Relationship Between the QT Indices and the Microvolt-Level T Wave Alternans in Cardiomyopathy

Nami Kuroda, MD; Yoshio Ohnishi, MD;
Kazumasa Adachi, MD; Mitsuhiro Yokoyama, MD

The relationship between the QT indices and microvolt-level T wave alternans (TWA) is unknown in cardiomyopathy, so the present study examined 86 patients with cardiomyopathy who experienced TWA during exercise testing (EXT). The QT interval (QT), duration from the Q wave to the peak of the T wave (QTp), duration from the peak to the end of the T wave and the dispersion of these parameters were measured by 12-lead electrocardiogram at rest and during EXT. In dilated cardiomyopathy (DCM), TWA was positive (TWA+) in 19 patients and negative (TWA-) in 17. No significant difference was observed between the TWA+ and TWA- groups in any parameter. In hypertrophic cardiomyopathy (HCM), TWA was positive in 24 patients and negative in 12. Max QTc, max QTpc and mean QTpc during EXT in the TWA+ group were significantly longer than those in the TWA- group. The sensitivity of TWA for ventricular tachycardia (VT) was high in DCM and HCM, and that of max QTc >500 ms during EXT for VT was high in HCM (93%). TWA is a useful predictor for VT in DCM and HCM, and prolonged max QTc during exercise has a prognostic value in HCM. Repolarization abnormality during exercise plays an important role in the genesis of VT in cardiomyopathy. (*Jpn Circ J* 2001; 65: 974–978)

Key Words: Cardiomyopathy; QT indices; T wave alternans

T wave alternans (TWA) is an electrocardiographic abnormality of beat-to-beat changes in the morphology of ventricular repolarization, which was first described by Mines in 1913.¹ Experimental and clinical observations indicate that TWA can be associated with an increased propensity for serious ventricular arrhythmias, particularly ventricular fibrillation^{2–7} and TWA can occur in clinical conditions, such as long QT syndrome,^{5,8} myocardial ischemia^{6,7,9,10} and metabolic and electrolyte disturbances.^{11,12} Visually apparent TWA on the electrocardiogram (ECG) has been a fairly uncommon finding in practice, but using the spectral method of Smith et al³ Rosenbaum et al found a strong correlation between the presence of TWA at the microvolt level and the electrophysiologic inducibility of ventricular arrhythmias.¹³

TWA shows a temporal dispersion of repolarization and because QT dispersion, calculated as the range of QT intervals ($QT_{max}-QT_{min}$), is associated with the risk of ventricular tachyarrhythmia and of sudden cardiac death in a broad spectrum of clinical conditions including congenital and acquired long QT syndromes,¹⁴ myocardial infarction^{15–17} and cardiomyopathies,^{18–21} it has been proposed as a simple noninvasive measurement of the spatial dispersion of repolarization available from the 12-lead body surface ECG.¹⁴

Since Antzelevitch et al showed ‘the transmural dispersion of repolarization’²² several studies^{23–25} have attempted to understand the abnormality of ventricular repolarization using not only the duration from the onset of the QRS

complex to the end of the T wave (QT), but also the duration from the onset of the QRS complex to the peak of the T wave (QTp) and the duration from the peak of the T wave to the end of the T wave (TpE). Both TWA and QT dispersion have been proposed as useful noninvasive tools for risk assessment of ventricular tachyarrhythmias. QT dispersion and these QT indices are generally measured at rest, and TWA is evaluated during exercise. In this study, we clarified the relationship between TWA and the QT indices (including QTp and TpE), particularly that of the QT indices during exercise, in cardiomyopathy. We compared the results from patients with dilated cardiomyopathy (DCM), a disease of contraction disturbance, with those from patients with hypertrophic cardiomyopathy (HCM), a disease of impaired relaxation.

Methods

Patients

The study group consisted of 47 patients with DCM (M:F = 37:10, 52±14 years old) and 39 patients with HCM (M:F = 36:3, 58±11 years old) who were referred to Kobe University Hospital. Informed consent was obtained from all participants. Beta-blockers and antiarrhythmic agents were discontinued for more than 5 times of their respective half-lives before examination.

