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Cardiac Repolarization Interval in End-Stage Diabetic and Nondiabetic Renal Disease

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Summary

Background and hypothesis: QT interval length is influenced by autonomic nervous activity. In patients with diabetic autonomic neuropathy, both prolongation and shortening of ventricular repolarization has been reported. We studied diabetic and nondiabetic uremic patients to assess the effects of autonomic neuropathy on QT interval length.

Methods: 24-hour electrocardiogram recordings were performed in 12 diabetic and 11 nondiabetic renal transplantation patients, and in 12 control patients. Mean and corrected QT interval (QTc) during the 24-h period and intervals at predetermined heart rates at day and night periods were determined. The degree of autonomic neuropathy was assessed with cardiovascular autonomic function tests and measurement of heart rate variability.

Results: In the diabetic group, severe autonomic neuropathy was present; in nondiabetic uremic patients, abnormalities were less severe. Mean QTc interval during 24 h was 444 ± 24, 447 ± 21, and 442 ± 19 ms in the diabetic and nondiabetic uremic patients, and in the control groups, respectively, without any between-group difference. QT and QTc interval length did not differ among the groups when measured at heart rates of 70, 80, 90, or 100 beats/min.

Conclusions: In patients with autonomic failure caused by diabetes and/or uremia, QT interval length cannot be used as a diagnostic indicator of cardiac autonomic neuropathy.

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Introduction

Autonomic neuropathy is a major complication of diabetes and is associated with markedly increased mortality and cardiac arrhythmias.[1–3] Autonomic nervous function is impaired also in terminal uremia.[4–7]

The length of the QT interval of the electrocardiogram (ECG) is influenced by alterations in heart rate and autonomic nervous activity.[8–10] There are inconsistent reports on QT interval in patients with diabetic autonomic neuropathy. Some indicate prolongation of QT interval in these patients, and this has been considered as a potential reason for their increased mortality.[11–15] In contrast, shortening of QT interval has also been reported.[16] In previous studies, the circadian variation of QT interval has been shown to be disturbed[10,17] or normal[16] in diabetic autonomic neuropathy. These discrepancies in QT measurement could be due to the problems in the heart rate correction of the measured QT interval.[16,18,19]

The purpose of the study was to evaluate the changes in QT and corrected QT interval (QTc) length and the circadian variation of QT interval in diabetic and uremic autonomic neuropathy. The usefulness of QT interval measurement in diagnosing diabetic and uremic autonomic neuropathy was assessed. Twenty-four h ambulatory ECG recordings were used. The presence of autonomic neuropathy was evaluated with common cardiovascular autonomic function tests as well as with measurements of heart rate variability (HRV), which are believed to be more sensitive in the detection of diabetic autonomic neuropathy than the cardiovascular tests of autonomic function.[20–23]

Methods

Study Subjects

Twelve uremic patients with diabetic nephropathy (age 36 ± 6 years; mean ± standard deviation) and 11 uremic patients with other renal disease (age 35 ± 8 years) undergoing renal

transplantation were studied. Twelve patients without any internal organ or neurologic diseases undergoing general surgery (age 37 ± 7 years) served as controls. The study protocol was approved by the Hospital Ethics Committee and all patients gave informed consent. All uremic patients were dialysis-dependent before transplantation. The diabetic and nondiabetic patients had been on dialysis therapy for 13 ± 5 and 13 ± 8 months, respectively. The duration of type 1 (juvenile) diabetes was 25 ± 4 years in the diabetic group. Before transplantation, 10 diabetic and 10 nondiabetic uremic patients had hypertension, 2 patients in each of the two uremic groups had diagnosed coronary artery disease. One patient in each uremic group had suffered previous myocardial infarction; the patient in the nondiabetic group had undergone coronary artery bypass surgery. In the preoperative chest x-ray, three diabetic patients had cardiac enlargement. In the preoperative ECG, left ventricular hypertrophy was present in one patient in each uremic group.

Assessment of Cardiovascular Autonomic Function

Cardiovascular autonomic function tests were performed 10–14 days after the transplantation, when the patients were still hospitalized but ambulant and free of disabling wound pain; these tests were followed by 24-h ambulatory ECG recording. Before the autonomic function tests, the patients had been without cardiovascular medication for at least 12 h. After the tests, they received their daily medication regularly during the recording; these medications are shown in Table I. During the study, one patient in each uremic group was still on dialysis, and additional two diabetic patients and one nondiabetic uremic patient had serum creatinine values >350 mmol/l.

In control patients, the cardiovascular autonomic function tests were performed when they were ambulant and no longer hospitalized. The ECG recordings were obtained while the subjects undertook their normal daily activities.

