ORIGINAL ARTICLES

Dynamics of Ventricular Repolarization in Patients with Dilated Cardiomyopathy Versus Healthy Subjects

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Background: Patients with impaired left ventricular function have a high risk of developing ventricular arrhythmias and sudden death. Among different markers of risk, the prolongation and regional heterogeneity of repolarization are of increasing interest. However, there are limited data regarding feasibility of analyzing repolarization parameters and their dynamics in 24-hour Holter ECG recordings.

Methods: Dynamic behavior of repolarization parameters was studied with a new automatic algorithm in digital 24-hour Holter recordings of 60 healthy subjects and 55 patients with idiopathic dilated cardiomyopathy (IDC). Repolarization parameters included the mean value of QT and QTc durations, QT dispersion, and peaks of QT duration and QT dispersion above prespecified thresholds.

Results: In comparison to healthy subjects, patients with IDC had lower heart rate variability, longer mean QT and QTc durations, higher content of QTc peaks >500 ms, longer QT dispersion and its standard deviation, and a higher content of peaks >100 ms of QT dispersion ($P < 0.01$ for all comparisons). These repolarization parameters were significantly higher in IDC patients after adjustment for age, sex, and heart rate variability. The parameters of repolarization dynamics correlated with SDNN in healthy subjects but not in dilated cardiomyopathy patients.

Conclusions: The automatic assessment of repolarization parameters in 24-hour digital ECG recordings is feasible and differentiates dilated cardiomyopathy patients from healthy subjects. Patients with dilated cardiomyopathy have increased QT duration, QT dispersion, and increased variability of QT dispersion reflecting variations in T-wave morphology, the factors which might predispose them to the development of arrhythmic events.

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Holter monitoring; repolarization; QT interval; dilated cardiomyopathy

Patients after myocardial infarction with impaired left ventricular function and patients with idiopathic dilated cardiomyopathy (IDC) have a high risk of developing malignant ventricular arrhythmias and sudden death. Among different markers of risk in these patients, the prolongation¹ and re-

gional heterogeneity of repolarization² are of increasing interest.

Ventricular repolarization abnormalities can be assessed by measuring the QTc interval as well as analyzing the differences between the maximum and minimum QT intervals ("QT dispersion") in

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surface ECG.¹⁻³ Both the parameters have been reported to be associated with an increased risk of arrhythmic events in patients with different heart diseases.¹⁻⁶ However, still there are controversial results in studies assessing the prognostic value of these parameters measured in surface ECG.⁷⁻¹⁵ Therefore, considering these limitations and the importance of circadian variations and autonomic nervous system (ANS) imbalance,¹⁶ we have proposed to study the dynamic behavior of these parameters derived from three orthogonal leads during 24-hour ECG monitoring periods using our new validated algorithm.¹⁷⁻²⁰ The aim of the present study was to evaluate whether the dynamic behavior of QT duration and dispersion, automatically computed with our custom-made algorithm,¹⁷⁻¹⁸ is able to distinguish a different pattern of ventricular repolarization in patients with idiopathic dilated cardiomyopathy when compared to healthy subjects (NRM).

METHODS

Study Population

Holter recordings of 60 healthy subjects (NRM) and 55 patients with idiopathic dilated cardiomyopathy enrolled in the IDEAL database (Intercity Digital ECG Alliance organized by University of Rochester Medical Center, Rochester, USA) served to investigate the differences in repolarization dynamics between these two groups. Healthy subjects had no previous history of any heart disease or other chronic disorders, they were symptom free, off-drugs, with normal physical examination and normal 12-lead ECG. In case of suspicion of any ECG changes, a normal echocardiogram and normal exercise test were required. IDC patients were identified based on left ventricular dysfunction with a left ventricular ejection fraction $\leq 40\%$ in the absence of ischemic or valvular heart disease (angiographically confirmed). All the IDC patients had to remain in sinus rhythm to be eligible for enrollment.

