ORIGINAL ARTICLES

Circadian Variation in QT Dispersion Determined from a 12-Lead Holter Recording: A Methodological Study of an Age- and Sex-Stratified Group of Healthy Subjects

Stig Hansen, M.D.,* Verner Rasmussen, M.D.,† Klaus Larsen, M.Sc., Ph.D.,‡
Christian Torp-Pedersen, M.D., D.M.Sc.,§ and Gorm Boje Jensen, M.D., D.M.Sc.*

From the *Department of Cardiology, †The Holter Laboratory, and ‡Department of Medical Statistics, Copenhagen University Hospital, Hvidovre, Denmark; and §Department of Cardiology, Copenhagen University Hospital, Bispebjerg, Denmark

Background: QT dispersion is considered to reflect inhomogeneity of myocardial repolarization.

Method: The circadian variation of QT interval dispersion was examined in 95 healthy subjects using 24-hour Holter monitoring. Three different methods of lead selection were applied: all 12 leads (QTdisp 12), only precordial leads (QTdisp 6), and the pair of leads selected at 3 a.m. in which the longest and shortest QT intervals were found in each individual subject (QTdisp 2).

Results: A preliminary methodological study including measurements from every minute in 10 subjects revealed no significant circadian variation using mean values of QTdisp 12, QTdisp 6, or QTdisp 2 obtained every hour, every 2, or every 4 hours, except in QTdisp 6, which demonstrated a significant circadian variation ($P < 0.01$) in 1-hour measurements. Analysis of all 95 subjects using measurements obtained every 4 hours revealed a significant circadian variation in QTdisp 12 and QTdisp 6 ($P < 0.0001$), whereas no circadian variation was seen in QTdisp 2. A subdivision into 10-year age groups revealed that subjects at age >50 years had a significant circadian variation in QTdisp 12 and QTdisp 6, but not in QTdisp 2. Only in males a significant circadian variation was seen in QTdisp 12 ($P < 0.0001$), whereas QTdisp 6 demonstrated a circadian variation both in females ($P < 0.001$) and in males ($P < 0.0001$).

Conclusions: Selection of leads is of crucial importance for repetitive measurements of QT dispersion. Circadian variation was detected in subjects over 50 years of age, when all 12 or only the 6 precordial leads were taken into account.

A.N.E. 2007;12(3):185–196

circadian variation; QT dispersion

QT dispersion is defined as the difference between the longest and shortest QT interval measured on a standard 12-lead electrocardiogram. QT dispersion was introduced in 1990 by Day et al.¹ proposing QT dispersion as an index of the spatial inhomogeneity of repolarization duration. Increased dispersion of ventricular repolarization may increase the risk of ventricular arrhythmia.²

The onset of acute myocardial infarction and sudden cardiac death (SCD) has a circadian variation with a peak incidence in the early morning hours^{3–5} and functional abnormalities of the autonomic ner-

vous system appear to be involved. Patients with diabetes mellitus and autonomic dysfunction have an increased QT dispersion compared with patients without autonomic dysfunction⁶ and treatment with beta-blockers in patients with heart failure is associated with a reduction in QT dispersion⁷ indicating that sympathetic deactivation may cause decreased QT dispersion.

Possibly, circadian variation in QT dispersion may be involved in increased risk of SCD in the early morning hours. The study of circadian variation of the QT dispersion in healthy subjects and

Address for reprints: Stig Hansen, Department of Cardiology 253, Copenhagen University Hvidovre Hospital, Kettegaard Alle 30, 2650 Hvidovre, Denmark. Fax: +0045-36-32-37-55; E-mail: hansson@dadlnet.dk

in patients may therefore shed light on the inhomogeneity of risk over time of day.

A variety of recording techniques have been used in the determination of the circadian variation of QT dispersion. Previously two or three lead recordings have demonstrated a possible circadian variation with larger values of QT dispersion during daytime compared to nighttime,⁸ or with larger values at night compared to daytime⁹ among healthy subjects. Twelve-lead Holter recordings in an hourly measurement demonstrated that the mean value of QT dispersion was significantly higher from 5 a.m. to 7 a.m. and from 2 p.m. to 4 p.m.¹⁰

The aim of the study was to present results of QT-interval measurements each minute over 24 hours in healthy subjects and to determine QT dispersion and its circadian variation. In this study, we focused on 2 aspects of circadian variation of QT dispersion. First, How can QT dispersion be measured in a way that would be clinically feasible, taking into account the number of leads to be measured, as well as the sampling intervals to be used; and second, What is the circadian variation of QT dispersion in normal subjects, and does it vary with age and gender?

MATERIALS AND METHODS

Study Population

A total of 137 healthy volunteers (aged 20–81 years) were included among responders to an invitation letter, which was sent to 1000 randomly selected inhabitants of Hvidovre municipal area, Copenhagen. Only subjects without known disease and medication were asked to contact the study group. Written informed consent was obtained from all participants and the regional ethical committee approved the study (KF 01-200/00). After interview and routine physical examination all 137 subjects were found to be eligible for 24-hour Holter monitoring.

