Effects of metoprolol on QT interval and QT dispersion in Type 1 diabetic patients with abnormal albuminuria

E. Ebbelhøj¹ · H. Arildsen² · K. W. Hansen¹ · C. E. Mogensen¹ · H. Mølgaard² · P. L. Poulsen¹

¹ Medical Department M (Diabetes and Endocrinology), Kommunehospitalet, Aarhus University Hospital, Aarhus C, Denmark

² Department of Cardiology, Skejby Hospital, Aarhus University Hospital, Aarhus, Denmark

Abstract

Aims/hypothesis. The excess mortality in diabetes is mainly due to cardiovascular causes and almost confined to patients with abnormal albuminuria. Compared to healthy subjects, diabetic patients have a prolonged QT interval and increased QT dispersion. In non-diabetic subjects, as well as in Type 1 diabetic patients with overt nephropathy, a prolonged QT interval and increased QT dispersion are associated with cardiac morbidity and mortality. There is an increasing number of studies on effects of beta blocker treatment on QT interval and QT dispersion in non-diabetic subjects. In contrast, there are no studies on the effects of beta blocker treatment on QT interval and QT dispersion in patients with diabetes. The aim of our study was to describe the effects of metoprolol treatment on QT interval and QT dispersion in a group of well-characterised Type 1 diabetic patients with elevated urine albumin excretion.

Methods. We studied the effects of 6 weeks of treatment with metoprolol (100 mg once daily, zero order kinetics formulation) in a randomised, placebo-controlled, double blind, crossover trial including 20 Type 1 diabetic patients. Patients were simultaneously monitored under ambulatory conditions with 24-h Holter-

monitoring, 24-h ambulatory blood pressure recording and 24-h fractionated urine collections. On days of investigation 12-lead electrocardiograms were recorded and autonomic tests performed.

Results. We found strong associations between both daytime and night-time blood pressure and heart-rate-corrected QT interval dispersion (QTc dispersion). Heart rate variability parameters indicating sympathetic and parasympathetic modulation showed strong correlations with heart-rate-corrected QT interval (QTc interval) and with QTc dispersion. Beta blocker treatment caused a decrease in QTc interval but no change in QTc dispersion.

Conclusions/interpretation. This study is the first to address the QTc interval and QTc dispersion in Type 1 diabetic patients treated with metoprolol. Beta blocker treatment caused a decrease in QTc interval but no change in QTc dispersion. These results may in part explain the pronounced cardioprotective effect of beta blocker treatment in diabetic patients with cardiovascular disease.

Keywords Beta blocker · Diabetes · 24-h ambulatory blood pressure · Heart rate variability · QT dispersion · QT interval · Urine albumin excretion

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E. Ebbelhøj (✉)

Medical Department M (Diabetes and Endocrinology),
Kommunehospitalet, Aarhus University Hospital,
8000 Aarhus C, Denmark

E-mail: e.ebbelhoj@dadlnet.dk

Tel.: +45-89492019, Fax: +45-89492010

Abbreviations: AMBP, ambulatory blood pressure · CCVHF, coefficient of component variance for HF · HF, high frequency oscillation · HF power, power of the high frequency oscillation · HRV, heart rate variability · LF, low frequency

Introduction

In the ECG, the length of the QT interval reflects ventricular depolarisation and repolarisation time [1]. The variability of the QT interval in the 12-lead ECG, known as the QT dispersion, is presumed to reflect repolarisation abnormalities [2]. The cardiac sym-

oscillation · LF power, power of the low frequency oscillation · Mean RR, mean of all normal RR intervals · QTc dispersion, heart-rate-corrected QT interval dispersion · QTc interval, heart-rate-corrected QT interval · UAE, urine albumin excretion

thetic nervous system seems to be a determinant of QT interval lengthening but does not appear to be involved in dispersion of ventricular repolarisation. However, these complex electrophysiological mechanisms have not yet been fully elucidated [3].

A prolonged QT interval and increased QT dispersion were associated with cardiac morbidity and mortality in apparently healthy subjects [1], in a population-based study [4], and in patients with coronary heart disease [5].

In diabetic patients, a prolonged QT interval (when compared to healthy subjects) [6, 7], as well as an increased QT dispersion [8, 9], have also been detected. A significant relation between QT interval prolongation and mortality in Type 1 diabetic patients with overt nephropathy has been reported [10, 11]. Independently of autonomic neuropathy, QT interval prolongation may play a role in the excess mortality of Type 1 diabetic nephropathic patients [12]. However, an increased QT dispersion has not been shown to be an independent marker of increased mortality in people with Type 1 diabetes [11].

