QT Intervals and QT Dispersion Determined from a 12-Lead 24-Hour Holter Recording in Patients with Coronary Artery Disease and Patients with Heart Failure

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Background: QT dispersion is considered an index of spatial inhomogeneity of repolarization duration and increased dispersion of ventricular repolarization is supposed to increase the risk of ventricular arrhythmia. Circadian variation in QT dispersion was investigated.

Methods: Three different modes of lead selection was used: all 12-leads (QTdisp 12), only precordial leads (QTdisp 6), and one pair of preselected leads (QTdisp 2) in a 24-hour Holter recording every fourth hour each comprising 10 consecutive measurements in 54 healthy subjects, 29 patients with coronary artery disease (CAD), and 29 patients with heart failure (HF).

Results: A significant circadian variation was observed in healthy subjects when modes QTdisp 12 and QTdisp 6 were used (Mean ± SD 35.58 ± 16.48 ms; $P < 0.0001$; and 28.82 ± 16.02 ms; $P < 0.0001$, respectively), and in patients with CAD (Mean ± SD 37.86 ± 17.87 ms; $P < 0.01$; and 28.72 ± 17.06 ms; $P < 0.0001$, respectively), whereas no circadian variation was observed in QTdisp 2. No circadian variation was observed in patients with HF irrespectively of lead selection. Patients with CAD without myocardial infarction (MI) had a circadian variation in QTdisp 12 (Mean ± SD 33.13 ± 14.86 ms; $P < 0.05$), whereas no circadian variation was observed in patients with MI (Mean ± SD 40.35 ± 18.80 ms; P = NS).

Conclusions: Circadian variation of QT dispersion was detected in healthy subjects and in patients with uncomplicated CAD, but not in those who had suffered a previous MI and in patients with HF. The number of leads among which selection of the longest and shortest QT intervals took place was critical for the disclosure of circadian variation of QT dispersion. **A.N.E. 2008;13(1):22–30**

circadian variation; QT dispersion; coronary artery disease; heart failure

QT dispersion defined as the difference between the longest and shortest QT interval measured on a standard 12-lead electrocardiogram is considered to be an expression of inhomogeneity of ventricular repolarization[1,2] and a marker of risk for ventricular arrhythmias.[3]

Patients with coronary artery disease and heart failure have an increased risk of sudden cardiac death. The onset of acute myocardial infarction and sudden cardiac death have a circadian variation with a peak incidence in the early morning hours.[4,5,6] Abnormalities of the autonomic nervous system appear to be involved in the genesis of sudden cardiac death. The sympathovagal tone may affect QT variability in healthy subjects[7] and treatment with beta-blockers in patients with heart failure is associated with a reduction in QT dispersion[8] indicating that sympathetic deactivation may cause decreased QT dispersion.

The circadian variation in QT dispersion has been investigated in healthy subjects,[9,10] patients with coronary artery disease,[11,12] and congestive heart failure[13,14] with conflicting observations. These studies vary in selection of leads and timing of measurements and therefore the results are difficult to compare. We have in a methodological

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study demonstrated that lead selection and sample length influence circadian variation of QT dispersion.[15]

In this study, QT dispersion was measured in Holter recordings from three groups: (A) Healthy subject matched for age and sex with the other groups, (B) Patients with chronic coronary artery disease (CAD), and (C) Patients with heart failure (HF). We used three different modes of lead selection: all 12 leads (QTdisp 12), only precordial leads (QTdisp 6), and one pair of preselected leads selected from a 12-lead ECG strip recorded at 0300 h (QTdisp 2). The aim was to investigate the profile of circadian variation of QT dispersion in these three groups of patients using the abovementioned modes of lead selection.

METHODS

The reproducibility of manually corrected measurements of QT interval in all available leads done every 30 minutes was analyzed using a paired *t*-test demonstrating no significant difference in respect to interobersever or intraobserver variability. We, in addition, demonstrated that QT interval measurement had an interobserver and intraobserver reproducibility with a relative error of 0.4% and 1.0% respectively, whereas calculation of QT dispersion had an interobserver reproducibility with a relative error of 2.8% and intraobserver reproducibility with a relative error of 16.4%.