One subject was excluded because of the finding of a previously undetected delta wave in the Holter ECG; another owing to first-degree AV block, and 40 were considered unfit for participation because of low amplitude of the T wave in more than four leads. The remainder 95 subjects were in regular sinus rhythm with QRS complexes of normal configuration and width. Distribution according to age and gender is presented in Table 1.

Table 1. Distribution of Age and Sex in the Study Group of 95 Subjects and in the Methodological Study of 10 Subjects (Round Brackets)

Age (Years)	Male	Female
20–29	9	6
30–39	9 (2)	5
40–49	8 (1)	4 (1)
50–59	13 (4)	8
60–69	12 (2)	8
70–81	4	9
All ages	55 (9)	40 (1)

Methods

QT dispersion measurement was performed semiautomatically using a commercially available recording and analysis equipment (Holter for Windows, Rozinn Electronics Inc, Glendale, NY), which recorded and stored three ECG leads continually on flash cards. In addition, a short 12-lead ECG segment was recorded and stored each minute over a 24-hour period. Skin electrodes were VL-00-S (Ambu Inc, Linthicum, U.K.). The recorded ECG was analyzed automatically, and the automatic measurements were visually checked by an experienced technician who made appropriate correction of cursor locations and excluded tracings in which the T wave was isoelectric or of too low amplitude for accurate determination of QT-interval length. Only recordings containing eight or more usable leads were accepted.

The end of T wave was defined as the intersection of the isoelectric line of the ECG tracing with the tangent to the inflection point to the descending part of the T wave. In the presence of a prominent U wave or a slurring endpoint of the T wave, the lead was excluded.

Among the recordings from the 95 subjects included 10 subjects were, due to optimal technical quality, selected for minute-by-minute analysis over the whole 24-hour period and included in a methodological study. QT dispersion was calculated as a mean over each of the twenty-four 1-hour periods.

For the measurement of QT dispersion three different modes of lead selection for identifying the longest and shortest QT interval were applied. In the first all 12 leads were considered (QTdisp 12), in the second only precordial leads were used (QTdisp 6), and in the third mode only the pair

Table 2. QT Intervals and QT Dispersion Analyzed Minute-by-Minute Over 24 Hour Using all Available Leads in Each of the 10 Subjects

Subject No.	QT Maximum, ms	QT Minimum, ms	QTdisp 12, ms
1	367.3 ± 0.91	347.2 ± 0.84	20.1 ± 0.23
2	398.6 ± 0.49	363.1 ± 0.47	35.5 ± 0.33
3	346.1 ± 0.39	325.1 ± 0.36	21.0 ± 0.24
4	406.3 ± 0.97	382.1 ± 0.86	24.3 ± 0.25
5	389.5 ± 0.99	359.8 ± 0.86	29.7 ± 0.32
6	368.3 ± 1.01	342.2 ± 1.07	26.1 ± 0.36
7	358.8 ± 1.25	332.5 ± 1.19	26.3 ± 0.38
8	391.0 ± 1.16	363.7 ± 1.23	27.3 ± 0.36
9	406.9 ± 0.61	388.0 ± 0.62	19.0 ± 0.19
10	388.9 ± 0.62	365.9 ± 0.45	23.0 ± 0.29
Range	346.1–406.9	325.1–388.0	19.0–35.5
Mean	384.3 ± 0.34	359.4 ± 0.32	24.8 ± 0.11

Mean ± (SE).

QTdisp 12 = All 12 leads included.

representing the longest and shortest QT intervals was preselected from the ECG strip recorded at 3 a.m. (QTdisp 2).

As the automatic setting of the cursor position was often imprecise and had to be meticulously checked and manually corrected, time consumption of this validating procedure was excessive, often amounting to more than 20 hours per subject. In consequence the sampling time was considerably reduced during the analysis of the whole study group of 95 subjects, in whom QT dispersion was calculated every fourth hour (0400–0800–1200–1600–2000–2400 hour) as the mean value of 10 consecutive ECG strips obtained at 1-minute intervals. As in the methodological study, three methods of lead selection were applied (QTdisp 12, QTdisp 6, and QTdisp 2). Measurements of uncorrected QT intervals and QT dispersion are presented in Table 2.

Statistical Analysis

Results are given as mean ± (SE) unless otherwise stated. Statistical calculations employed SAS software version 8.02 (SAS Institute Inc, Cary, NC).

The reproducibility of the intraobserver (repeated measurements by the same observer) and interobserver (measurements performed by two different observers) variability is expressed in relative errors according to the formula $(A-B)/((A+B)/2)$, where A and B are the repeated values of the same measurement. The interobserver and intraobserver reproducibility were analyzed by comparing the means of QT interval and QTdisp 12 at each point

of time in each subject performing a t test for the means.

MIXED models were used to analyze for circadian variation due to the possibility of this method to take into account specific individual effects (random effects) as well as correlation patterns over time. MIXED models can incorporate different variance-covariance and error structures, and regard interindividual difference in time-dependent changes. Mean ± (SE) values of QT dispersion were achieved at each level of time using time as a fixed factor. $P < 0.05$ was considered as the limit of statistical significance.

RESULTS

In this study, we demonstrated that the selection of leads for measurement of QT dispersion had important consequences for the results of analysis. We demonstrated a significant circadian variation in QTdisp 12 and QTdisp 6, whereas no circadian variation was seen in QTdisp 2. A subdivision into 10-year age groups revealed that subjects with age >50 years had a significant circadian variation in QTdisp 12 and QTdisp 6, but not in QTdisp 2.