Measurement of the Microvolt-Level TWA

TWA was measured at rest and during controlled bicycle exercise testing (EXT) using a CH2000 system (Cambridge Heart Inc, Bedford, MA, USA), which used the spectral method described by Smith et al.³ We performed TWA testing as described previously.²⁶ If there was a sustained alternans voltage (V_{alt}) ≥1.9 μV and alternans ratio (R) ≥3 with an onset heart rate ≤110 beats/min during EXT, TWA was defined as positive (TWA+). If alternans was not present during a sustained interval of exercise without arti-

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Division of Cardiovascular and Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

Mailing address: Yoshio Ohnishi, MD, Division of Cardiovascular and Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, 7-5-2 Kusunoki-cho, Chuoku, Kobe 650-0017, Japan

Table 1 Relationship Between T Wave Alternans and QT Indices

	Dilated cardiomyopathy				Hypertrophic cardiomyopathy			
	Rest		EXT		Rest		EXT	
	TWA+	TWA-	TWA+	TWA-	TWA+	TWA-	TWA+	TWA-
<i>TWA</i>	19	17	15	11	24	12	21	8
<i>QT indices (ms)</i>								
<i>Max QTc</i>	465.3±33.2	449.3±38.0	507.2±21.9	500.4±41.3	506.5±35.2	496.9±37.7	515.0±30.8*	486.2±21.6*
<i>Min QTc</i>	381.3±32.2	380.1±31.7	409.7±30.4	419.2±42.0	403.8±38.1	407.2±34.2	421.6±30.4	411.8±19.8
<i>Mean QTc</i>	427.7±19.8	419.5±31.7	442.5±83.9	465.1±37.7	460.5±32.1	456.1±21.4	472.8±27.6	452.2±19.0
<i>QTcd</i>	83.0±38.0	68.8±25.9	97.3±26.2	81.3±28.1	104.7±31.5	93.8±28.6	93.4±26.4	74.4±17.2
<i>Max QTpc</i>	365.4±38.4	347.7±32.9	370.5±29.2	373.1±32.3	378.8±34.1	363.8±14.3	381.1±20.0*	355.0±21.8*
<i>Min QTpc</i>	292.1±19.5	287.5±27.5	304.4±23.1	312.1±26.9	297.4±34.8	290.5±17.1	305.4±28.1	286.3±26.9
<i>Mean QTpc</i>	327.7±13.1	320.4±27.2	343.1±22.2	343.0±29.2	343.3±24.4	336.0±21.5	346.8±20.3*	325.8±21.9*
<i>QTpcd</i>	67.9±23.1	60.3±21.0	72.9±19.8	61.3±22.7	81.4±26.7	73.4±19.2	75.7±26.5	68.7±12.2
<i>Max TpEc</i>	153.2±30.2	136.2±23.3	165.7±23.3	163.6±28.3	165.4±27.2	173.1±48.0	172.2±25.5	166.7±21.0
<i>Min TpEc</i>	64.8±21.3	57.0±14.1	73.5±21.3	81.1±26.9	74.1±14.6	76.1±19.1	82.7±14.8	89.4±14.4
<i>Mean TpEc</i>	104.4±17.1	94.9±11.6	119.4±20.5	122.3±24.3	119.1±15.9	128.2±36.6	126.0±17.1	126.3±14.8
<i>TpEd</i>	88.4±27.8	79.2±28.1	92.2±24.5	82.6±24.1	91.2±28.8	97.0±42.3	89.5±26.2	77.4±16.3

TWA, T wave alternans; EXT, exercise testing; QT, onset of the QRS complex to the end of the T wave; QTp, duration from the onset of the QRS complex to the peak of the T wave; TpE, duration from the peak of the T wave to the end of the T wave; QTd, QTpd, TpEd, dispersion of each parameter defined as the difference between the longest and shortest interval; QTc, QTcd, QTpc, QTpcd, TpEc, TpEd, corrected values. * $p < 0.05$.