Repolarization Analysis

The dynamic behavior of repolarization was analyzed using digital (200 samples per second) Holter recordings (Burdik-Spacelab, Milton, WI, USA) acquired using X, Y, Z-lead system. Repolarization parameters evaluated in 24-hour Holter recordings

included: QT and QTc durations, QT dispersion, and the presence of peaks of QT duration > 500 ms and peaks of QT dispersion > 100 ms. The cutoff values of 500 ms for QTc duration and 100 ms for QT dispersion were obtained as the best thresholds for identifying patients with cardiac events in our previous studies.¹⁷⁻²⁰

The custom-made algorithm^{17,18} to study the repolarization parameters included the following signal processing procedures:

1. A previously developed and validated detector of wave boundaries in ECG signals was applied to each of the three leads. Briefly, it included the following steps: ECG signal preprocessing with a low-pass differentiator, QRS detection, QRS onset detection, and T-wave end detection. The QRS onset and T-wave end detection are based on the first derivative of the ECG signal. To identify the T-wave end, a search window is defined from the QRS position. The highest slope value of the downward arm of T-wave (upward if the T-wave is inverted) is the maximum (minimum in the inverted T-wave) in the differentiated ECG signal in the previously defined window. A threshold is defined as this highest slope value divided by a constant factor. The value of the constant factor has been experimentally adjusted.²⁰ The T-wave end is considered when the differentiated signal reaches this threshold. A similar procedure is used to identify the QRS onset.
2. Measurement of QT intervals in each consecutive beat of the three leads, using the detection algorithm described above. Incorrect QT values can result when noise, premature ventricular complexes, or other abnormalities are present. As the priority of the algorithm is to get reliable statistical results from the 24-hour recordings, the next post-processing step is applied to identify the QT values that can be considered correctly measured.
3. Post-processing of QT values by comparing QT of a specific beat to the averaged QT computed from five accepted preceding beats. The new QT is considered well measured when its value is within $\pm 10\%$ of the preceding averaged QT. The QT values out of this range are rejected. This procedure is applied in the three leads throughout 24-hour recording.^{17,18}
4. Calculation of QTc according to Bazett's formula using preceding RR.

5. Calculation of QT dispersion as the difference between the maximum and the minimum intervals measured from X, Y, Z leads. When the QT values of one or more leads are rejected in step (3) for a specific beat, the QT dispersion is not calculated for this beat.
6. Calculation of mean QT dispersion.

The mean QT and QTc values are reported for the lead where there is the maximum number of accepted QT values, in step (3) of the signal processing algorithm. The standard deviations of QT, QTc, and QTd are calculated using all accepted values obtained from 24-hour recording. QT variability measures (QTSD and QTcSD) were also adjusted for heart rate variability (SDNN) by simply dividing repolarization variability parameter by SDNN.

A set of 1000 beats, with different T-wave morphologies and different noise levels, was used for the QT dispersion algorithm validation. The results automatically obtained by the algorithm were compared with those obtained manually by two experts (expert-one and expert-two). The manual measurements were made on paper ECGs using exactly the same beats in the same leads. The mean difference and standard deviation between manual and automatic QTd measures were of the same order (automatic vs expert-one = 0.62 ± 12 ms, automatic vs expert-two = -0.34 ± 11.90 ms) as obtained between the experts (expert-one vs expert-two = 0.26 ± 13.09 ms).

Statistical Analysis

All results are expressed as mean values $\pm$ standard deviation. A non-parametric analysis of variance (Mann-Whitney U test) was used to statistically analyze the differences between both the groups of subjects. Statistical significance was assumed for P values < 0.05 . The associations among the different ventricular repolarization parameters or between measurements of ventricular repolarization variability and heart rate variability were evaluated using Spearman correlation coefficients. Multivariate logistic regression analyses were performed to determine whether studied repolarization parameters remained different between two studied groups after adjustment for age, sex, and SDNN.