QT dispersion measurement was performed semiautomatically using a commercially available recording and analysis equipment (Holter for Windows, Rozinn Electronics Inc, Glendale, NY), which recorded electrocardiograms digitally and stored three ECG-leads continuously and in addition recorded a short 12-lead ECG segment each minute over a 24-hour period. 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 the end point. 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 of the endpoint of the T wave the lead was excluded.

We have previously demonstrated,[15] that measurement every fourth hour during the 24-hour period is sufficient to demonstrate a circadian variation of QT dispersion in healthy subjects. Each measurement was performed every fourth hour comprising 10 consecutive measurements of QT maximum and QT minimum. At each point of time QT dispersion was calculated.

The analysis of circadian variation of QT intervals, QTdisp 12, QTdisp 6, and QTdisp 2 was based on uncorrected and heart rate corrected values obtained with Bazett's formula.[16]

Study Population

Seventy-six healthy volunteers 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. After interview and routine physical examination, one subject was excluded due to the finding of a first degree A-V block, and 21 were considered unfit for participation due to low amplitude of the T Wave in more than four leads. All included subjects were in sinus rhythm with QRS complexes of normal configuration and width. A total of 54 subjects were included.

Seventy-nine patients with chronic coronary heart disease participating in the CLARICOR[17] study were asked to participate in Holter recording before entering the CLARICOR study. Fifty patients were considered unfit for participation due to low T wave in more than four leads. All included were in regular sinus rhythm with QRS complexes of normal configuration and width except two subjects who had left bundle branch block. A total of 29 patients with coronary artery disease were included.

Over a period of 3 months, 71 patients with congestive heart failure were consecutively included in the outpatient clinic at Copenhagen University Hospital, Hvidovre Hospital. A medical history was obtained including medication and a physical examination was performed on the same day as the Holter recording began. Forty-two patients were considered unfit for participation due to low T wave in more than four leads leaving a total of 29 patients with congestive heart failure to be included. Only patients with an echocardiographically established ejection fraction $\leq$ 40% were asked to participate.

Table 1. Characteristics of Healthy Subjects, Patients with Coronary Artery Disease (CAD) and Patients with Heart Failure (HF)

	Healthy Subjects	CAD	Heart Failure
Number	54	29	29
Age mean (SD)	63(9)	65(8)	68(7)
Age range	54–81	50–81	53–84
Female/male	25/29	7/22	10/19
MI	0	19	17
Angina	0	10	4
Arterial hypertension	0	9	5
Diabetes mellitus	0	4	3
RBBB	0	0	2
LBBB	0	2	9
Beta-blockers	0	9	11
Diuretics	0	8	27
ACE-inhibitors	0	6	19

CAD = Coronary artery disease; HF = Heart failure; RBBB = right bundle branch block; LBBB = left bundle branch block.

All participants gave informed consent and the regional ethical committee approved the study (KF 01–079/01, 01–080/01).

Statistical Analysis

Results are given as mean ± (SD) unless otherwise stated. Statistical calculation was done using SAS System (SAS 8.02), (SAS Institute Inc, Cary, NC, USA).

Mixed models analysis was 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. $P < 0.05$ was considered as the limit of statistical significance.

RESULTS

In Table 1 the clinical characteristics of all three study groups are listed: (A) 54 healthy subjects, (B) 29 patients with coronary artery disease, and (C) 29 patients with heart failure.

Table 2 demonstrates the mean ± SD values of QTc maximum, QTc minimum, QTdisp 12, QTdisp 6, and QTdisp 2 in the three groups. A significant difference was found in patients with coronary artery disease compared with healthy subjects with respect to mean values of QTc maximum, QTc minimum, QTdisp 12, and QTdisp 2 (all $P < 0.0001$), but not with QTdisp 6. Patients with heart failure had a significant difference in mean values of QTc maximum, QTc minimum, QTdisp 12, QTdisp 6, and QTdisp 2 (all $P < 0.0001$) compared to healthy subjects.

In Table 3 the results of analysis using mixed-models analysis for circadian variation in QTdisp 12, QTdisp 6, and QTdisp 2 every fourth hour in patients with coronary artery disease, patients with heart failure, and healthy subjects are presented. A significant circadian variation in QTdisp 12 was observed in healthy subjects ($P < 0.0001$) and in patients with coronary artery disease ($P < 0.01$), but not in patients with heart failure (P = NS). In the group of healthy subjects and patients with coronary artery disease the mean value of QTdisp 12 at 0400–0500 was significantly higher than those recorded at the five other points of time.