Reproducibility

The reproducibility of manually corrected measurements of QT interval in every 30th minute in all available leads done independently by two investigators was tested in 10 subjects.

The interobserver reproducibility of QT interval had a relative error of 0.9% and the intraobserver

reproducibility had a relative error of 0.5%, which is considered to be acceptable. The interobserver and intraobserver reproducibility of QT dispersion measured in one pair of leads, which was selected by the observers each minute in each of the 10 subjects, had a relative error of 20% and 38%, respectively. In an attempt to explain the interobserver variability, an investigation was performed revealing no systematic difference in measurement fault between the two observers. No significant difference was found either in respect to interobserver or to intraobserver variability comparing the means of QT interval and QTdisp 12 at each point of time in each subject in a t test for the means.

Methodological Study of 10 Subjects

In Table 2, the mean $\pm$ (SE) of QT-interval measurements (QT maximum and QT minimum) in each of the 10 subjects are presented together with the mean $\pm$ (SE) of QT dispersion. As appears from Table 2, the ranges and standard deviations indicate a rather homogeneous study group.

In Table 3, the mean $\pm$ (SE) of QTc dispersion obtained with two heart rate correction formulas (Bazett¹¹ and Fridericia¹²) and uncorrected QT dispersion are presented including the investigation of circadian variation. No difference in statistical significance was observed whether the analysis was performed on uncorrected or heart rate corrected QT dispersion mean values. In Table 4, the results of QT dispersion measured over 1-hour periods are presented using three methods of lead selection (QTdisp 12, QTdisp 6, and QTdisp 2) and decreasing sampling period, that is, all 24, every second and every fourth 1-hour period listed in columns

(1), (2), and (3), respectively. The content of each column was analyzed for circadian variation using a MIXED model analysis, the result of which is presented as P values in the bottom line.

Effect of Lead Selection

Comparing the values listed in the three columns marked (1) in Table 4, a systematic decline of QT dispersion was observed as the number of leads available for selection was reduced. Restricting selection to precordial leads (QTdisp 6) or to one preselected pair of leads (QTdisp 2) resulted in a reduction of QT dispersion by 20% in the former and by 70% in the latter case.

Analyzing the QT dispersion values listed in the columns marked (1) for circadian variation a P value below 0.05 appeared when only precordial leads were used for selection (QTdisp 6), whereas the P values were above the level of significance when all 12 (QTdisp 12) and one preselected pair of leads (QTdisp 2) was used. The results seem to indicate that use of precordial leads only is superior to the other two modes of lead selection in detecting circadian variation of QT dispersion.

Effect of Length of Sampling Interval

From Table 4 it appears that reducing the number of 1-hour periods from 24 to 12 and 6 (columns (1), (2), and (3) in the analysis of circadian variation resulted in increasing P values when 12 or 6 leads (QTdisp 12 and QTdisp 6) were compared, whereas a slight tendency in the opposite direction was observed when only one pair of leads (QTdisp 2) was taken into consideration. In the latter case, the P values were much higher than those found in the former two cases.

Table 3. Mean $\pm$ (SE) Values of QT Maximum, QT Minimum, and QT Dispersion Obtained with Two Different Correction Formulas in the Group of 10 subjects

	Mean $\pm$ SD		
	QT Interval Maximum, ms	QT Interval Minimum, ms	QTdisp12, ms
QT	384.3 $\pm$ 0.34	359.4 $\pm$ 0.32	24.8 $\pm$ 0.11
Circadian variation P value	<0.0001	<0.0001	NS
QTc Bazett	402.3 $\pm$ 0.19	376.3 $\pm$ 0.19	30.0 $\pm$ 0.11
Circadian variation P value	<0.005	<0.05	NS
QTc Fridericia	395.8 $\pm$ 0.17	370.2 $\pm$ 0.17	25.6 $\pm$ 0.11
Circadian variation P value	<0.0001	<0.0001	NS

P values of MIXED models analysis of circadian variation are presented.
QTdisp 12 = All 12 leads included.

Table 4. QT Dispersion Measured Over 24 Hours by Three Different Methods of Lead Selection and Three Lengths of Sampling Interval Including all 24, Every Second and Fourth Hour 1-Hour Periods in 10 Healthy Subjects

