECG.⁴

Corrected QT (QTc) Interval The QTc interval was calculated using Bazett's formula ($QTc = QT / \sqrt{RR}$).¹⁰ When the ECG was in AF rhythm, the QT interval was corrected using the preceding RR interval to the beat for QT measurement.

QT Dispersion QT dispersion was defined as the difference between the maximum and minimum QT intervals measured in all 12 leads on ECG recording.⁹

Morphology of T-U Waves and Changes During Bepridil Therapy In this study, abnormality in the T-U wave morphology was classified into 5 categories. 'Fused U' was defined as the fusion of positive T- and U-waves forming T-U complex. 'Slurred' was defined as the appearance of low amplitude positive deflection consecutive to the latter part of the T-wave. 'Bifid' was defined as the appearance of plural positive peaks in the T-wave. 'Biphasic' was defined as the composition of positive and negative deflections in T-U complex. 'Negative' was defined as negative monophasic T-U wave complex. **Figure 1** shows representative examples of the abnormal T-U wave morphologies defined in this study. QT interval data of each trace are summarized in the table in **Figure 1**. Because the measurement of QT interval was highly dependent on T-U wave morphology, we employed the method of QT measurement as described above to achieve reproducible measurement. The morphologies of T-U waves were evaluated in each ECG recording before and during bepridil therapy in each case. In this study, configuration of the T-U wave morphologies before and during bepridil

therapy, and change in T-U wave morphologies, ie, newly appeared morphological abnormalities in T-U waves during bepridil, were used as the parameters.

Arrhythmic Events and Predicting Factors

Including the retrospective observation, the appearance of ventricular arrhythmic events, ie, symptomatic VT, Tdp or VF, was checked in all patients. The study population was divided into 2 groups with and without ventricular arrhythmic events during bepridil therapy, and the clinical, electrocardiographic and echocardiographic data were compared. ECG data during bepridil therapy were principally evaluated under the stable condition of bepridil administration, ie, with a stable intake of bepridil and 8 weeks after starting bepridil (stable phase). In patients with ventricular arrhythmic events, ECG was recorded as much as possible around that episode (event phase). In selected patients in whom the events appeared before 8-week bepridil administration, ECG data before that event were used as the ECG in the stable phase. Using the data obtained in this study, univariate and multivariate analyses were performed to determine the parameters predicting ventricular arrhythmic events.

Statistical Analysis

Continuous data are presented as the mean $\pm$ standard deviation, and categorical data are presented using absolute frequencies. Statistical analyses between continuous variables were performed with one-way ANOVA and categorical data was compared using the chi-squared test. Statistical analysis was performed with JMP 7 software for Windows (SAS Institute Inc, Cary, NC, USA). A P-value of <0.05 was considered significant.

Results

Arrhythmic Events and Patients' Characteristics

During the follow-up period of 92 ± 9 weeks, ventricular arrhythmic events were observed in 6/113 patients. Of the 6 events, 1 was VT with syncope, 3 were Tdp and 2 were VT/VF, which needed to be rescued by cardiopulmonary resuscitation, including external defibrillation. The clinical characteristics of the total population, the event-free group ($n=107$) and event group ($n=6$) are summarized in **Table 1**. There was no significant difference between event-free and event groups in these clinical backgrounds in the basic state before bepridil administration. **Table 2** shows the clinical data of 6 patients in the event group. The duration of bepridil therapy before arrhythmic events varied between 3 weeks and 5 years. The dose of bepridil was highest, ie, 200 mg/day, in 5/6 patients with arrhythmic events. In 3/6 patients, digitalis was used together with a beta-blocker, although the heart rate in the event phase did not show a significant difference. Only 2/6 patients exhibited a low level of serum potassium (<4.0 mmol/L) in the event phase, and the other 1/6 patients showed relatively low LVEF.