RESULTS

Among 60 healthy subjects, there were 26 (43%) males and 34 (57%) females with mean age of the group 37.8 ± 16 years. The IDC group consisted of 55 patients, 45 (82%) males and 10 (18%) females, with mean age of the group 48.5 ± 13 years and with mean EF $24 \pm 8.5\%$. IDC patients were treated with beta-blockers (25%), ACE-inhibitors (82%), digoxin (38%), diuretics (51%), and antiarrhythmic drugs (36%).

Studied Holter-derived parameters are presented in Table 1. The IDC patients had lower heart rate

Table 1. Repolarization Parameters in 24-Hour ECG Recordings from Healthy Subjects and Patients with Idiopathic Dilated Cardiomyopathy

	NRM N = 60	IDC N = 55	P
Mean RR (ms)	790.3 ± 119.2	775.1 ± 101.6	NS
SDNN (ms)	143.3 ± 51.3	115.7 ± 56.3	0.002
Mean QT (ms)	370.6 ± 24.6	416.2 ± 40.5	<0.001
SD QT (ms)	29.8 ± 9.4	30.0 ± 11.1	NS
SDQT/SDNN	0.21 ± 0.05	0.31 ± 0.17	<0.001
Mean QTc (ms)	419.4 ± 21.1	472.7 ± 44.6	<0.001
SD QTc (ms)	23.1 ± 8.0	24.8 ± 10.5	NS
SDQTc/SDNN	0.17 ± 0.06	0.26 ± 0.20	0.002
Mean QTd (ms)	27.1 ± 10.3	54.5 ± 30.4	<0.001
SD QTd (ms)	19.1 ± 7.6	29.4 ± 16.1	<0.001
SDQTd/SDNN	0.13 ± 0.06	0.28 ± 0.22	<0.001
% Peaks QTc >500 ms	1.75 ± 3.1 (0.45)	29.7 ± 35.5 (9.33)	<0.001
% peaks QTd >100 ms	1.8 ± 2.4 (0.69)	13.3 ± 18.0 (5.37)	<0.001

Values are expressed in mean $\pm$ SD. Median values are given in parentheses for data with non-normal distribution.

variability as measured by lower SDNN values ($P = 0.002$). When compared to NRM, the IDC patients had significantly longer mean QT and mean QTc ($P < 0.0005$ for both) and a significantly higher content (%) of QTc peaks >500 ms (30 vs 2 on average, respectively; $P < 0.0005$). The absolute values of standard deviations of QT and QTc intervals were similar in both the groups; however, after adjustment for SDNN, both QT and QTc showed significantly higher variability in IDC patients than in healthy subjects (Table 1).

The IDC patients had a significantly higher mean QT dispersion, standard deviation of QT dispersion, and content (%) of peaks >100 ms of QT dispersion ($P < 0.0005$ for all). An example of these differences is shown in Figure 1.

There were several differences in repolarization patterns between NRM and IDC individuals. A mean QTc >460 ms and a mean QTd >55 ms were present in 30 (55%) and 21 (38%) IDC patients, respectively, but never in healthy subjects. Only 19 (34%) IDC patients showed simultaneously a mean QTc <460 ms and a mean QTd <55 ms.

All healthy subjects presented $<20\%$ of beats with QTc >500 ms and $<10\%$ of beats with a QTd >100 ms, whereas 22 (40%) and 21 (38%) IDC patients reached this percentage of beats, respectively.

Almost all repolarization parameters significantly correlated with mean RR and SDNN values in healthy subjects, while in IDC patients most of the correlations were insignificant (Table 2). In particular, there was a significant positive association between RR versus QTd and SDNN versus QTd indicating that in healthy subjects bradycardia and increased HRV contribute to increased QT dispersion. Variability of QT duration and dispersion also showed positive correlations with RR and SDNN in healthy subjects (Fig. 2). The only correlation coefficients that differed significantly between IDC patients and healthy subjects were those of percentage QTc peaks versus RR and versus SDNN ($P < 0.01$ for difference in correlation coefficients between groups).

In IDC patients, who had substantial left ventricular dysfunction (mean EF = 24%) and lower SDNN levels than healthy subjects, the above significant associations were usually not present indicating a disconnection between HRV and QT parameters in the disease conditions.