Fig 1. Comparison of the maximum QTc, QTpc and TpEc at rest and during EXT between the TWA+ (Black) and TWA- (White) groups in hypertrophic cardiomyopathy (HCM). The maximum levels of QTc and QTpc during EXT in the TWA+ group were significantly longer than those in the TWA- group ($p < 0.05$). EXT, exercise testing; NS, not significant; TWA, T wave alternans; TWA+, TWA positive; TWA-, TWA negative.

fact at a heart rate ≥ 105 beats/min, TWA was negative (TWA-). If a record did not meet the positivity or negativity criteria, the record was considered indeterminate.

Measurement of QT Indices

Simultaneously with the measurement of TWA, we recorded a standard 12-lead ECG at rest and at a heart rate of 105 beats/min with a paper speed of 25 mm/s. The investigator was blinded with respect to the patient profile. On each recording we manually measured QT, QTp and TpE. The end of the T wave was defined as a return to the isoelectric line. In the presence of the U wave, the QT interval was measured to the nadir of the T and U waves. Leads where the end of T wave was unmeasurable because of a flat T wave, the biphasic T wave or excessive noise were excluded from further analysis. Dispersion of each parameter was defined as the difference between the longest and shortest interval (QTd, QTpd, TpEd). At a heart rate of 105 beats/min (EXT), we measured these electrocardiographic parameters in 3 consecutive beats and used the average value of 3 beats for analysis. Patients with prolonged QRS duration (QRS > 120 ms), indeterminate TWA and inaccurate detection of QT parameters were excluded from analysis. Inaccurate QT parameter detection was mainly caused by the small number (< 9) of measurable leads. The maximal

(max), minimal (min) and mean value of these intervals at rest (QT, QTp, TpE) and during exercise (EXT QT, EXT QTp, EXT TpE), dispersion of these intervals (QTd, QTpd, TpEd, EXT QTd, EXT QTpd, EXT TpEd) and all these intervals corrected using Bazett's formula²⁷ (QTc, QTpc, TpEc) were used as parameters in analysis.

Statistical Analysis

We compared the mean, maximum and minimum values and dispersion of all intervals on the ECG recordings. Data were expressed as mean $\pm$ 1SD and were compared using the unpaired t-test between TWA+ and TWA-. Probability was considered significant at $p < 0.05$.

Results

Relationship Between TWA and the QT Indices

DCM TWA was positive in 19, negative in 17 and indeterminate in 11 patients. Three patients with a QRS duration > 120 ms (2 in TWA+ and 1 in TWA-) and 11 patients with indeterminate TWA were excluded from further analysis. We could measure QTd at rest in all patients. Of the 26 patients for whom we could measure QTd during EXT, TWA was positive in 15 and negative in 11 patients. No significant difference was observed in any

Fig 2. Representative case of HCM in a 66-year-old male. (Right panel) Trend graph of TWA, (Left panel) 12-lead ECG during EXT at the heart rate of 105 beats/min. In 24-h Holter monitoring, nonsustained VT was detected. Max QTc during EXT was 518 ms (leads II and V4) and TWA was positive. HCM, hypertrophic cardiomyopathy; TWA, T wave alternans; EXT, exercise testing; VT, ventricular tachycardia.

Table 2 Prediction of Ventricular Tachycardia

	DCM	HCM
TWA		
Se (%)	100	90
Sp (%)	58	37
PA (%)	67	55
QTd (rest) (≥ 80 ms)		
Se (%)	43	70
Sp (%)	58	26
PA (%)	54	41
QTd (EXT) (≥ 80 ms)		
Se (%)	47	20
Sp (%)	73	84
PA (%)	58	52
Max QTc (EXT) (≥ 500 ms)		
Se (%)	57	90
Sp (%)	26	32
PA (%)	35	52

DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; Se, sensitivity; Sp, specificity; PA, predictive accuracy. Other abbreviations as in Table 1.

of the QT indices between the TWA+ and TWA- groups, either at rest or during EXT (Table 1).