QT-Related Parameters

Changes in QT-related parameters, ie, QT, QTc intervals and QT dispersion, are shown in **Figure 2**. QT and QTc intervals were prolonged and QT dispersion was increased by bepridil administration both in event-free and event groups. Significant differences between before bepridil and the stable phase were observed in event-free groups. The reason for insignificance in event groups was considered due to the limited number of patients in the event group; however, even in the

Table 2. Clinical Characteristics of Patients in the Event Group

Patient no.	Event	Parameters of metabolic function				Serum electrolyte and BNP				Electrocardiogram				Echocardiogram					
		Total bilirubin (mg/dl)	GOT (IU/L)	GPT (IU/L)	Creatinine (mg/dl)	K (mmol/L)		Ca (mg/dl)		Wide QRS complex Before bepridil	Heart rate (beats/min) Event phase	LAD (mm)	LVDD (mm)	IVSth (mm)	PWth (mm)	LVEF (%)			
						Before bepridil	Event phase	Before bepridil	Event phase										
1	VT	0.7	15	17	0.77	4.2	4.7	8.9	7.8	+	86	55	62	11	11	60			
2	VF	1.1	67	55	0.84	4.7	4.1	8.9	8.7	+	NA	48	42	9	9	64			
3	Tdp	0.6	25	17	1.30	4.3	5.3	8.7	7.2	+	50	39	60	8	11	63			
4	Tdp	0.7	36	53	0.80	3.7	3.1	9.9	8.2	-	107	47	45	11	9	62			
5	Tdp	1.4	34	22	0.86	4.6	3.7	8.2	8.3	-	63	45	62	10	11	45			
6	VT	0.4	15	20	0.65	4.2	4.0	9.5	9.7	-	55	36	50	8	6	64			

Abbreviations see in text.

Figure 2. This figure shows changes in QT-related parameters in event-free and event groups. Note that parameters in the event phase were available only in the event group. Bepridil-induced prolongation of QT and corrected QT (QTc) intervals and increased QT dispersion were significant in the stable phase in the event-free group. Bepridil-induced prolongation of QT and QTc intervals was significant only in the event phase in the event group. A significant difference between event-free and event groups was observed in the QTc interval before bepridil. See text for details.

event group, the prolongation of QT and QTc intervals was significant between before bepridil and the event phase. There were no significant differences between event-free and event groups in these parameters except the QTc interval before bepridil administration, which was longer in the event group than the event-free group.

T-U Wave Morphology

Figure 3 shows representative examples of the analysis of T-U wave morphology and QT intervals in two cases, each from event-free and event groups. In case 1, ‘fused U’ was observed in all V₂₋₅ leads before bepridil and was similarly present in the stable phase during bepridil therapy, but bifid T newly appeared in V₃₋₅ leads in the stable phase, so that the newly appeared abnormality in the stable phase in this case was determined as ‘bifid’. In case 2, only the bifid T was observed in V₄ lead before bepridil, and biphasic and negative T-waves newly appeared in the stable phase during bepridil therapy, so the newly appeared abnormality in the stable phase in this case was determined as ‘biphasic’ and ‘negative’. In case 2, the amplitudes of T-U waves in leads V₄ and V₅ were quite low, and were determined as a complex of T-U waves, and then the QT intervals in these leads were measured as 0.56 s. The numbers in parentheses, ie, 0.38 and 0.36 s, are the QT intervals in these leads if the latter phase of T-U waves were excluded from the measurement as U-waves.

Figure 4 summarizes the incidence of abnormal T-U wave morphology before and during bepridil therapy in event-free and event groups. In the event-free group, the incidences of fused U, bifid and total, ie, any T-U wave abnormality, were increased in the stable phase but the incidence of negative

T-wave was rather decreased in comparison with before bepridil. In the event group, the incidences of negative and total were increased in stable and event phases in comparison with before bepridil.

Prediction of Ventricular Arrhythmic Event During Bepridil Therapy

To determine the predicting factors of ventricular arrhythmic events during bepridil therapy, uni- and multivariate analyses were performed comparing electrocardiographic parameters between event and event-free groups (**Table 3**). In univariate analysis, the QTc interval before bepridil, the presence of a wide QRS complex due to ventricular pacing or bundle-branch block before bepridil, the presence of a biphasic or negative T-U wave in the stable phase and the new appearance of biphasic or negative T-U wave exhibited significant differences between groups; however, in multivariate analysis, only newly appeared negative T-U wave abnormality was an independent predicting factor of ventricular arrhythmic events (odds ratio 10.13, 95% confidence interval 0.031–2.302, P=0.041).