Multivariate analysis revealed that repolarization parameters differentiate healthy subjects from IDC

Figure 1. Examples of RR (ms), QT (ms), and QTd (ms) in a healthy control (A) and in a patient with idiopathic dilated cardiomyopathy (B). No differences in RR (ms) were observed between these two patients, but a higher mean value of QT and a substantially higher QT dispersion was observed in the patient with IDC.

patients independent of age, sex, and heart rate variability measured using SDNN (Table 3).

DISCUSSION

In this study, we investigated whether the dynamic behavior of repolarization parameters (that may be markers or triggers of sudden death) is different in patients with idiopathic dilated cardiomyopathy as compared with healthy subjects. QT

Table 2. Spearman Correlations between Heart Rate (RR) and SDNN and Studied Parameters of Repolarization in Healthy Subjects and Patients with Idiopathic Dilated Cardiomyopathy

	QT	QTSD	QTc	QTcSD	QTd	QTdSD	%QTc Peaks	%QTd Peaks
NRM								
RR	0.68 (<0.005)	0.31 0.01	-0.03 NS	0.29 0.02	0.37 0.003	0.49 (<0.005)	0.37 (<0.005)	0.53 (<0.005)
SDNN	0.48 (<0.01)	0.77 (<0.01)	0.06 NS	0.59 (<0.01)	0.37 (<0.01)	0.39 (<0.01)	0.44 (<0.01)	0.38 (<0.01)
IDC Patients								
RR	0.37 (<0.01)	0.14 NS	-0.29 0.03	-0.01 NS	0.25 NS	0.21 NS	-0.24* NS	0.19 NS
SDNN	0.15 NS	0.53 (<0.01)	-0.25 NS	0.32 (0.01)	0.06 NS	0.05 NS	-0.15* NS	0.02 NS

Table represents r correlations and P values.

*P value < 0.01 for comparison of correlation coefficients between healthy subjects and IDC patients.

duration and QT dispersion were found to be significantly higher in patients with IDC than in NRM. QT duration variability expressed in absolute values was similar in both the groups, whereas when adjusted for SDNN it was higher in IDC versus healthy subjects. Variability of QTd was also higher in IDC patients. The IDC patients had an increased number of peaks of QT lengthening and QT dispersion that was not observed or was observed very infrequently in healthy subjects. Specifically, a mean QT duration threshold value of >460 ms and mean QT dispersion >55 ms were not found in healthy subjects, whereas they were observed in 55% and 38% IDC patients, respectively. These findings indicate that IDC patients have abnormalities of repolarization manifested as prolongation of QT duration and increased QT dispersion.

In agreement with our findings, other studies have also shown an increased dispersion of QT interval evaluated by measurements of the standard 12-lead surface ECG in patients with dilated cardiomyopathy.^{21,22} The lengthening of QT intervals and the presence of QT dispersion in surface ECG have been considered markers of bad prognosis in different substrates of patients.³⁻¹⁰

The exact electrophysiologic mechanisms of ventricular arrhythmias in patients with idiopathic dilated cardiomyopathy are not completely understood. Experimental models have suggested that tachycardia-induced cardiomyopathy is associated with a prolonged and heterogeneous repolarization that may lead to reentrant arrhythmias and with increase in the incidence of ventricular tachycardia and sudden death.^{23,25}

The predictive value of QT dispersion in patients with dilated cardiomyopathy with a moderate to severe ventricular dysfunction remains controversial.^{12-14,15,26,27} In patients with dilated cardiomyopathy presenting a mild dysfunction of the ventricle, QT dispersion was not able to differentiate those individuals who will versus those who will not suffer arrhythmic events during the follow-up.¹² Similarly, QT dispersion neither was associated with increased mortality nor differentiated the mode of death in a population of patients with heart failure from ELITE II substudy.¹⁴ However, both increased QTc interval and QT dispersion were found to be associated with higher mortality in another population of patients with moderate and severe left ventricle dysfunction.¹⁵