HCM TWA was positive in 24, negative in 12 and indeterminate in 3 patients. One patient with a QRS duration >120 ms in the TWA+ group and 3 patients with indeterminate TWA were excluded from further analysis. We could measure QTd at rest in all patients. Of the 29 patients for whom we could measure QTd during EXT, TWA was positive in 21 and negative in 8 patients. Although no significant difference was observed between

the 2 groups in any of the QT indices at rest, max QTc, max QTpc and mean QTpc during EXT in the TWA+ group were significantly longer than those in the TWA- group (max QTc: 515.0 ± 30.8 ms vs 486.2 ± 21.6 ms, $p < 0.05$; max QTpc: 381.1 ± 20.0 ms vs 355.0 ± 21.8 ms, $p < 0.05$; mean QTpc: 346.8 ± 20.3 ms vs 325.8 ± 21.9 ms, $p < 0.05$) (Table 1, Fig 1). No difference was observed in the other parameters during EXT. Fig 2 shows a representative case of HCM. TWA was positive and max QTc during EXT was 518 ms.

QTd and QTcd during EXT in the TWA+ groups tended to be long in both DCM and HCM cases, but statistical significance was not observed.

Prediction of Ventricular Tachycardia

The sensitivities of TWA, QTd at rest, QTd during EXT and max QTc during EXT for ventricular tachycardia (VT: defined as ventricular ectopic beats continuing for more than 3 beats in 24-h Holter monitoring with an average recording times of 3.1 times, or bedside monitoring) are shown in Table 2. The sensitivities of TWA for VT were 100% in DCM and 90% in HCM. The sensitivity of QTd at rest with more than 80 ms for VT was 70% in HCM, and the specificities of QTd during EXT with more than 80 ms for VT were 73% in DCM and 84% in HCM. The sensitivity of max QTc during EXT with more than 500 ms for VT was 90% in HCM.

Discussion

Many experimental and clinical studies have demonstrated that heterogeneous repolarization contributes to the triggering of ventricular arrhythmia and sudden cardiac

death in high-risk patients with long QT syndrome,¹⁴ hypertrophic cardiomyopathy^{18–20} or chronic heart failure.^{18,21} QT dispersion has been proposed as a simple noninvasive measurement of dispersion of repolarization, available from the 12-lead surface ECG¹⁴ and is considered to reflect the spatial dispersion of repolarization.

On the other hand, TWA has been described as a strong predictor of the inducibility of sustained VT in clinical conditions such as long QT syndrome^{5,8} and myocardial ischemia.^{6,7,9,10} Recently, Murda'h et al²⁸ and Momiyama et al²⁹ suggested that HCM patients at high risk for ventricular arrhythmic events often showed TWA. Moreover, Adachi et al reported that TWA detected during exercise may be a useful noninvasive marker for arrhythmic risk in patients with DCM.²⁶ TWA is considered to reflect the temporal dispersion of repolarization, but the correlation between QT dispersion and TWA has not been clarified. Aroundas et al reported a moderate correlation between QTc at rest and TWA,³⁰ but in their study, 62% of the study population had coronary artery disease, so the relationship between TWA and the QT indices in cardiomyopathy could not be inferred.

We measured the QT interval at rest and during exercise and compared the results with those for TWA. In DCM, no significant difference was observed in the QT indices between the TWA+ and TWA– groups, either at rest or during EXT. In HCM, although no significant difference in the QT indices was observed between the 2 groups at rest, max QTc, max QTpc and mean QTpc during EXT were significantly longer in the TWA+ group than in the TWA– group. These results suggest that in DCM, TWA is not related to the QT indices either at rest or during exercise as a parameter for ventricular repolarization, but in HCM, there is a close relationship between both TWA and a prolonged max QT interval, especially the QT peak interval during EXT. Mezilis et al analyzed QTec (the onset of QRS to the end of T wave) and QTac (the onset of QRS to the apex of T wave) immediately before (sample A) and 1 h after (sample B) nonsustained VT in HCM and found that there was not a significant difference in QTec, but that QTac was significantly longer in sample A than sample B.³¹ Yoshimura et al³² measured QT dispersion (QTD) and QT peak dispersion (QTaD) at rest and at peak exercise level, and compared these parameters between hypertensive patients with and without left ventricular hypertrophy (LVH). The QTD and QTaD at rest did not differ between the patients with and without LVH, but at peak exercise level, the QTaD in patients without LVH was decreased compared with the baseline, but was significantly increased in patients with LVH. Moreover, they correlated the QTaD at peak exercise level with the left ventricular mass index. The explanation for their results was that the hypertrophy of myocyte may cause an extension of the action potential duration, and proliferation of cardiac interstitial tissue may be associated with a shortened action potential duration or electrical quiescence. We also thought that these features could cause repolarization inhomogeneity of the ventricle, in which case TWA and a prolonged max QT interval during exercise would be the parameters of repolarization inhomogeneity. Taking into consideration the results of the 2 other studies and the present results, the prolongation of not only QT duration but also QT peak duration in HCM may closely correlate with ventricular tachyarrhythmia. Recently, Antzelevitch et al showed that the peak of the T wave reflects the full repolarization of the epicardium and