Cardiovascular autonomic function tests: Six standard noninvasive tests of cardiovascular autonomic function were performed:[24,25]

1. Beat-to-beat heart rate variation during deep breathing. The difference between minimum and maximum heart rate was determined in six consecutive cycles to calculate the mean difference.
2. Valsalva maneuver. Three to five consecutive maneuvers were performed and the largest Valsalva ratio was used for the results.

TABLE I Cardiovascular medication of the patients during study

	Diabetic nephropathy (n = 12)	Nondiabetic nephropathy (n = 11)	Control (n = 12)
Beta blocker	6	4	0
Ca^{++} channel blocker	5	6	0
Nitrates	2	1	0
Alpha blocker	0	1	0

3 and 4. Heart rate response to standing. The maximum/minimum R-R ratio was determined in the first 30 s following the patients' standing up. Also, the maximum increase in heart rate was determined by subtracting the mean heart rate during the last 30 s of the resting period before standing up from the maximum heart rate after standing up.

5. Blood pressure response to standing. The fall in systolic arterial pressure after 3 min of standing was determined using cuff sphygmomanometry.
6. Blood pressure response to sustained hand grip. The increase in diastolic arterial pressure from the resting value to the last measurement during hand grip was calculated.

The result of each test was classified as abnormal, borderline, or normal according to the age-related reference values previously determined in the national (Finnish) population.[24,25] The results were scored: abnormal = 0, borderline = 1, normal = 2. The tests were classified into those based on heart rate response, reflecting mainly parasympathetic function, and those based on arterial pressure response, reflecting mainly sympathetic function. The scores of the respective tests were then combined. The total score of all tests was also calculated.

Analysis of heart rate variability: The 24-h ambulatory ECG was obtained using a two-channel recorder (Marquette model 8500, Milwaukee, Wisc., USA). The tapes were analyzed on a Marquette 8000 computer-based scanner with HRV software. The QRS complex and arrhythmia classification provided by the scanner was examined, and errors were edited by the operator. Complexes classified as ectopic beats or other arrhythmias or noise are not included in the analysis by the HRV software. The computer program uses fast Fourier transform calculation to compute spectral densities of the R-R interval variability. Amplitude spectra were obtained and quantified as the square root of the power obtained by integrating the specific frequency bands under the spectral density curve. Thirty 48-min spectra were obtained from each 24-h recording, and three frequency bands were analyzed: high frequency (HF) from 0.15 to 0.4 Hz, low frequency (LF) from 0.041 to 0.15 Hz, and very low frequency (VLF) from 0.008 to 0.041 Hz. The mean amplitude (ms) during the 24-h period was calculated for each frequency band.

QT Interval Analysis

Mean hourly heart rates were determined by computer from the 24-h recordings. For every hour, a steady period where the heart rate represented the mean of that hour was searched from the recordings, and a tracing was printed out. To compare the QT intervals at same heart rates, tracings were obtained also at frequencies 60, 70, 80, 90, and 100 beats/min during daytime (9 A.M. to 3 P.M.) and nighttime (11 P.M. to 5 A.M.), if they were represented. A deviation of ± 2 beats/min in rate was allowed. The tracings were accepted to represent the specified rates only if the heart rate had remained stable over the preceding minute. From the tracings, heart rate, R-R interval, and QT interval were manually deter-

TABLE II Results of cardiovascular autonomic function tests

	Diabetic nephropathy (n = 12)	Nondiabetic nephropathy (n = 11)	Control (n = 12)
Heart rate response	0.5 (0–3)	5 (1–7)	8 (3–8)[a]
Arterial pressure response	2 (1–4)	3 (2–4)	4 (4–4)[b]
Total scores	3 (1–7)	8 (3–10)	12 (7–12)[c]

Combined scores of the tests shown. Values are median (range).
[a] = A vs. B and B vs. C: $p<0.05$, A vs. C: $p<0.001$.
[b] = C vs. A and B: $p<0.001$.
[c] = A vs. B: $p<0.01$, A vs. C: $p<0.001$, B vs. C: $p<0.05$.
Abbreviations: A = diabetic nephropathy, B = nondiabetic nephropathy, C = control.