The measurement of ventricular repolarization by using QT dispersion is not free from criticisms related to methodological and conceptual aspects of this method.²⁷ Whether QT dispersion represents projection phenomena⁹ or local effects of heterogeneous repolarization,⁷ or both, QT dispersion could be considered as an indirect measure of changes in T-wave morphology among studied ECG leads. Manual computation of QTd also raises several concerns related to poor reproducibility of the method. Automatic algorithms quantifying QT dispersion from digital ECG seem to be a better approach eliminating observer factor of poor reproducibility.²⁸ In our study, we utilized a novel computer algorithm computing QT dispersion continuously in 24-hour Holter recording.^{17,18} This particular approach was highly reproducible and could be considered as a method of choice for QT dispersion.

Figure 2. Correlation between QT (ms) and SDNN in a healthy subject (A) and in an ICD patient (B) (r Spearman correlation). IDC = Idiopathic dilated cardiomyopathy; NRM = healthy subjects.

When the algorithms used to identify the endpoint of the T-wave use the intersection between the tangent and the baseline, these procedures are affected by the slope and the amplitude of the T-wave. In such circumstances, it is useful weighting the QT intervals with the slope and the amplitude of the T-wave.²⁹ The algorithm used in the present study is based on a more robust procedure. It identifies the endpoint of the T-wave when the differentiated ECG signal reaches the highest slope di-

vided by a constant factor, and this procedure is not sensitive to the absolute values of the slope or the amplitude of the T-wave. The evaluation results obtained with the proposed algorithm, using the CSE multilead measurement database,³⁰ presented a mean $\pm$ standard deviation of 4 ± 10 ms when analyzing the differences between QT interval values estimated by the algorithm and the QT interval measured from the mean referee estimates of the CSE database. As the QT interval measurements

Table 3. Multivariate Logistic Regression Analysis of Repolarization Parameters Differentiating Patients with Idiopathic Dilated Cardiomyopathy from Healthy Subjects after Adjustment for Age, Sex, and SDNN

Model	Parameters	OR IDC versus NRM	95% CI	P value
Baseline Clinical Model				
	Age	1.28	1.09–1.52	0.002
	Sex	1.48	0.59–1.73	<0.001
	SDNN	1.17	1.04–1.19	0.034
Repolarization parameters				
	QT	1.66	1.43–1.89	<0.001
	QTSD	1.29	1.06–1.75	0.002
	QTc	1.63	1.41–1.87	<0.001
	QTcSD	1.18	1.04–1.41	0.027
	QTd	1.46	1.29–1.75	<0.001
	QTdSD	1.31	1.11–1.52	<0.001
	%QTc peaks	1.43	1.23–1.71	<0.001
	%QTd peaks	1.32	1.13–1.55	<0.001

are not dependent on the slope and the amplitude of the T-wave, the QT dispersion measurements are also not affected by these parameters.

Ventricular repolarization abnormalities may vary over time as the result of changes in the myocardial substrate, in response to changes in the autonomic nervous system, changes due to circadian variations or presence of ischemia.^{5,16,27} Using 12-lead ECG recordings of 30 minutes, it has been recently demonstrated that QT dispersion shows fluctuations uncoupled from variations in heart rate,³¹ which is in agreement with previous results obtained during pacing at different intervals or during exercise.^{32,33}

The variation of QT interval during 24-hour ECG recordings has been shown to have a prognostic significance for the occurrence of arrhythmic events. We previously found that patients with past myocardial infarction who developed sustained ventricular arrhythmias during follow-up show a higher incidence of sudden increases of QTc peaks (>500 ms) during 24-hour ECG recordings than a matched population without arrhythmic events.¹⁹ In this study, we observed that not only QT duration but also QT dispersion shows a dynamic behavior. QT dispersion demonstrated a substantial variation over a 24-hour period, being substantially higher in IDC patients than in healthy controls. Interestingly, SDQT or SDQTc, measuring variability of QT in absolute terms unadjusted for HRV was not significantly different between groups despite significantly different mean QTc duration.