Using precordial leads (QTdisp 6), a significant circadian variation was demonstrated in the group of healthy subjects ($P < 0.0001$) and in patients with coronary artery disease ($P < 0.0001$), but not in patients with heart failure (P = NS). In the group of healthy subjects and patients with coronary artery disease, time specific mean values of QTdisp 6 were lower during daytime compared to nighttime, whereas time specific mean values of QTdisp 6 in patients with heart failure were of same magnitude during the whole 24-hour period.

No significant circadian variation of QT dispersion determined from a pair of preselected leads (QTdisp 2) was seen irrespectively of study group.

Table 2. Twenty-Four-Hour Mean ± (SD) Values of QTc Maximum, QTc Minimum, and QT Dispersion Measured by Three Different Modes of Lead Selection (QTdisp 12, QTdisp 6, and QTdisp 2) in Healthy Subjects, Patients with Coronary Artery Disease (CAD), and Patients with Heart Failure (HF)

	Qtc Maximum	Qtc Minimum	Qtdisp 12	Qtdisp 6	Qtdisp 2
Healthy	416.62(26.32)	378.06(24.59)	35.58(16.48)	28.82(16.02)	13.74(16.64)
CAD	433.06(26.85)†	391.82(22.54)†	37.86(17.87)†	28.72(17.06)	19.57(17.52)†
HF	464.91(40.94)‡	408.72(38.32)‡	49.97(19.89)‡	37.28(18.58)‡	27.79(17.47)‡

†$P < 0.001$ versus healthy subjects; ‡ $P < 0.0001$ versus healthy subjects.

Table 3. QT Dispersion Measured by Three Different Modes of Lead Selection Every Fourth Hour over 24-Hours

Inclusion Period	N	Qtdisp 12 Ms	Qtdisp 6 Ms	Qtdisp 2 Ms
Healthy subjects	54			
0400–0500		43.24 ± (17.76)	37.69 ± (17.59)	14.24 ± (21.42)
0800–0900		35.63 ± (15.64)	28.63 ± (15.22)	15.50 ± (16.27)
1200–1300		31.99 ± (14.81)	25.73 ± (13.50)	13.44 ± (13.77)
1600–1700		33.19 ± (15.97)	26.13 ± (15.13)	13.11 ± (14.46)
2000–2100		33.55 ± (16.49)	25.42 ± (15.41)	13.23 ± (13.16)
0000—0100		35.87 ± (15.62)	30.31 ± (15.35)	12.91 ± (19.05)
Circadian variation				
P-value		<0.0001	<0.0001	NS
Patients with coronary artery disease	29			
0400–0500		40.37 ± (18.11)	33.81 ± (18.92)	20.87 ± (19.99)
0800–0900		40.77 ± (19.04)	32.58 ± (18.90)	20.98 ± (16.32)
1200–1300		34.23 ± (16.60)	24.25 ± (14.14)	17.04 ± (14.98)
1600–1700		36.35 ± (15.83)	25.31 ± (14.80)	19.40 ± (18.88)
2000–2100		34.98 ± (17.29)	24.79 ± (14.60)	16.74 ± (13.80)
0000–0100		40.49 ± (18.97)	31.54 ± (17.52)	22.40 ± (19.57)
Circadian variation				
P-value		<0.01	<0.0001	NS
Patients with heart failure	29			
0400–0500		50.97 ± (20.36)	37.72 ± (20.60)	24.74 ± (17.12)
0800–0900		52.02 ± (21.38)	38.93 ± (20.07)	28.76 ± (17.75)
1200–1300		46.80 ± (19.20)	34.30 ± (16.35)	27.51 ± (16.75)
1600–1700		49.56 ± (19.45)	37.87 ± (18.07)	28.13 ± (17.77)
2000–2100		49.00 ± (18.95)	35.95 ± (17.67)	29.49 ± (16.93)
0000–0100		51.50 ± (19.61)	38.90 ± (18.07)	28.15 ± (18.20)
Circadian variation				
P-value		NS	NS	NS

Time-specific mean values ± (SD) and P-values of mixed models analysis for circadian variation are presented.
QTdisp 12 = All leads included.
QTdisp 6 = Only precordial leads included.
QT disp 2 = One pair of preselected leads included.