Time Interval	QTdisp 12, ms			QTdisp 6, ms			QTdisp 2, ms		
	(1) All 24 Hour	(2) Every Second Hour	(3) Every Fourth Hour	(1) All 24 Hour	(2) Every Second Hour	(3) Every Fourth Hour	(1) All 24 Hour	(2) Every Second Hour	(3) Every Fourth Hour
0000–0100	26.3	26.3	26.3	20.7	20.7	20.7	8.3	8.3	8.3
0100–0200	28.2			23.4			8.6		
0200–0300	27.9	27.9		22.3	22.3		8.5	8.5	
0300–0400	26.4			21.0			7.3		
0400–0500	27.6	27.6	27.6	22.8	22.8	22.8	8.4	8.4	8.4
0500–0600	27.4			22.9			6.5		
0600–0700	26.6	26.6		21.8	21.8		9.5	9.5	
0700–0800	24.3			19.9			4.9		
0800–0900	23.7	23.7	23.7	18.5	18.5	18.5	6.9	6.9	6.9
0900–1000	23.8			18.6			6.5		
1000–1100	23.4	23.4		18.1	18.1		7.2	7.2	
1100–1200	24.0			18.8			6.5		
1200–1300	25.0	25.0	25.0	19.6	19.6	19.6	7.1	7.1	7.1
1300–1400	24.2			19.4			6.6		
1400–1500	24.7	24.7		19.3	19.3		6.7	6.7	
1500–1600	24.3			19.1			6.3		
1600–1700	24.1	24.1	24.1	18.1	18.1	18.1	6.5	6.5	6.5
1700–1800	22.7			17.3			7.9		
1800–1900	24.8	24.8		18.2	18.2		8.7	8.7	
1900–2000	23.4			17.5			8.4		
2000–2100	24.1	24.1	24.1	18.1	18.1	18.1	9.5	9.5	9.5
2100–2200	24.2			17.9			8.1		
2200–2300	23.2	23.2		18.2	18.2		7.7	7.7	
2300–2400	25.0			19.9			8.6		
Mean	25.0			19.6			7.5		
Circadian variation	NS	NS	NS		NS	NS	NS	NS	NS
P value	(0.1564)	(0.2393)	(0.3794)	<0.01	(0.0508)	(0.1827)	(0.9373)	(0.8835)	(0.7787)

Mean values and P values of MIXED models analysis of circadian variation are presented in the three bottom lines. QTdisp 12 = All leads included; QTdisp 6 = Precordial leads only; QTdisp 2 = One pair of preselected leads.

The results indicate superiority of long sampling intervals compared to shorter ones in disclosing circadian variation of QT dispersion.

Analysis of the Whole Group of Patients

Owing to excessive time consumption of the minute-to-minute analysis used in the methodological study, the sampling interval had to be reduced in this investigation. Instead of including all analyzable ECG strips within a 1-hour period, only a sequence of 10 consecutive minutes was used for calculation of QT dispersion and only every fourth hour. In Table 5, the results are presented for each of the three methods of lead selection, which were also used in the methodological study. For compari-

son, corresponding values from the methodological study, in which complete 1-hour periods were included, are presented in brackets.

Effect of Lead Selection

The systematic decline of QT dispersion observed in the methodological study when the number of selectable leads was restricted from 12 (QTdisp 12) to 6 (QTdisp 6) or 2 (QTdisp 2) was also present in the analysis of the whole study group of 95 subjects (19% and 64% reduction compared to 20% and 70% in the methodological study), the data of which are presented in Table 5.

The analysis for circadian variation using a MIXED model procedure resulted in low P values

Table 5. QT Dispersion Measured Every Fourth Hour by Three Different Methods of Lead Selection Each Time Including 10 Consecutive Minutes within Each of the Stated Inclusion Periods in 95 Subjects

Time	QTdisp 12, ms	QTdisp 6, ms	QTdisp 2, ms
0000–0100	34.1 (26.3)	28.9 (20.7)	12.2 (8.3)
0400–0500	38.4 (27.6)	33.3 (22.8)	12.0 (8.4)
0800–0900	33.8 (23.7)	27.4 (18.5)	13.1 (6.9)
1200–1300	31.7 (25.0)	23.7 (19.6)	11.5 (7.1)
1600–1700	32.7 (24.1)	25.4 (18.1)	12.0 (6.5)
2000–2100	32.5 (24.1)	24.9 (18.1)	11.8 (9.5)
Circadian variation			
P value	<0.0001	<0.0001	NS

Mean values are listed together with corresponding values from the methodological study (round brackets). P values of MIXED models analysis of circadian variation are presented in the bottom line.

QTdisp 12 = all leads included; QTdisp 6 = precordial leads only; QTdisp 2 = 1 pair of preselected leads.

($P < 0.0001$) when all 12 (QTdisp 12) or precordial leads only (QTdisp 6) were considered, whereas the level of statistical significance was not attained when only one preselected pair of leads (QTdisp 2) was used. The analysis of QTdisp 12 and QTdisp 2 demonstrated no circadian variation, whereas QTdisp 6 resulted in statistical significance ($P < 0.0001$) irrespectively of correction formula (Table 6).

Comparison with Results of Methodological Study

The values of QT dispersion measured every fourth hour using a reduced sampling interval were considerably higher than the corresponding values of the methodological study as it appears from Table 5. In addition a considerably wider range of QT dispersion values was observed in each of the three

different lead selection procedures (QTdisp 12, QTdisp 6, and QTdisp 2), demonstrating in a simple way the presence of circadian variation, which was statistically confirmed in the two former cases.

In Table 7, the results of QT dispersion measurement every fourth hour within each of six 10-year age ranges (20–29, 30–39, 40–49, 50–59, 60–69, 70–81) are presented together with the mean values of each of the three different modes of lead selection. For each 10-year age group in each of the three different lead-selection modes (QTdisp 12, QTdisp 6, and QTdisp 2), a P value using MIXED model analysis for circadian variation is listed. In the bottom line of Table 7 are listed the mean values and P values for circadian variation of QTdisp 12, QTdisp 6, and QTdisp 2 for the whole group (95 subjects).