Variability of QT seems to be predominantly driven by heart rate variability. Simultaneously,

QT dispersion (reflecting changes in repolarization morphology) shows increased variability both in absolute terms and when adjusted for SDNN. These findings are in agreement with observations by Berger et al.³⁴ who reported that QT liability (based on T-wave stretching approach reflecting morphology of repolarization) is higher in IDC patients than in controls.

Our analysis of the relationship between QTd and SDNN seems to indicate that in IDC patients, depressed HRV does not influence QTd indicating therefore that variability of QTd is mostly determined by myocardial factors. QT dispersion and QTd peaks measured during 24-hour recordings with our algorithm might be useful in identifying patients with abnormal dynamics of repolarization. The prognostic significance of QT dispersion variability and of QT dispersion peaks is not yet established and further studies with long-term follow-up are needed in populations of patients with IDC and also in ischemic patients that present higher mortality. It is necessary to detect whether parameters of repolarization are good enough to predict mortality or we need to use the newer ones.

SUMMARY

An assessment of dynamic features of repolarization duration and dispersion could be performed automatically from a 24-hour Holter recording. Our computerized algorithm quantifying beat-to-beat changes in QT duration and QT dispersion was validated by demonstrating significant difference in the tested parameters between healthy subjects and

patients with IDC. Future studies with long-term follow-up evaluating the prognostic significance of such methodology for predicting cardiac events in IDC and other groups of patients are needed.