TABLE III Measurements of heart rate variability in the frequency domain

	Diabetic nephropathy (n = 12)	Nondiabetic nephropathy (n = 11)	Control (n = 12)
HF (ms)	3 ± 1[a]	9 ± 7	14 ± 8
LF (ms)	6 ± 3[a]	16 ± 10	23 ± 12
VLF (ms)	15 ± 3[a]	25 ± 8	30 ± 11

Amplitudes of variability averaged from the hourly values of 24-h recordings. Group means given. HF = 0.15–0.40 Hz, LF = 0.041–0.15 Hz, VLF = 0.008–0.041 Hz. Values are mean ± SD.
[a] $p<0.05$ among diabetic, nondiabetic, and control groups.
Abbreviations: HF = high frequency, LF = low frequency, VLF = very low frequency, SD = standard deviation.

mined by one blinded experienced author (L.L.). The QT interval was measured from the onset of the QRS complex to the end of the T wave, defined as a return to the T-P baseline. If U waves were present, the QT interval was measured to the nadir of the curve between the T and U waves.[26] QTc was calculated using Bazett's formula.[27] Four consecutive cardiac cycles were measured, and the mean QT and QTc values were used. Mean QT and QTc intervals for the 24-h period were calculated from the hourly values.

Statistics

Among groups, Fisher's exact test (the Freeman-Halton exact test) was used to compare the scores of the autonomic tests, Kruskall Wallis multiple comparison with Z test was used to compare other variables, and the Wilcoxon signed ranks test was used to compare the individual night- and daytime QT intervals at the same heart rates. Two-way analysis of variance for repeated measures with Newman Keuls comparison was used to compare the circadian variation of heart rate and QT interval among the groups. For within-group comparisons, one-way analysis of variance for repeated measures was used. Linear correlation and regression analysis were used to determine correlations between autonomic function and QT interval as well as the dependency of the heart rate on the QT interval. Correlation coefficient and the slope and intercept of the regression line for the QT interval against the R-R interval were calculated for each individual, and pooled data were used for comparison among the groups. The calculations were performed with the StatXact software by CyTEL Software Corporation, Cambridge, Mass., and SOLO 4.0 software by BMDP Statistical Software Inc., Los Angeles, Calif., USA. Data are expressed as mean and standard deviation if not otherwise stated. A probability of <0.05 was taken as significant.

Results

Cardiovascular Autonomic Function

In the diabetic group, severe autonomic neuropathy was common, which could be demonstrated by both cardiovascular autonomic function tests and heart rate variability (Tables II and III). In the nondiabetic uremic group, less severe impairment of autonomic function was found (Tables II and III).

Heart Rate

The mean heart rate during 24 h did not differ among the groups (80 ± 7, 81 ± 11, 76 ± 11 beats/min in diabetic, nondiabetic, and control groups, respectively). Minimum heart rate was significantly higher and maximum heart rate significantly lower in the diabetic group than in the other two groups (minimum 65 ± 5, 57 ± 10, 51 ± 10 beats/min, and maximum 114 ± 19, 134 ± 22, 139 ± 11 beats/min in diabetic, nondiabetic, and control groups, respectively, $p<0.05$ among diabetic and other groups). In all groups, a circadian variation was present in that heart rates were lower at night ($p<0.01$) (Fig. 1).

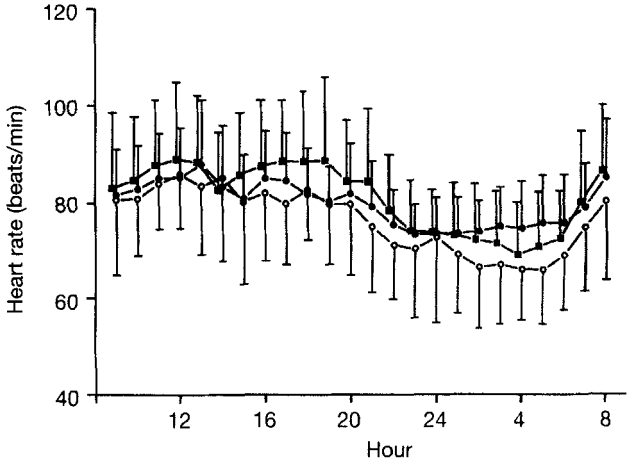

FIG. 1 Mean hourly heart rate during 24 h electrocardiographic recordings in diabetic (●) and nondiabetic (■) nephropathy patients and in control (○) patients.