The results indicate that QT dispersion increased with age and was significantly higher in subjects aged 50 years or older compared to younger

Table 6. Uncorrected and Corrected Values of QT Dispersion Measured Every Fourth Hour by Three Different Methods of Lead Selection in 95 Subjects

	QT Dispersion		
	All 12 Leads Included	Precordial Leads Only	1 Pair of Preselected Leads
QTdisp uncorrected values	33.9 ± 0.22	27.3 ± 0.21	12.1 ± 0.21
P values	<0.0001	<0.0001	NS
QTdisp Bazett	36.8 ± 0.24	29.5 ± 0.22	13.1 ± 0.23
P values	NS	<0.0001	NS
QTdisp Fridericia	35.6 ± 0.32	28.7 ± 0.21	12.8 ± 0.22
P values	NS	<0.0001	NS

Mean ± (SE) values and P values of MIXED models analysis of circadian variation are presented.

Table 7. QT Dispersion Measured Every Fourth Hour Each Time Including 10 Consecutive Values Using Three Different Methods of Lead Selection in Relation to Age in 95 Subjects

Age Years	(n)	Time	QTdisp 12 ms	P	QTdisp 6 ms	P	QTdisp 2 ms	P
20–29	(15)	0000–0100	33.4	NS	28.0	0.05	12.0	NS
		0400–0500	36.4		30.8		10.3	
		0800–0900	34.0		27.9		11.9	
		1200–1300	30.6		20.8		10.0	
		1600–1700	34.0		25.6		10.5	
		2000–2100	31.8		23.7		10.2	
30–39	(14)	0000–0100	30.7	NS	25.4	NS	11.1	NS
		0400–0500	30.0		26.0		9.6	
		0800–0900	30.4		24.6		10.1	
		1200–1300	32.2		23.6		10.8	
		1600–1700	32.3		24.6		10.2	
		2000–2100	29.9		23.2		11.5	
40–49	(12)	0000–0100	30.7	NS	28.2	NS	10.9	NS
		0400–0500	28.9		25.4		7.1	
		0800–0900	29.5		24.3		7.6	
		1200–1300	31.1		22.9		5.6	
		1600–1700	29.1		22.5		10.8	
		2000–2100	31.4		25.7		8.1	
50–59	(21)	0000–0100	37.4	<0.0001	32.7	<0.0001	9.1	NS
		0400–0500	43.4		38.7		14.2	
		0800–0900	32.8		26.2		13.2	
		1200–1300	30.4		23.7		11.6	
		1600–1700	31.2		24.5		13.5	
		2000–2100	32.3		24.1		11.5	
60–69	(20)	0000–0100	35.3	<0.05	29.6	<0.005	14.5	NS
		0400–0500	42.2		37.0		12.5	
		0800–0900	37.9		31.3		17.5	
		1200–1300	32.8		26.0		15.5	
		1600–1700	35.9		28.6		13.7	
		2000–2100	33.8		26.5		14.8	
70–81	(13)	0000–0100	34.3	<0.02	27.6	<0.0005	16.7	NS
		0400–0500	44.6		37.2		16.9	
		0800–0900	36.7		28.4		16.2	
		1200–1300	33.2		24.5		13.2	
20–81	(95)	1600–1700	32.2	<0.0001	24.9	<0.0001	11.6	NS
		2000–2100	35.2		25.9		13.6	
			33.9		27.3		12.1	

Mean values and P value of a MIXED models analysis of circadian variation are presented.

QTdisp 12 = all leads included; QTdisp 6 = precordial leads only; QTdisp 2 = 1 pair of preselected leads.

individuals, irrespectively of which mode of lead selection was applied. In addition, the MIXED model analysis demonstrated a statistically significant circadian variation in the older age group when all 12 (QTdisp 12) or precordial leads (QTdisp 6) were included in the lead-selection procedure, whereas no such variation could be detected in subjects under 50 years of age. Figure 1 presents for each 10-year age group the circadian profile of each of the three modes of lead selection (QTdisp 12, QTdisp 6, and QTdisp 2).

MIXED models analysis revealed a considerable interaction between subject and time indicating im-

portant differences of circadian variation of QT dispersion in individuals.

Gender Difference

Table 8 demonstrates the results of QT-dispersion measurement with mean $\pm$ (SE) values of each of the three different modes of lead selection every fourth hour in relation to gender. A significant circadian variation was observed in males when all 12 leads (QTdisp 12) were used ($P < 0.0001$), and in both females and males when precordial leads (QT disp 6) were used ($P < 0.001$

Figure 1. The circadian profile in each of the three modes of lead selection (QTdisp 12, QTdisp 6, and QTdisp 2) for each 10-year age group is presented. P values of a MIXED models analysis of circadian variation are specified for each of the three modes of lead selection in each 10-year age group.

and $P < 0.0001$, respectively), whereas no circadian variation was observed when only a preselected pair of leads (QTdisp 2) was used.