The main results did not depend on outliers. Analyses were repeated with exclusion of 10% highest and lowest values without changing the overall results.

Table 4 demonstrates the circadian variation in QT and QTc maximum, QT and QTc minimum, and average QTc intervals using all 12-leads in healthy subjects, patients with coronary artery disease, and patients with heart failure. In all three groups a circadian variation in QT maximum, QT minimum, and average QT interval was observed ($P < 0.0001$). A circadian variation in QTc maximum was observed only in patients with coronary artery disease ($P < 0.05$), whereas no circadian variation was observed in patients with heart failure and healthy subjects. Only in healthy subjects QTc minimum demonstrated a significant circadian variation ($P < 0.005$), whereas no circadian variation was observed in patients with heart failure and in patients with coronary artery disease. A significantly lower time specific mean value of QTc minimum at 0400–0500 ($P < 0.005$) compared to the rest of the day was seen in the group of healthy subjects, whereas in patients with coronary artery disease a significantly lower time specific mean value of QTc maximum was observed at 1200–1300 ($P < 0.01$) compared with rest of the day. Time specific mean values of average QTc intervals using all 12-leads demonstrated a circadian variation in healthy subjects ($P < 0.005$) and patients with coronary artery disease ($P < 0.005$), whereas no circadian variation was observed in patients with heart failure.

Table 5 demonstrates the analysis of circadian variation in QTc maximum, QTc minimum, and QTdisp 12 in patients with coronary artery disease according to previous myocardial infarction (MI) or not. The 24-hour mean ± SD value of QTdisp 12 was 33.13 ± 14.86 ms in patients with coronary artery disease without myocardial infarction, whereas in patients with coronary artery disease with myocardial infarction the 24 hour mean ± SD value of QTdisp 12 was 40.35 ± 18.80 ms. Patients

Table 4. Time-Specific Mean Values ± (SD) of Uncorrected and Heart Rate Corrected QT Maximum Intervals, QT Minimum Intervals and Average QT Intervals Using All 12-Leads Measured Every Fourth Hour in 10 Consecutive Minutes Are Presented and at the Bottom Line of Each Section the P-Value for Mixed Model Analysis for Circadian Variation Is Presented