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REFERENCES

- Schwartz PJ, Wolf S. QT interval prolongation as predictor of sudden death in patients with Myocardial infarction. *Circulation* 1987;557:1074-1077.
- Dinerman JL, Berger RD, Haigney MCP, et al. Dispersion of ventricular activation and recovery in patients with idiopathic dilated cardiomyopathy. *Am J Cardiol* 1997;79:970-974.
- 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.
- Miorelli M, Buja G, Melacini P, et al. QT interval variability in hypertrophic cardiomyopathy patients with cardiac arrest. *Int J Cardiol* 1994;45:121-127.
- Zareba W, Moss AJ, la Cessie S. Dispersion of ventricular repolarization and arrhythmic cardiac death in coronary artery disease. *Am J Cardiol* 1994;74:550-553.
- Perkiomaki JS, Koistinen MJ, Yli-Mayry S, et al. Dispersion of the QT interval in patients with and without susceptibility to ventricular tachyarrhythmias after previous myocardial infarction. *J Am Coll Cardiol* 1995;26:174-179.
- Zabel M, Portnoy S, Franz MR. Electrocardiographic indexes of dispersion of ventricular repolarization: An isolated heart validation study. *J Am Coll Cardiol* 1995;25:746-752.
- Zabel M, Klingenhoben T, Franz MR, et al. Assessment of QT dispersion for prediction of mortality or arrhythmic events after myocardial infarction. Results of a prospective, long term follow up study. *Circulation* 1998;97:2543-2550.
- Kors JA, Van Herpen G, Van Bommel JH. QT dispersion as an attribute of loop morphology. *Circulation*. 1999;99:1458-1463.
- De Bruyne MC, Hoes AW, Kors JA, et al. Prolonged QT interval predicts cardiac and all cause mortality in the elderly. *Eur Heart J* 1999;20:278-284.
- Surawicz B. Will QT dispersion play a role in clinical decision making? *J Cardiovasc Electrophysiol* 1996;7:777-784.
- Fei L, Goldman JH, Prasad K, et al. QT dispersion and RR variations on 12-lead ECGs in patients with congestive heart failure secondary to idiopathic dilated cardiomyopathy. *Eur Heart J* 1996;17:258-263.
- Kautzner J, Malik M. QT interval dispersion and its clinical utility. *PACE* 1997;20:2625-2640.
- Gang Y, Ono T, Hnatkova K, et al. ELITE II investigators. QT dispersion has no prognostic value in patients with symptomatic heart failure: An ELITE II substudy. *Pacing Clin Electrophysiol* 2003;26:394-400.
- Padmanabhan S, Silvet H, Amin J, et al. Prognostic value of QT interval and QT dispersion in patients with left ventricular dysfunction: Results from a cohort of 2265 patients with an ejection fraction of $< \text{or} = 40\%$. *Am Heart J* 2003;145:132-138.
- Cinca J, Moya A, Figueras J, et al. Circadian variations in the electrical properties of the human heart assessed by sequential bedside electrophysiologic testing. *Am Heart J* 1996;112:315-321.
- Caminal P, Blasi A, Vallverdú M, et al. New algorithm for QT dispersion analysis in XYZ-lead Holter ECG. Performance and applications. *IEEE Comput Cardiol* 1998;1:709-712.
- Laguna P, Thakor N, Caminal P, et al. New algorithm for QT interval analysis in 24 h Holter ECG: Performance and applications. *Med Biol Eng Comput* 1990;28:67-73.
- Homs E, Marti V, Guindo J, et al. Automatic measurement of corrected QT interval in Holter recordings: Comparison of its dynamic behavior in patients after myocardial infarction with and without life-threatening arrhythmias. *Am Heart J* 1997;134:181-187.
- Laguna P, Janè R, Caminal P. Automatic detection of wave boundaries in multilead ECG signals: Validation with the CSE Data Base. *Comput Biomed Res* 1994;27:45-60.
- Barr CS, Naas A, Freeman M, et al. QT dispersion and sudden unexpected death in chronic heart failure. *Lancet* 1994;343:327-329.
- Pye M, Quinn AC, Cobbe SM. QT interval dispersion: A non-invasive marker of susceptibility to arrhythmia in patients with sustained ventricular arrhythmias? *Br Heart J* 1994;71:511-514.
- Pak PH, Nuss HB, Tunin RS, et al. Repolarization abnormalities, arrhythmia and sudden death in canine tachycardia-induced cardiomyopathy. *J Am Coll Cardiol* 1997;30:576-584.
- Zhu WX, Johnson SB, Brandt R, et al. Impact of volume loading and load reduction on ventricular refractoriness and conduction properties in canine congestive heart failure. *J Am Coll Cardiol* 1997;30:825-833.
- Akar FG, Rosenbaum DS. Transmural electrophysiological heterogeneities underlying arrhythmogenesis in heart failure. *Circ Res* 2003;93:638-645.
- Grimm W, Steder U, Menz V, et al. QT dispersion and arrhythmic events in idiopathic dilated cardiomyopathy. *Am J Cardiol* 1996;78:458-461.
- Malik M, Batchvarov VN. Measurement, interpretation and clinical potential of QT dispersion. *J Am Coll Cardiol* 2000;36:1749-1766.
- Murray A, McLaughlin NB, Campbell RW. Measuring QT dispersion: Man versus machine. *Heart* 1997;77:539-542.
- Lund K, Nygaard H, Pedersen AK. Weighting the QT intervals with the slope or the amplitude of the T wave. *Ann Noninvas Electrocardiol*. 2002;7(1):4-9.
- Willems JL, Arnaud P, Van Bommel JH, et al. *J Am Coll Cardiol* 1987;10(6):1313-1321.
- Galeano EJ, Ohnishi Y, Yoshida A, et al. Usefulness of beat-to-beat QT dispersion fluctuation for identifying patients with coronary heart disease at risk for ventricular arrhythmias. *Am J Cardiol* 2001;88:1235-1239.
- Zabel M, Woosley RL, Franz MR. Is dispersion of ventricular repolarization rate dependent? *PACE* 1997;20:2405-2411.
- Umetani K, Komori S, Ishihara T, et al. Relation between QT interval and heart rate. *Am J Cardiol* 1999;84:1135-1137.
- Berger RD, Kasper EK, Baughman KL, et al. Beat-to-beat QT interval variability: Novel evidence for repolarization lability in ischaemic and nonischaemic dilated cardiomyopathy. *Circulation* 1997;96:1557-1565.