DISCUSSION

QT dispersion has been interpreted in a variety of ways:¹³ Inhomogeneity of QT interval in the myocardium, variable projections of the T wave loop into individual ECG leads or simply a measurement inaccuracy. The clinical implications of QT dispersion has been assessed in several settings: ischemic heart disease,¹⁴ congestive heart failure,¹⁵ the Long QT Syndrome,¹⁶ and arterial hypertension.¹⁷ The evaluation of the prognostic value of QT dispersion is different in various settings. In general the effect is disappointing. However, measurements have not been standardized regarding which leads determine QT maximum and QT minimum, sampling interval, influence of number of ECG leads, and method for demarcation of the T wave.

To assess if a circadian variation of QT dispersion occurs in patients and the clinical implications of this variation, it is mandatory to characterize the optimal measurement circumstances, and to characterize circadian variation in QT dispersion in normal subjects.

The results presented here are the first to show a complete measurement of QT maximum and QT minimum in all leads every minute during 24 hours in 10 subjects. The results showed that the selection of leads for measurement of QT dispersion has important consequences for the results of analyses.

In the methodological study we demonstrated that the magnitude of QT dispersion was critically dependent on the method used for selection of ECG leads in the search for the longest and short-

est QT interval at any given point of time. Inclusion of all technically acceptable leads—at least eight—demonstrated significantly higher values in this case than when precordial leads or particularly when only one pair of leads from a 12-lead ECG recorded during the nighttime were considered. We furthermore demonstrated that a significant circadian variation could be detected when all available data from all 24 hours were in use, but only when the search for longest and shortest QT value was restricted to the six precordial leads.

In the methodological study of the 10 subjects, we analyzed QT dispersion in 1-hour periods using three different methods of lead selection. The values from the night period (0000–0700) were higher than those from the remainder of the 24-hour period suggesting a circadian variation, which could be statistically documented when only precordial leads were considered. A similar variation was seen in Table 5 indicating that the 10 subjects constituted a fairly good sample of the whole study group of 95 subjects. Smaller values of QTdisp 12, QTdisp 6, and QTdisp 2 are observed in Table 4 compared with Table 5, which could be explained by the fact that the 10 subjects in Table 4 were included only if they had a Holter ECG recording with few noise artifacts. The 10 subjects consisted of 9 males age between 33 and 69 years and 1 female age 46 years, findings, which may contribute to the observed difference. The apparent discrepancy between the results of the 10 meticulously analyzed recordings and those of the whole group of 95 recordings most likely reflects the different composition of the groups as to age and gender, the small group of 10 being younger and predominantly of male gender both favoring high technical quality of recordings. The values obtained by the

Table 8. QT Dispersion Measured Every Fourth Hour Each Time Including 10 Consecutive Values Using Three Different Methods of Lead Selection in Relation to Gender in 95 Subjects

	QTdisp 12		QTdisp 6		QTdisp 2	
	Female	Male	Female	Male	Female	Male
0000–0100	33.10 (2.13)	34.78 (1.63)	28.33 (1.97)	29.00 (1.60)	12.44 (2.03)	12.09 (1.68)
0400–0500	38.00 (2.13)	38.69 (1.63)	32.69 (1.97)	33.39 (1.60)	12.00 (2.03)	12.06 (1.68)
0800–0900	35.55 (2.13)	32.57 (1.63)	28.12 (1.97)	26.42 (1.60)	13.35 (2.03)	12.98 (1.68)
1200–1300	33.14 (2.13)	30.65 (1.63)	24.40 (1.97)	22.79 (1.60)	11.16 (2.03)	11.77 (1.68)
1600–1700	33.45 (2.13)	32.11 (1.63)	26.02 (1.97)	24.48 (1.60)	12.66 (2.03)	11.49 (1.68)
2000–2100	33.28 (2.13)	31.85 (1.63)	25.38 (1.97)	24.07 (1.60)	12.63 (2.03)	11.28 (1.68)
Circadian variation P value	NS	<0.0001	<0.001	<0.0001	NS	NS

Mean $\pm$ (SE) values and P value of a MIXED models analysis of circadian variation are presented.

three methods are comparable to other findings described by Zaidi et al.,¹⁸ who found QT dispersion to be $37 \pm (17)$ ms in healthy subjects.

Circadian variation of QT dispersion in healthy subjects has been suggested by Ishida et al.,⁸ Molnar et al.,⁹ Lee et al.,¹⁰ Yetkin et al.,¹⁹ Batur et al.,²⁰ Bilan et al.,²¹ and Bonnemeier et al.,²² but the results are contradictory and the studies have different setups in respect to number of leads used, measurement frequency, and whether heart rate correction of QT dispersion is used or not.