Discussion

We have evaluated clinical and electrocardiographic parameters in patients with long-term bepridil therapy and documented several interesting and important findings. First, we observed considerable ventricular arrhythmic events in 6/113 patients during the follow-up period of 92±9 weeks. Second, morphological changes in T-U waves before and during bepridil therapy were evaluated systematically and was realized that up to 73% of patients might exhibit any type of T-U

Figure 3. This figure shows representative examples of the analysis of T-U wave morphology in actual cases. Left panel shows ECG traces of a case in the event-free group. In this case, ‘fused U’ was observed in all V₂₋₅ leads before bepridil and ‘bifid’ T newly appeared in leads V₃₋₅ in the stable phase during bepridil therapy. The newly appeared T-U wave abnormality in this case was determined as ‘bifid’. Right panel exhibits traces in a case in the event group. In this case, only ‘bifid’ T was observed before bepridil, but ‘biphasic’ and ‘negative’ T newly appeared in the stable phase during bepridil therapy. In the event phase, ‘bifid’, ‘biphasic’, and ‘negative’ newly appeared in this case. The QT intervals evaluated in each lead are shown below. In case 2, the amplitudes of T-U waves in leads V₄ and V₅ were quite low, and the T-wave end was determined as the end of T-U complex. As a result, QT intervals in these leads were 0.56 s. The numbers in parentheses, ie, 0.38 and 0.36 s, are the QT intervals when the latter phase of T-U wave was excluded from the measurement as U wave. See text for details.

wave abnormality during stable bepridil administration, even patients without ventricular arrhythmic events. Third, of these changes in T-U wave morphologies, the increased incidence of biphasic or negative T-U wave abnormality was more prominent in patients with ventricular arrhythmic events in comparison with those without events. Finally, although several factors exhibited a difference between event-free and event groups, the new appearance of negative T-wave was the only independent predicting factor of ventricular arrhythmic events in multivariate analysis.

Characteristics of Morphological Changes in T-U Wave During Bepridil Therapy

In the present study, morphological abnormalities in T-U wave were classified into 5 categories, and the incidence of the presence or appearance of these changes was evaluated in 113 patients with stable bepridil therapy. To the best of our knowledge, this is the first trial of systematic analysis of

T-U wave morphology. The results showed any type of T-U wave abnormality in 33–44% patients in our classification even before bepridil therapy, and the incidence increased from 44 to 73% in patients without ventricular arrhythmic events and from 33 to 100% in patients with events. In the event-free group, the increased incidence of fused U and bifid was significant but, in contrast, in event patients, the increased negative incidence was significant (Figure 4). It has been reported that bepridil blocks multi-ion channels, such as I_{Kr}, I_{Ks},^{11,12} I_{to}, I_{K1},¹³ I_{Kur},¹⁴ I_{Na}, I_{Ca-L},¹⁵ I_{Ca-T},¹⁶ etc, and this medicine is considered to affect the repolarization phase and T-wave. In clinical patients, the change in T-U waves during bepridil therapy was characterized by not only QT prolongation but also a flattened and broadened T wave and the increased amplitude of positive U-waves,^{6,7} and this characteristic is very similar to that in hypokalemia.¹⁷ Although the mechanism or genesis of U-waves is unclear, the flattening or broadening of T-waves might be explained by the

Figure 4. This figure summarizes the incidence of abnormal T-U wave morphology before and during bepridil therapy in event-free and event groups. Note that data in the event phase were only available in the event group. In the event-free group, the incidences of T-U wave morphological abnormalities of fused U, bifid and total were increased in the stable phase. In the event group, the negative and total incidences of T-U wave morphological abnormalities were increased in stable and event phases. See text for details.

Table 3. Uni- and Multivariate Analyses of Electrocardiographic Parameters in Event-Free and Event Groups