QT Interval during 24 Hours

Mean QT and QTc intervals calculated from the hourly values over the 24 h recording did not differ among the groups (QT 388 ± 28, 389 ± 32, 397 ± 30 ms, and QTc 444 ± 24, 447 ± 21, 442 ± 19 ms in diabetic, nondiabetic, and control groups, respectively). In all groups there was a circadian variation in the QT interval ($p<0.001$), following the circadian variation of heart rate (Fig. 2). In QTc interval, no circadian variation was observed in any group (Fig. 3). A strong correlation between R-R interval and QT interval was found in all groups. The correlation was poorer ($p<0.05$ between the diabetic and the two other groups) in the diabetic than in the other two groups ($r^2 = 0.59 \pm 0.23, 0.72 \pm 0.19$, and 0.82 ± 0.15 in the diabetic, nondiabetic, and control groups, respectively). There was no difference among the groups in the slope or intercept of the regression line for the QT interval against R-R interval (slope = $0.22 \pm 0.09, 0.22 \pm 0.06$, and 0.23 ± 0.08; intercept = $200 \pm 60, 210 \pm 40$, and 200 ± 40 ms in the diabetic, nondiabetic, and control groups, respectively).

The mean QTc interval length of the 24 h recording did not correlate with the results of the autonomic function tests or the mean high frequency (HF), low frequency (LF), and very low frequency (VLF) amplitudes when analyzed within the entire study population. A correlation was found between the mean QT interval and the mean HF amplitude ($p<0.05$), but not with the other indices of autonomic function. When calculated separately for every hour, the QT interval correlated positively with HF, LF, and VLF from midnight to morning ($p<0.01$ for all).

QT Intervals at Specified Heart Rates

There was no difference among the groups in QT and QTc intervals at predetermined heart rate levels either during the day or the night. The differences between the nighttime and daytime QT and QTc intervals at same heart rate levels were analyzed at heart rates of 70 and 80 beats/min. The number of patients having the other frequencies both at daytime and nighttime was too small for comparison. The nocturnal QT and QTc intervals were not different from the daytime values in either of the uremic groups when measured at the same heart rate levels. In the control group, the QT (416 ± 17 vs. 401 ± 14 ms) and QTc (448 ± 19 vs. 434 ± 16 ms) intervals at a heart rate of 70 beats/min were longer at night than in the daytime ($p<0.05$). At a heart rate of 80 beats/min, QTc interval was longer at night (455 ± 21 vs. 440 ± 15 ms, $p<0.05$).

Discussion

Severe autonomic neuropathy shown by the cardiovascular autonomic function tests and HRV was observed in patients with type I insulin-dependent diabetes of long duration and uremia. In contrast to previous studies,[10–17] we now report that QT and QTc intervals are stable in healthy subjects and also in patients with diabetic uremia and with other end-stage renal disease. We suggest that the inconsistency in the reported alterations of the QT interval in autonomic neuropathy could be due to uncontrolled sampling and a bias originating from rate correction. Our QT intervals were measured by one blinded experienced author. The systematic deviation in measurements is, therefore, negligible. Also, there was no correlation between the autonomic function tests and QT or QTc interval length. The positive correlation between hourly QT intervals and indices of HRV which occurred mainly during the night hours was most probably caused by the lower heart rates and thus longer QT intervals during these hours.

There is evidence that the heart rate dependency of the QT interval is changed in diabetic autonomic neuropathy.[12] In our study, however, the heart rate dependency, determined with

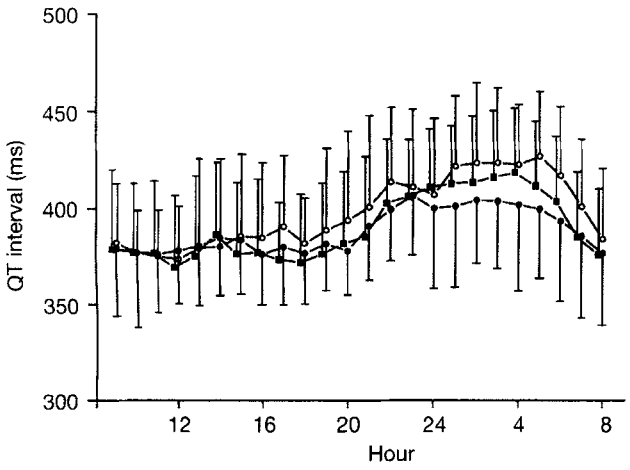

FIG. 2 Mean hourly QT interval length during 24 h electrocardiographic recordings in diabetic (●) and nondiabetic (■) nephropathy patients and in control (○) patients.