Using all 12 leads available Yetkin et al.¹⁹ and Batur et al.²⁰ observed a significantly higher QTc dispersion in the morning and daytime compared to nighttime, whereas Lee et al.¹⁰ agreed with our observation that QT dispersion had a higher value at night compared to daytime. Malik et al.²³ did not find any significant difference between day and night in a 12-lead Holter recording. Ishida et al.⁸ and Bilan et al.²¹ used a three-channel ECG recording system, and Molnar et al.⁹ used a two-lead ECG recording system. Similar to our observations a reduced number of leads resulted in lower values of QT dispersion. Ishida et al.⁸ and Bilan et al.²¹ demonstrated a circadian variation of QT dispersion with lower values at night, whereas Molnar et al.⁹ demonstrated higher values of QT dispersion at night compared to daytime. Michelucci et al.²⁴ demonstrated no circadian variation in healthy subjects. They used three orthogonal leads, which is known to underestimate QT dispersion.²⁵

Bonnemeier et al.²² used a two-channel recorder system in the demonstration of diurnal variation of QT-interval variability with a significant increase in the morning hours (6–9 a.m.), but they observed no significant difference in the circadian profile of QT-interval variability among the decades. This is contrary to our observation of circadian variation in the older subjects (age over 50 years) both in respect to QTdisp 12 and QT disp 6. When we reduced the number of leads to two, we observed no circadian variation among the decades, which is in accordance with the findings of Bonnemeier et al.,²² who also used only one pair of leads.

It is suggested^{23,26} that heart rate correction formulas should not be used in the analysis of QT dispersion. The present investigation demonstrated that the significance of circadian variation of QTdisp 12 was influenced by the use of heart rate correction formulas.

It has been argued²⁷ that heterogeneity of ventricular repolarization could be considered to be

measurable mainly from precordial leads (V_1 – V_6), because limb leads are remote from cardiac source, and therefore reflect only a vector of the electrical potential. We found a significant circadian variation in QTdisp 6, which were more pronounced at each measured hour than in the QTdisp 12. The same age-related circadian variation in QTdisp 6 was seen as in QTdisp 12. We achieved similar results using only precordial leads in comparison with the method using all 12 leads, which could favor the argumentation that only precordial leads should be used in the measurement of QT dispersion. Several studies^{28,29} used only precordial leads in their single measurement of QT dispersion. This is the first report to present results from a study of circadian variation of QT dispersion measured exclusively from precordial leads.

Enhanced parasympathetic activity is known to be cardioprotective in terms of malignant arrhythmias, whereas sympathetic activity can trigger malignant arrhythmias.³⁰ Although vagal activity is higher during the night resulting in an antifibrillatory effect, the influence of sleep on cardiac autonomic tone is more complex than an isolated increase of vagal tone or a generalized inhibition of sympathetic activity.³¹ Sleep is considered to be a dynamic condition with both a background of parasympathetic activity and interrupted surges in sympathetic nerve activity during REM.³² The observed decrease of QTdisp 12 and QTdisp 6 in the morning hours could be due to higher REM surges, which are particularly pronounced and of longer duration in the hours before awakening.³⁰

Heart rate variability has been used in the study of cardiac autonomic activity and a decline of cardiac vagal modulation due to a decrease of nocturnal parasympathetic activity is observed with increasing age.³² The observed circadian variation of QTdisp 12 and QTdisp 6 in subjects older than 50 years could be due to a combination of vagal withdrawal and elevated sympathetic tone.

Limitations

Continuous ECG recording with 12-lead measurements during 24 hours is difficult, because routine daily activity influences the quality of recording. This could result in omitting of recorded minutes that would otherwise be of interest. In addition, postural changes during Holter monitoring may affect QT dispersion.

CONCLUSION

Lead selection proved to be important for the detection of circadian variation, which in addition was highly dependent on length sampling period. In the methodological study, a significant circadian variation in QT dispersion could be detected only when the number of leads to be considered was restricted to the six precordial leads, and when usable measurements from every minute was used.

In the study of all 95 subjects, a highly significant circadian variation in QT dispersion was demonstrated when all 12 or 6 precordial leads were included despite the use of a fixed abbreviated sampling period. When studying the relation to age, it appeared that circadian variation was confined to the older age groups. A significant circadian variation was observed in males when all 12 leads or the precordial leads were used in the measurement of QT dispersion, whereas in females only a circadian variation was observed when precordial leads were used. A significant interaction between subjects and time was seen indicating that no similarities between the subjects exist, although a general circadian variation is observed. This illustrates that the circadian variation in QT dispersion must be taken with reservation.