the end of the T wave reflects full repolarization of the M cell region.²² The time interval between the peak and the end of the T wave therefore represents the transmural dispersion of repolarization. We compared QTp, TpE and those dispersion. In DCM, no significant difference was observed in any parameter between the TWA+ and TWA– groups, either at rest or during EXT. In HCM, the max QTpc and mean QTpc during EXT in the TWA+ group was significantly longer than that in the TWA– group. In our present study, no significant difference was observed in any parameter of TpE.

From the point of view of the relationship between T wave morphology and the QT indices, Yi et al reported that QT end dispersion and QT peak dispersion correlated with the complexity of the T wave assessed by principal component analysis (PCA), and that the PCA ratio was significantly increased in HCM with nonsustained VT than in HCM without VT.³³ Kishore et al reported that no significant difference was observed in QT max and QT mean between the high risk and the low risk groups of HCM, and that QT dispersion in the high risk group was significantly longer than in the low risk group in HCM.³⁴ However, both those studies only examined the patients at rest and furthermore, in all reports of QT interval and dispersion during exercise, the patients had ischemic heart disease. Our present study is the first to investigate the relationship between TWA and QTp, TpE and QTd not only at rest but also during exercise in non-ischemic cardiomyopathy (DCM and HCM). Considering that HCM patients have normal cardiac systolic function, these findings suggest that the repolarization abnormality plays a more important role in the genesis of VT in HCM than in DCM.

In the present study, the sensitivity of TWA for VT was quite high in DCM and HCM. The sensitivity of QTd during EXT with more than 80 ms was lower, but its specificity was higher than those of TWA and QTd at rest with more than 80 ms. The sensitivity of max QTc during EXT with more than 500 ms for VT was 90% in HCM. Therefore, TWA should prove to be a useful and noninvasive tool for the risk stratification of sudden death in cardiomyopathies, and the measurement of the QT interval during exercise may be valuable for the prediction of sudden death in HCM.

In HCM, the rate of TWA positivity was higher than that in DCM. Recently, Shimizu et al suggested that intracellular calcium handling is linked to the mechanism of TWA in the long QT model.³⁵ The existence of a disorder in calcium handling has been reported in HCM,³⁶ and furthermore, it has been reported that the sensitivity to catecholamines is increased in the hypertrophic myocardium.³⁷ If calcium handling and/or catecholamines are correlated with the mechanism of TWA, TWA occurs more easily in HCM than in DCM.

Study Limitations

In some cases, measurement of the QT interval during exercise was difficult because the baseline of the ECG was trembling and the end of the T wave became unclear with increasing heart rate. In our preliminary study, intra-observer reproducibility in QT measurement during exercise was excellent ($r^2=0.94$, $p<0.01$), therefore the present results are reliable for understanding the repolarization abnormality in cardiomyopathy.

With regard to patient selection, those with atrial fibrillation or who could not exercise with a heart rate over 105 beats/min were excluded from further analysis and so partic-

ularly for DCM, high-risk patients may have been excluded.

Conclusion

TWA is not related to the QT indices at rest or during exercise in DCM. However, it is a useful predictor for VT in DCM and HCM, and prolonged max QTc during exercise has prognostic value in HCM. Repolarization abnormality during exercise plays an important role in the genesis of VT in HCM.