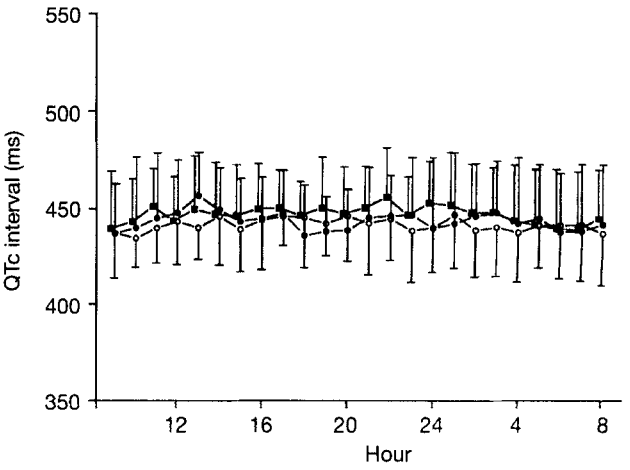

FIG. 3 Mean hourly corrected QT interval (QTc) length during 24 h electrocardiographic recordings in diabetic (●) and nondiabetic (■) nephropathy patients and in control (○) patients.

linear regression, was similar in all groups. The slightly poorer correlation between QT and RR intervals in the diabetic group might indicate irregularities in repolarization. It has been shown that the relation between QT and RR intervals is heart rate-dependent in healthy subjects, and that one simple adjustment equation cannot be used over a wide range of heart rate.[28] The use of a nomogram or different linear regression equations for different RR intervals[28] and the use of an exponential formula[19] have been suggested. However, in our present study, these problems were avoided by also comparing the QT intervals at same heart rates, without correction. Our results indicate that autonomic neuropathy does not significantly affect QT interval length, at least when measured from a single lead corresponding to V_5.

The QT intervals were measured at the prevailing heart rate levels of each hour when assessing the circadian effect. This would diminish the risk of taking the ECG samples at very deviant physiologic states of the subject. Furthermore, the heart rate was required to be stabilized before sampling. This would diminish the fluctuation in the QT/R-R interval relationship induced by a delay in QT interval adaptation to a rate change.[29–31] Particularly, the QTc interval would become falsely prolonged when corrected to the abnormally high resting heart rates seen in patients with autonomic neuropathy.

An obvious circadian variation in the length of the heart rate-corrected QT interval has been reported in healthy subjects.[10, 11, 16] The heart rate-independent prolongation of the QT interval during the night at a frequency of 70 beats/min and the prolongation of the QTc interval at frequencies of 70 and 80 beats/min, seen only in the control patients, could indicate a circadian variation of the QT interval in healthy subjects and support the previous studies.

In both uremic groups, the abnormalities in the cardiovascular autonomic function tests and HRV might have been affected by cardiovascular diseases[32, 33] and by medication of the patients, but the changes were severe enough to be predominantly caused by autonomic nervous dysfunction. The number of patients with coronary artery disease was small, and severe heart failure was not present in any patient. However, most of the uremic patients were hypertensive. It has been shown that beta-blocking agents without intrinsic beta-agonist activity increase HRV.[34, 35] Thus, their use would counteract, not falsely increase the abnormalities found in HRV. The Ca^{2+} channel blockers probably have no effect on HRV.[34] It can be criticized that the study was done after renal transplantation, and thus, theoretically, some improvement of autonomic nervous function could have occurred. This might be true in nondiabetic uremic patients,[36] but it has been shown that diabetic autonomic neuropathy is not affected by renal transplantation.[37]

It is unlikely that the use of beta-blocking agents masked the possible lengthening of the QT interval in our patients, as these agents have only minor effects on QT interval length.[8, 38–40] Moderate prolongation of the QT interval has been reported in hypertensive and ischemic heart diseases and cardiomyopathies.[41] The cardiovascular diseases in our patients were probably not severe enough to cause QT interval prolongation.

Recently, it has been suggested that the regional dispersion of the QT interval, defined as the maximum difference in the QT intervals measured in the 12 leads of a standard ECG, may reflect the repolarization abnormalities better than QT interval length.[42–44] Increased dispersion, correlated with increased risk of arrhythmia and sudden death, has been shown in patients with long QT interval syndrome, hypertrophic cardiomyopathy, and chronic heart failure.[45–47] In our earlier study, markedly increased QT dispersion in routine 12-lead ECGs was found in the same patient population, especially in those with diabetic nephropathy and severe autonomic neuropathy.[48] QT dispersion as an index of abnormal repolarization seems to be potentially useful. Larger studies, however, are needed to show its diagnostic and predictive value in autonomic neuropathy and cardiovascular diseases caused by diabetes and uremia.

Conclusion

It is well known that autonomic neuropathy increases mortality in diabetic patients.[2, 3] A close connection of QT interval prolongation with increased mortality in these patients is not supported by our study, as no prolongation was found. Measurement of the single-lead QT interval length cannot be used to diagnose autonomic neuropathy, and it does not help in assessing cardiovascular risk in these patients.

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