Study Group (N)	QT Maximum ms	Qtc Maximum ms	QT Minimum ms	Qtc Minimum ms	Average QT Intervals ms	Average QTc Intervals ms
Healthy (54)						
0400–0500	416.81 ± (31.11)	417.08 ± (28.16)	373.57 ± (29.54)	373.87 ± (28.03)	400.18 ± (28.13)	400.47 ± (25.71)
0800–0900	377.77 ± (30.92)	417.00 ± (26.49)	342.15 ± (31.10)	377.49 ± (25.97)	362.26 ± (29.87)	399.46 ± (23.27)
1200–1300	365.58 ± (25.56)	413.95 ± (24.91)	333.59 ± (23.56)	377.66 ± (22.19)	350.45 ± (23.83)	396.69 ± (20.90)
1600–1700	371.03 ± (26.85)	414.45 ± (25.06)	337.84 ± (28.35)	377.01 ± (22.46)	355.80 ± (26.24)	397.24 ± (21.29)
2000–2100	379.09 ± (26.56)	419.69 ± (25.30)	345.55 ± (23.54)	382.49 ± (21.50)	363.55 ± (23.72)	402.44 ± (21.38)
0000–0100	396.89 ± (29.17)	417.55 ± (27.52)	361.02 ± (27.04)	379.81 ± (25.92)	381.90 ± (27.25)	401.75 ± (25.35)
Circadian variation P-value	<0.0001	NS	<0.0001	<0.005	<0.0001	<0.005
CAD (29)						
0400–0500	426.25 ± (30.48)	435.94 ± (24.56)	385.88 ± (26.44)	394.80 ± (23.00)	408.72 ± (26.72)	418.09 ± (21.79)
0800–0900	397.29 ± (35.15)	436.04 ± (28.12)	356.52 ± (31.90)	390.98 ± (20.72)	377.76 ± (32.33)	414.47 ± (22.66)
1200–1300	382.24 ± (32.91)	427.85 ± (25.90)	348.01 ± (31.81)	389.21 ± (21.40)	365.91 ± (31.00)	409.44 ± (21.84)
1600–1700	383.29 ± (29.73)	432.81 ± (29.97)	346.94 ± (29.36)	391.34 ± (23.88)	364.85 ± (28.37)	411.71 ± (24.27)
2000–2100	393.12 ± (28.63)	430.74 ± (24.68)	358.15 ± (26.69)	392.34 ± (21.73)	376.07 ± (26.23)	412.00 ± (20.88)
0000–0100	410.76 ± (33.18)	434.96 ± (26.67)	370.28 ± (27.69)	392.28 ± (24.13)	393.22 ± (28.80)	416.40 ± (21.78)
Circadian variation P-value	<0.0001	<0.05	<0.0001	NS	<0.0001	<0.005
HF (29)						
0400–0500	432.45 ± (41.48)	462.75 ± (41.14)	381.48 ± (43.92)	407.77 ± (41.20)	408.79 ± (41.15)	437.24 ± (39.27)
0800–0900	415.03 ± (48.24)	469.50 ± (43.49)	363.01 ± (46.06)	410.09 ± (37.39)	388.97 ± (46.44)	439.68 ± (38.05)
1200–1300	395.58 ± (40.24)	460.46 ± (40.18)	348.78 ± (38.88)	405.76 ± (37.58)	372.46 ± (38.05)	433.43 ± (36.56)
1600–1700	413.49 ± (42.92)	464.16 ± (39.30)	363.93 ± (39.54)	408.21 ± (33.40)	389.72 ± (40.46)	437.20 ± (33.72)
2000–2100	411.77 ± (42.85)	466.73 ± (41.91)	362.77 ± (41.38)	411.02 ± (39.72)	387.57 ± (40.18)	439.25 ± (38.42)
0000–0100	428.69 ± (44.14)	465.85 ± (39.19)	377.18 ± (46.53)	409.44 ± (40.18)	404.11 ± (43.41)	438.94 ± (37.11)
Circadian variation P-value	<0.0001	NS	<0.0001	NS	<0.0001	NS

Table 5. Circadian Variation of QTc Maximum, QTc Minimum, and QT Dispersion Using All 12-Leads (QT disp 12) Every Fourth Hour in Patients with Coronary Heart Disease with or without myocardial Infarction (MI)

	QTc Maximum Ms MI		QTc Minimum Ms MI		QTdisp 12 Ms MI	
	Yes	No	Yes	No	Yes	No
0400–0500	437.58 ± (27.70)	432.82 ± (16.77)	398.24 ± (26.04)	393.07 ± (19.40)	40.88 ± (19.06)	39.41 ± (16.19)
0800–0900	440.14 ± (27.41)	428.24 ± (27.93)	394.21 ± (19.45)	390.80 ± (23.58)	43.67 ± (20.41)	35.27 ± (14.72)
1200–1300	429.81 ± (28.88)	424.10 ± (18.56)	390.97 ± (23.80)	394.22 ± (16.68)	37.55 ± (17.85)	27.93 ± (11.65)
1600–1700	432.56 ± (31.71)	433.28 ± (26.50)	391.75 ± (23.81)	398.91 ± (23.13)	38.72 ± (16.23)	31.83 ± (14.06)
2000–2100	432.00 ± (24.76)	428.33 ± (24.47)	394.07 ± (22.88)	397.13 ± (22.01)	37.39 ± (18.56)	30.39 ± (13.51)
2400–0100	437.93 ± (28.85)	429.31 ± (20.92)	395.19 ± (26.10)	394.92 ± (23.71)	43.92 ± (19.49)	33.97 ± (16.14)
Circadian variation P-value	<0.05	NS	NS	NS	NS	<0.05

Time-specific mean values and at the bottom P-values of mixed models analysis for circadian variation are presented.

with coronary artery disease without MI had a significant circadian variation in QTdisp 12 ($P < 0.05$), whereas patients with MI had no circadian variation in QTdisp 12. Patients with coronary artery disease with myocardial infarction had a circadian variation in QTc maximum ($P < 0.05$), whereas no circadian variation in QTc maximum was observed in the group without myocardial infarction. No circadian variation in QTc minimum was observed irrespectively of previous myocardial infarction.