References

- Mines GR: On functional analysis by the action of electrolytes. *J Physiol* 1913; **46**: 188–235
- Adam DR, Smith JM, Akselrod S, Nyberg S, Powell AO, Cohen RJ: Fluctuations in T-wave morphology and susceptibility to ventricular fibrillation. *J Electrocardiol* 1984; **17**: 209–218
- Smith JM, Clancy EA, Valeri CR, Ruskin JN, Cohen RJ: Electrical alternans and cardiac electrical instability. *Circulation* 1988; **77**: 110–121
- Nearing BD, Huang AH, Verrier RL: Dynamic tracking of cardiac vulnerability by complex demodulation of the T wave. *Science* 1991; **252**: 437–440
- Schwartz PJ, Malliani A: Electrical alternation of the T wave: Clinical and experimental evidence of its relationship with the sympathetic nervous system and with the long Q-T syndrome. *Am Heart J* 1975; **89**: 45–50
- Salerno JA, Previtali M, Panciroli C, Klersy C, Chimienti M, Regazzi Bonora M, et al: Ventricular arrhythmias during acute myocardial ischaemia in man: The role and significance of R-ST-T alternans and the prevention of ischaemic sudden death by medical treatment. *Eur Heart J* 1986; **7**(Suppl A): 63–75
- Turitto G, El-Sherif N: Alternans of the ST segment in variant angina: Incidence, time course and relation to ventricular arrhythmias during electrocardiographic recording. *Chest* 1988; **93**: 587–591
- Platt SB, Vijgen JM, Albrecht P, Van Hare GF, Carlson MD, Rosenbaum DS: Occult T wave alternans in long QT syndrome. *J Cardiovasc Electrophysiol* 1996; **7**: 144–148
- Puletti M, Curione M, Righetti G, Jacobellis G: Alternans of the ST segment and T wave in acute myocardial infarction. *J Electrocardiol* 1980; **13**: 297–300
- Nearing BD, Oesterle SN, Verrier RL: Quantification of ischaemia-induced vulnerability by precordial T-wave alternans analysis in dog and human. *Cardiovasc Res* 1994; **28**: 1440–1449
- Ricketts HH, Denison EK, Haywood LJ: Unusual T-wave abnormality: Repolarization alternans associated with hypomagnesemia, acute alcoholism, and cardiomyopathy. *JAMA* 1969; **207**: 365–366
- Navarro-Lopez F, Cinca J, Sanz G, Periz A, Magrina J, Betriu A: Isolated T wave alternans. *Am Heart J* 1978; **95**: 369–374
- Rosenbaum DS, Jackson LE, Smith JM, Garan H, Ruskin JN, Cohen RJ: Electrical alternans and vulnerability to ventricular arrhythmias. *N Engl J Med* 1994; **330**: 235–241
- Day CP, McComb JM, Campbell RWF: QT dispersion: An indication of arrhythmia risk in patients with long QT intervals. *Br Heart J* 1990; **63**: 342–344
- Schwartz PJ, Wolf S: QT interval prolongation as predictor of sudden death in patients with myocardial infarction. *Circulation* 1978; **57**: 1074–1077
- Ahnve S, Gilpin E, Madsen EB, Froelicher V, Henning H, Ross J: Prognostic importance of QTc interval at discharge after acute myocardial infarction: A multicenter study of 865 patients. *Am Heart J* 1984; **108**: 395–400
- Locati E, Schwartz PJ: Prognostic value of QT interval prolongation in post myocardial infarction patients. *Eur Heart J* 1987; **8**(Suppl A): 121–126
- Davey PP, Bateman J, Mulligan IP, Forfar C, Barlow C, Hart G: QT interval dispersion in chronic heart failure and left ventricular hypertrophy: Relation to autonomic nervous system and Holter tape abnormalities. *Br Heart J* 1994; **71**: 268–273
- Buja G, Miorelli M, Turrini P, Melacini P, Nava A: Comparison of QT dispersion in hypertrophic cardiomyopathy between patients with and without ventricular arrhythmias and sudden death. *Am J Cardiol* 1993; **72**: 973–976