	Event-free group	Event group	Univariate P-value	Multivariate		
				95%CI	OR	P-value
Before bepridil						
Heart rate (beats/min)	74±2	71±6	0.898			
QT (s)	0.41±0.01	0.46±0.03	0.110			
QTc (s ^{1/2})	0.45±0.01	0.49±0.01	0.028*	−0.9039 to 1.3974	1.66	0.648
QT dispersion (s)	0.061±0.004	0.083±0.010	0.082			
Wide QRS complex due to PM or BBB (with/without)	18/89	3/3	0.042*	−0.7359 to 1.4667	2.23	0.459
Abnormal T-U wave						
Fused U (%)	14	0	0.325			
Slurred (%)	2	0	0.735			
Bifid (%)	5	17	0.202			
Biphasic (%)	17	17	0.992			
Negative (%)	17	0	0.273			
Stable phase						
Heart rate (beats/min)	62±1	60±3	0.794			
QT (s)	0.49±0.01	0.54±0.05	0.229			
QTc (s ^{1/2})	0.49±0.01	0.53±0.04	0.272			
QT dispersion (s)	0.097±0.007	0.088±0.024	0.808			
Abnormal T-U wave						
Fused U (%)	36	17	0.324			
Slurred (%)	7	17	0.347			
Bifid (%)	24	33	0.618			
Biphasic (%)	25	67	0.027*	−0.7371 to 1.4655	1.98	0.527
Negative (%)	9	50	0.002*	−0.2196 to 1.8523	5.09	0.114
Newly appeared T-U wave abnormality						
Fused U (%)	32	17	0.436			
Slurred (%)	7	17	0.347			
Bifid (%)	24	33	0.618			
Biphasic (%)	18	67	0.004*	−0.5106 to 1.7361	3.39	0.261
Negative (%)	4	50	<0.0001*	0.031 to 2.302	10.13	0.041*

Univariate P-values indicate comparison between event-free and event groups.
CI, confidence interval; OR, odds ratio.

decrease in I_{K1} ¹⁸ and I_{K1} ¹⁹ just as under hypokalemic conditions. Because the electrophysiological properties are different among endocardial, epicardial and M cells in the ventricular muscle, the action of potassium channel blocker would not be homogeneous in the myocardium. For example, I_{Kr} and I_{Ks} blocking results in more prominent prolongation in the action potential duration in M and epicardial cells than endocardial cells, and it leads to changes in the morphology of T-waves.²⁰ In Tdp, it can be speculated that considerable transmural dispersion of repolarization is caused by prolongation of action potential duration preferentially in M cells as well as early after depolarization-induced extrasystole, which can both be caused by reduction in the net repolarizing current.²¹ In patients with arrhythmic events during bepridil therapy, the I_{Kr} ¹¹ and I_{K1} ¹³ blocking effect, which was observed with a high concentration of bepridil, might appear as well as an excess of the I_{Ks} blocking effect, leading to an imbalance in ventricular transmural repolarization, and might cause morphological changes in T-U waves, such as biphasic or negative. As in case 2 in **Figure 3**, T-U waves in lead V₂ exhibited a marked change in morphology in the event phase. Although the precise mechanism is unclear, imbalance in transmural repolarization might be one reason because the latter phase of prolonged T wave in lead V₂ in the event phase seems to coincide with the phase of a positive and separated T-U wave before bepridil.

The QT interval is an important indicator predicting Tdp.^{9,22} and there is general agreement that a QT interval of >500 ms indicates a significant risk of pro-arrhythmia during therapy with anti-arrhythmic agents.²³ However, the appearance of broadened or flattened T waves and the fusion of prominent positive U-waves might cause difficulties in measurement of the QT interval because these changes make it difficult to determine the T-wave end. During bepridil therapy, inclusion or exclusion of a 'fused U-wave' or 'slurred T-wave end' are common problems in measurement of the QT interval,²⁴ and there is no consensus about the QT measurement. These differences in the method of QT measurement will cause considerable variety in practical QT intervals, which might affect the importance of this common clinical indicator, at least in patients with bepridil therapy. For example, in case 2 in **Figure 3**, the measurement of QT interval is controversial. Because of the low amplitudes of T- and U-waves in leads V₄ and V₅, the determination of T-wave ends seems quite difficult. In the present study, we determined these waves as a complex of T-U wave and could not distinguish the U-wave from the T-wave, and the QT intervals were measured as QT-U intervals, ie, 0.56 s. However, if the latter phase of T-U waves were excluded from the measurement as U-waves, the QT intervals in these leads were 0.38 and 0.36 s. The former measurement would probably be useful for physicians to exclude high-risk patients for ventricular arrhythmic events during bepridil therapy, but it might also lead to overestimation of the QT interval in some cases. At least in our previous evaluation,²⁴ the QT measurement, including the positive U-wave, was not a good predictor of ventricular arrhythmic events because of the high overestimation of QT interval in patients without events.