After a follow-up of 3.5 years, 12 patients with heart failure had died. The 24-hour mean ± SD value of QTdisp 12 was 50.83 ± 20.68 ms in the fatal cases, and 49.37 ± 19.30 ms in survivors, which demonstrated no significant difference between the two groups (P = NS). Analysis of the circadian variation in QT disp 12 in patients with heart failure also demonstrated no significant difference between fatal cases and survivors. Similarly, no significant difference of circadian variation of QTdisp 12 was observed between those with or without brandle block, diabetes, sex, or use of beta-blockers in patients with heart failure. A significant difference was observed when patients with heart failure were subdivided according to ejection fraction (EF): $EF \leq 30$, $30 < EF < 45$, $EF \geq 45$. Patients with heart failure with $EF \leq 30$ or $EF \geq 45$ had no circadian variation, whereas in the group of patients with heart failure with $30 < EF < 45$ a significant circadian variation was observed ($P < 0.05$).

As it appears in Table 6 no difference in significance was observed in the circadian profile of QTdisp12, QTcdisp 12, QTdisp 6, and QTcdisp 6, QTdisp 2, and QTcdisp 2 comparing the uncorrected and corrected values obtained with Bazett's formula, except in patients with coronary artery disease when we compared the analysis of QTdisp 12 ($P < 0.01$) with QTcdisp 12 (P = NS).

DISCUSSION

We demonstrated in this study a significant circadian variation in healthy subjects and patients with coronary artery disease, when all 12-leads (QTdisp 12) or only precordial leads (QTdisp 6) were used, but not when only a preselected pair of leads (QTdisp 2) was used during the 24 hours. No circadian variation of QT dispersion was observed in patients with heart failure irrespectively of lead selection. A significant circadian variation of QTc maximum was demonstrated in patients with coronary artery disease, whereas healthy subjects had a

Table 6. Uncorrected and Heart Rate Corrected Mean ± (SD) Values of QT Intervals and QT Dispersion in Each of the Three Different Lead Selection Modes (QTdisp 12, QTdisp 6, and QTdisp 2) Including P-values in the Analysis of Circadian Variation Using Mixed Models

	Healthy Subjects		Coronary Artery Disease		Heart Failure	
	Mean ± (SD)	P-Value Circadian Variation	Mean ± (SD)	P-Value Circadian Variation	Mean ± (SD)	P-Value Circadian Variation
QTdisp 12	35.58 ± (16.48)	<0.0001	37.86 ± (17.87)	<0.01	49.97 ± (19.89)	NS
QTcdisp 12	38.56 ± (17.88)	<0.005	41.23 ± (19.70)	NS	56.19 ± (23.07)	NS
QTdisp 6	28.82 ± (16.02)	<0.0001	28.72 ± (17.06)	<0.0001	37.28 ± (18.58)	NS
QTcdisp 6	31.09 ± (17.05)	<0.0001	31.11 ± (18.38)	<0.0005	41.77 ± (20.92)	NS
QTdisp 2	13.74 ± (16.64)	NS	19.57 ± (17.52)	NS	27.79 ± (17.47)	NS
QTcdisp 2	14.99 ± (17.83)	NS	21.07 ± (18.62)	NS	31.40 ± (19.96)	NS
QTmax	384.50 ± (33.31)	<0.0001	398.83 ± (35.31)	<0.0001	416.17 ± (44.97)	<0.0001
QTcmax	416.62 ± (26.32)	NS	433.06 ± (26.85)	<0.05	464.91 ± (40.94)	NS
QTmin	348.95 ± (30.68)	<0.0001	360.96 ± (32.03)	<0.0001	366.19 ± (44.07)	<0.0001
QTcmin	378.06 ± (24.59)	<0.005	391.82 ± (22.54)	NS	408.72 ± (38.32)	NS
RR	862.43 ± (154.38)	<0.0001	857.85 ± (150.03)	<0.0001	815.98 ± (172.36)	<0.0001

significant circadian variation in QTc minimum. No circadian variation was observed in patients with coronary artery disease and with myocardial infarction, whereas in patients without myocardial infarction a circadian variation was observed. No difference in mean values of QT dispersion or circadian variation of QT dispersion was observed between fatal cases and survivors in the group of patients with heart failure.