- Yi G, Elliott P, McKenna WJ, Prasad K, Sharma S, Guo XH, et al: QT dispersion and risk factors for sudden cardiac death in patients with hypertrophic cardiomyopathy. *Am J Cardiol* 1998; **82**: 1514–1519
- Grimm W, Steder U, Menz V, Hoffmann J, Grote F, Maisch B: Clinical significance of increased QT dispersion in the 12-lead standard ECG for arrhythmia risk prediction in dilated cardiomyopathy. *Pacing Clin Electrophysiol* 1996; **19**(PtII): 1886–1889
- Antzelevitch C, Shimizu W, Yan GX, Sicouri S: Cellular basis for QT dispersion. *J Electrocardiol* 1998; **30**(Suppl): 168–175
- Savelieva I, Yap YG, Guo XH, Hnatkova K, Camm AJ, Malik M: Relation of ventricular repolarization to cardiac cycle length in normal subjects, hypertrophic cardiomyopathy, and patients with myocardial infarction. *Clin Cardiol* 1999; **22**: 649–654
- O'Donnell J, Knoebel SB, Lovelace DE, McHenry PL: Computer quantitation of QT and terminal T wave (aT-eT) intervals during exercise: Methodology and results in normal men. *Am J Cardiol* 1981; **47**: 1168–1172
- Sundqvist K, Sylven C: Cardiac repolarization properties during standardized exercise test as studied by QT, QT peak and terminated T-wave intervals. *Clin Physiol* 1989; **9**: 419–425
- Adachi K, Ohnishi Y, Shima T, Yamashiro K, Takei A, Tamura N, et al: Determinant of microvolt-level T-wave alternans in patients with dilated cardiomyopathy. *J Am Coll Cardiol* 1999; **34**: 374–380
- Bazett HC: An analysis of the time relationships of the heart. *Heart* 1920; **7**: 353–370
- Murda'h MA, Nagayoshi H, Albrecht P, Kautzner J, Momiyama Y, Camm AJ, et al: T-wave alternans as a predictor of sudden death in hypertrophic cardiomyopathy (abstract). *Circulation* 1996; **94**: I-669
- Momiyama Y, Hartikainen J, Nagayoshi H, Albrecht P, Kautzner J, Saumarez RC, et al: Exercise-induced T-wave alternans as a marker of high risk in patients with hypertrophic cardiomyopathy. *Jpn Circ J* 1997; **61**: 650–656
- Armoundas AA, Osaka M, Mela T, Rosenbaum DS, Ruskin JN, Garan H, et al: T-wave alternans and dispersion of the QT interval as risk stratification markers in patients susceptible to sustained ventricular arrhythmias. *Am J Cardiol* 1998; **82**: 1127–1129
- Mezilis NE, Parthenakis FI, Kanakarakis MK, Kanoupakis EM, Vardas PE: QT variability before and after episodes of nonsustained ventricular tachycardia in patients with hypertrophic cardiomyopathy. *Pacing Clin Electrophysiol* 1998; **21**(PtII): 2387–2391
- Yoshimura M, Matsumoto K, Watanabe M, Yamashita N, Sanuki E, Sumida Y: Influence of exercise on QT dispersion in hypertensive patients with left ventricular hypertrophy without coronary artery disease. *Jpn Circ J* 1999; **63**: 881–884
- Yi G, Prasad K, Elliott P, Sharma S, Guo XH, McKenna WJ, et al: T wave complexity in patients with hypertrophic cardiomyopathy. *Pacing Clin Electrophysiol* 1998; **21**(PtII): 2382–2386
- Kishore R, Kautzner J, Carol P, Malik M, McKenna WJ: QT interval and QT dispersion used as prognostic factors in hypertrophic cardiomyopathy (abstract). *Pacing Clin Electrophysiol* 1995; **18**(PtII): 930
- Shimizu W, Antzelevitch C: Cellular and ionic basis for T-wave alternans under long-QT conditions. *Circulation* 1999; **99**: 1499–1507
- Nordin C: Abnormal Ca²⁺ handling and the generation of ventricular arrhythmias in congestive heart failure. *Heart Failure* 1989; **5**: 143–154
- Toshima H, Koga Y: Increased cardiovascular responses to epinephrine and norepinephrine in patients with hypertrophic cardiomyopathy. In: Toshima H, Maron BJ, editors. *Cardiomyopathy Update 2: Hypertrophic Cardiomyopathy*. Tokyo: University of Tokyo Press, 1988: 141–153