REFERENCES

- Day CP, McComb JM, Campbell RW. QT dispersion: An indication of arrhythmia risk in patients with long QT interval. *Br Heart J* 1990;63:342-344.
- Perkiömäki J, Koistinen M, Yli-Mäyry S, et al. Dispersion of QT Interval in patients with and without susceptibility to ventricular tachyarrhythmias after previous myocardial infarction. *J Am Coll Cardiol* 1995;26:174-179.
- Muller JE, Stone PH, Turi ZG, et al. Circadian variation in the frequency of onset of acute myocardial infarction. *N Engl J Med* 1985;313:1315-1322.
- Rocco MB, Barry J, Campbell S, et al. Circadian variation of transient myocardial ischemia in patients with coronary artery disease. *Circulation* 1987;75:395-400.
- Willich SN, Levy D, Rocco MB, et al. Circadian variation in the frequency of sudden cardiac death in the Framingham Heart Study population. *Am J Cardiol* 1987;60:801-806.
- Wei K, Dorian P, Newman D, et al. Association between QT dispersion and autonomic dysfunction in patients with diabetes mellitus. *J Am Coll Cardiol* 1995;26(4):859-863.
- Bonnar CE, Davie AP, Caruana L, et al. QT dispersion in patients with chronic heart failure: β blockers are associated with a reduction in QT dispersion. *Heart* 1999;81:297-302.
- Ishida S, Nakagawa M, Fujino T, et al. Circadian variation of QT Interval dispersion. *J Electrocardiol* 1997;30(3):205-210.
- Molnar J, Rosenthal JE, Weiss JS, et al. QT interval dispersion in healthy subjects and survivors of sudden cardiac death: Circadian variation in a twenty-four-hour assessment. *Am J Cardiol* 1997;79:1190-1193.
- Lee K-T, Lai W-T, Chu C-S, et al. Circadian variation of QT dispersion determined by twelve-lead Holter electrocardiography. *Cardiology* 2003;100:101-111.
- Bazett JC. An analysis of time relations of electrocardiograms. *Heart* 1920;7:353-367.
- Fridericia LS. Die systolendauer im elektrokardiogramm bei normalen menschen und bei herzkranken. *Acta Med Scand* 1920;53:469-486.
- Malik M, Batchvarov V. Measurement, interpretation and clinical potential of QT dispersion. *J Am Coll Cardiol* 2000;36:1749-1766.
- Glancy JM, Garratt CJ, Woods KL, et al. QT dispersion and mortality after myocardial infarction. *Lancet* 1995;345:945-948.
- Watson RM, Schwartz JL, Maron BJ, et al. Inducible polymorphic ventricular tachycardia and ventricular fibrillation in a subgroup of patients with hypertrophic cardiomyopathy at high risk for sudden death. *J Am Coll Cardiol* 1987;10:761-764.
- Zareba W, Konecki JA, Timothy K, et al. Principal component analysis of spatial dispersion of repolarization in LQT1 and LQT3 gene carriers. *J Am Coll Cardiol* 1999;33(Suppl.):114A.
- Perkiömäki JS, Ikäheimo MJ, Pikkujämsä SM, et al. Dispersion of the QT interval and autonomic modulation of heart rate in hypertensive men with and without left ventricular hypertrophy. *Hypertension* 1996;28:16-21.
- Zaidi M, Robert A, Fesler R, et al. Dispersion of ventricular repolarisation: A marker of ventricular arrhythmias in patients with previous myocardial infarction. *Heart* 1997;78:371-375.
- Yetkin E, Şenen K, Ileri M, et al. Diurnal variation of QT dispersion in patients with and without coronary artery disease. *Angiology* 2001;52:311-316.
- Batur K, Aksöyek Oto A, et al. Circadian variations of QTc dispersion: Is it a clue to morning increase of sudden cardiac death?. *Clin Cardiol* 1999;22:103-106.
- Bilan A, Witczak A, Palusiński R, et al. Circadian rhythm of the QT interval dispersion in healthy subjects. Correlation with heart rate variability circadian pattern. *J Electrocardiol* 2005;38:36-42.
- Bonnemeier H, Wiegand UKH, Braasch W, et al. Circadian profile of QT interval and QT interval variability in 172 healthy volunteers. *PACE* 2003;26(Pt. II):377-382.
- Malik M, Batchvarov V. QT dispersion. Clinical Approaches to Tachyarrhythmias, Volume 12. Armonk, NY, Futura Publishing Company, Inc., 2000, pp. 44-45.
- Michelucci A, Conti A, Frati M, et al. Circadian pattern of the QT dispersion using three orthogonal leads of a Holter ECG in patients with heart failure. *Ann Noninvasive Electrocardiol* 1998;3:32-37.
- Hnatkova K, Malik M, Yi G, et al. Adjustment of QT dispersion assessed from 12 lead electrocardiogram for different number of analysed electrocardiographic leads: Comparison of stability of different methods. *Br Heart J* 1994;72:390-396.
- Vassilikos VP, Karagounis LA, Psychogios A, et al. Correction for heart rate is not necessary for QT dispersion in individuals without structural heart disease and patients with ventricular tachycardia. *Ann Noninvasive Electrocardiol* 2002;7:47-52.
- Statters D, Malik M, Ward D, et al. QT dispersion: Problems of methodology and clinical significance. *J Cardiovasc Electrophysiol* 1994;5:672-685.
- Yunus A, Gillis A, Traboulsi M, et al. Effect of coronary angioplasty on precordial QT dispersion. *Am J Cardiol* 1997;79:1339-1342.
- Raj S, Mitchell B, Wyse D, et al. Precordial QT dispersion does not predict inducibility of ventricular

- tachyarrhythmias at post-revascularization electrophysiologic study. *J Interv Card Electrophysiol* 2002;6:25-33.
30. Schwartz PJ, Rovere MT, Vanoli E. Autonomic nervous system and sudden cardiac death. Experimental basis and clinical observations for post-myocardial infarction risk stratification. *Circulation* 1992;85(Suppl. I):77-91.
31. Somers VK, Dyken ME, Mark AL, et al. Sympathetic-nerve activity during sleep in normal subjects. *N Engl J Med* 1993;328:303-307.
32. Bonnemeier H, Wiegand UKH, Brandes A, et al. Circadian profile of cardiac autonomic nervous modulation in healthy subjects: Differing effects of ageing and gender on heart rate variability. *J Cardiovasc Electrophysiol* 2003;14:791-799.