In the present study, we measured the QT intervals objectively in accordance with the T-U wave morphologies and the data were confirmed by several blinded investigators. The results showed that QT and QTc intervals were not significant predictors of ventricular arrhythmic events in this study, although the QTc interval before bepridil administration was longer in the event group than the event-free group in uni-

variate analysis. This does not reject the usefulness of the QT interval as a predictor of ventricular arrhythmia because it was only evaluated in our method in this study. To use the QT interval as the ultimate predictor of ventricular arrhythmia, a method for reproducible QT measurement is required.

Prediction of Ventricular Arrhythmic Events During Bepridil Therapy and Clinical Implication

Several reports have mentioned Tdp during bepridil therapy.^{25,26} In the present study, we observed ventricular arrhythmic events with considerable incidence, ie, 6/113 patients, so prediction of these events should be an extremely important issue during bepridil therapy. However, this incidence does not directly indicate the prevalence of ventricular arrhythmic event during bepridil therapy because 1 patient with arrhythmic episode was transferred to our hospital due to the event. We cannot directly conclude that bepridil was the only factor which caused ventricular arrhythmic events in these cases because changes in other factors, such as electrolytes, autonomic nervous activity, progression of basic disease, etc, cannot be excluded. However, because this study compared patients with and without ventricular arrhythmic event under the same condition of bepridil therapy, we might be able to discuss predictions during bepridil therapy.

Several factors have been reported which can facilitate the occurrence of ventricular arrhythmia during bepridil therapy, ie, hypokalemia (<4.0 mmol/L), bradycardia (<50 beats/min), older age, concomitant use of other medicines which might prolong QT interval, congestive heart failure, and ischemic heart disease,²⁵⁻²⁷ etc. In the event phase, 2/6 patients exhibited a low level of serum potassium (<4.0 mmol/L) and 3/6 patients suffered from co-use of digitalis and a β -blocker, although they did not show a significant difference from patients without events. As shown in **Table 2**, event patients did not show significant bradycardia (<50 beats/min), but the participation of bradycardia cannot be rejected because the heart rate was not monitored continuously. Additionally, the dose of bepridil was 200 mg/day in 5/6 patients with arrhythmic events. Although the dose of bepridil was not detected as a significant predictor of arrhythmic events in this study, we have to consider the possibility that a higher dose of bepridil might be one of the factors causing ventricular arrhythmia by considering the results of J-BAF.³

In the present study, we also evaluated several clinical factors as predictors of ventricular arrhythmic events with other electrocardiographic parameters, including QT and QTc intervals and T-U wave morphologies. The results showed that the newly appeared T-U wave 'negative' abnormality was the only independent predicting factor of ventricular arrhythmic events in multivariate analysis although univariate analysis showed several other factors as predictors. This indicates that analysis of T-U wave morphology is a feasible and useful index to predict ventricular arrhythmic events during bepridil therapy. Because this method is simple and is not affected by the definition of T-wave end, this parameter might become a reliable way to predict ventricular arrhythmic events. In contrast, QT and QTc were not related to ventricular arrhythmic events in the same analysis in this study, at least from the definition of QT measurement in this study. An innovative method for QT measurement might use the QT interval as the ultimate predictor of ventricular arrhythmia during class III anti-arrhythmic drug therapy, but this seems to be difficult because of morphological changes in T-U waves. In accordance with the results of the present study, the analysis of T-U wave morphology might be con-

sidered to play a role in assisting the QT measurement and its interpretation for the prediction of ventricular arrhythmia.

We did not evaluate the electrocardiographic parameters in the event phase as a predictor of ventricular arrhythmic events in this study. This is simply because these parameters were not available in event-free patients, and the parameters around the event seemed unsuitable for 'prediction' of the events, even in patients with arrhythmic events. However, our results showed significant differences in T-U wave morphological parameters between event-free and event groups, even in evaluation in the stable phase during bepridil therapy; therefore, they can be predictors of ventricular arrhythmic events in clinical practice.

Study Limitations

This study reports interesting results but it also has several limitations. First, although the number of patients was more than 100, the number of event patients was limited to compare patients with and without ventricular arrhythmic events. Second, data of the serum concentration of bepridil was not evaluated. Finally, the follow-up period varied among patients and was limited in some patients. These issues should be solved in a larger population of patients with a different study design.

Conclusion

In patients with stable bepridil treatment, a change in T-U wave morphology was an independent predictor of ventricular arrhythmic events. Analysis of the T-U wave was considered to be useful to assist the QT interval and other indices to predict future ventricular arrhythmic events in patients with bepridil therapy.

Disclosure

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