Two other studies[11,12] have demonstrated that QT dispersion has a circadian variation in patients with coronary artery disease and in healthy subjects. We found that the circadian variation of QT dispersion in healthy subjects was mainly due to variations in QTc minimum, whereas in patients with coronary artery disease the circadian variation of QT dispersion was due to changes in QTc maximum, which both are opposite to the observations done by Yetkin et al.[12] This study[12] included a population of patients with acute ischemia, whereas we studied a group of patients with chronic coronary artery disease. Stierle et al[18] and Yunus et al[19] reported that QT dispersion increases due to a decrease in QT minimum during acute ischemia similar to the findings done by Yetkin et al.[12] We observed an increase of QT dispersion due to an increase in QTc maximum, which could be explained by the fact that we investigated patients with chronic coronary artery disease.

Our study also demonstrated that patients with coronary artery disease without myocardial infarction had a circadian variation in QT dispersion in contrast to, patients with a previous myocardial infarction. Transmural necrosis has been demonstrated to cause regional autonomic denervation.[20,21] This regional denervation can increase action-potential duration, which again can change QT dispersion depending on autonomic tone. Patients with coronary artery disease without myocardial infarction might imitate healthy subjects in respect of demonstrating a circadian variation with an increase of QT dispersion (QTdisp 12) in the morning hours, whereas patients with coronary artery disease with myocardial infarction have an autonomic dysfunction, which might contribute to the loss of circadian variation.

We observed no circadian variation of QT dispersion in patients with heart failure irrespective of which mode of lead selection was used in the measurement of QT dispersion. This is contrary to observations done by Kinoshita et al.[13] and Bonnar et al.[14] Kinoshita et al.[13] demonstrated in 11 patients with a 12-lead recording that QT dispersion was increased in the afternoon compared to the morning hours, whereas Bonnar et al.[14] described a significant increase in QT dispersion and QTc dispersion from 6 am to 8 am. Bonnar et al.[14] included eight patients with heart failure using 12-leads measurement in a nine time-point process, whereas in our investigation 29 patients were included with three different modes of lead selection (QTdisp 12, QTdisp 6, and QTdisp 2) in 6 time periods each comprising 10 consecutive measurements.

We demonstrated no difference in mean values of QT dispersion observed in the fatal cases compared to the survivor group in patients with heart failure. Only patients with a moderately reduced ejection fraction (30% < EF < 45%) had a significant circadian variation. The demonstration of circadian variation observed only in patients with moderately reduced ejection fraction most likely is a random finding due to multiple comparisons.

No difference in mean QT dispersion or circadian variation of QT dispersion was observed between the fatal cases and in the survivor group of patients with heart failure. This is in line with a number of studies,[22,23,24] demonstrating that QT dispersion had no prognostic value regarding all cause mortality, cardiac mortality, or cardiac arrhythmias in patients with heart failure.

We observed that mean values of QT dispersion were increased in patients with heart failure compared with healthy subjects, which is in accordance with previous reports.[8,25,26,27,28] The larger mean values of QT dispersion could be a result of myocardial remodeling resulting in a slower and heterogeneous ventricular repolarization. The remodeling includes changes in left ventricular size and function, which may also influence ventricular repolarization.[29]

We, in addition, demonstrated that the significance of circadian variation of QT dispersion did not change, neither when the analysis was performed on uncorrected values nor on corrected values obtained with Bazettapos;s formula, except when all 12-leads were used in the measurement of QT dispersion in patients with coronary artery disease. We demonstrated that the circadian variation of QT intervals was blunted by heart rate correction formula, which is a finding in agreement with previous study.[30]

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

A circadian variation was observed in healthy subjects and patients with coronary artery disease when all 12-leads (QTdisp 12) or only precordial leads (QTdisp 6) were used. In healthy subjects a circadian variation of QTc minimum was observed, whereas in patients with coronary artery disease a circadian variation of QTc maximum was observed. Also, a significant circadian variation was observed in patients with coronary artery disease without myocardial infarction, whereas in patients with coronary artery disease with myocardial infarction no circadian variation was observed. In patients with heart failure no circadian variation was observed irrespective of lead selection mode.

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