The excess mortality in diabetes is almost confined to patients with abnormal albuminuria and is mainly due to cardiovascular causes [13, 14].

The importance of beta blockers in treatment of patients with acute myocardial infarction is well established and the cardiac protective effect of beta blocker treatment after myocardial infarction is even more pronounced in the diabetic population.

Knowledge of the effect of beta blocker treatment on QT interval and QT dispersion in non-diabetic subjects is increasing. In healthy volunteers acute selective beta blockade was able to prevent abnormalities in heart-rate-corrected QT interval (QTc interval) and heart-rate-corrected QT interval dispersion (QTc dispersion) induced by hypoglycaemia [15]. Again, in healthy volunteers chronic beta blocker treatment resulted in an increased QTc interval (using Bazetts formula) [16]. Patients suffering from chronic heart failure [17] and idiopathic dilated cardiomyopathy [18] had a reduction in QTc dispersion following beta blockade.

However, studies of the effects of beta blocker treatment on QT interval and QT dispersion in diabetic patients have not been done. The aim of this study, therefore, was to describe the effects of metoprolol treatment on QT interval and QT dispersion in a group of well-characterised Type 1 diabetic patients with abnormal albuminuria.

Subjects and methods

General

Data on heart rate variability (HRV), urine albumin excretion (UAE) and ambulatory blood pressure (ABMP) have been published previously [19].

Table 1. Baseline characteristics

Characteristic	Values
Sex (male/female)	15/5
Age (years)	38.8±11.7
BMI (kg/m ²)	25.8±3.5
Insulin dose geometric mean $\times/\div$ tolerance factor (units/kg body weight)	0.61 $\times/\div$ 1.32
Diabetes duration (years)	21.7±7.0
Auscultatory blood pressure start (sys/dia) (mm Hg)	133/82±12/6
Daytime AMBP (sys/dia) (mm Hg)	134/82±11/9
Night-time AMBP (sys/dia) (mm Hg)	120/70±11/8
Ramipril dose (mg)	5.5±3.0
ACE-inhibitor treatment duration (years)	2.7±1.9
UAE geometric mean $\times/\div$ tolerance factor (μ g/min)	109.7 $\times/\div$ 2.8
Serum-creatinine (μ mol/l) (range)	78 (53–107)
Serum potassium (mmol/l)	4.6±0.4
HbA _{1c} (%)	9.2±1.0
Total cholesterol (mmol/l)	5.25±1.09
Smoking status (non-smoking/smoking)	10/10

Values are means $\pm$ SD, except when indicated. AMBP, ambulatory blood pressure; sys/dia, systolic/diastolic; UAE, urine albumin excretion

Patients

Twenty Type 1 diabetic patients with abnormal albuminuria (UAE $\geq$ 20 μ g/min in three overnight urine collections) were included in the study. None had evidence of heart disease or other chronic diseases by history, physical examination or 12-lead electrocardiogram. For inclusion, patients had to have been treated with ACE-inhibitors for at least 6 months prior to inclusion. They received no other antihypertensive treatment apart from diuretics (five patients received furosemide or thiazid). During the study period all patients were treated with the same ACE-inhibitor (Ramipril, Astra Zeneca, Albertslund, Denmark). No alterations in medications were made during the study period. Characteristics at baseline are given in Table 1. The study was approved by the ethics committee of the county of Aarhus and The National Medical Board. Patients gave their written informed consent before participating. The study was monitored by the GCP-unit (Good Clinical Practice Unit) at Aarhus University Hospital.

Study design

This was a randomised, placebo-controlled, double blind, crossover trial studying the effects of 6 weeks of treatment with metoprolol 100 mg once daily (Selo-Zok, zero order kinetics formulation, Astra Zeneca, Albertslund, Denmark), given in addition to ongoing treatment with ACE-inhibitors. A four-week wash-out period was interposed between the two treatment periods. Before and after the first treatment period, and after the second treatment period, patients were simultaneously monitored under ambulatory conditions with 24-h AMBP, 24-h Holter-monitoring and 24-h fractionated urine collections done according to patient sleeping patterns. On the days of investigation, blood samples were collected, and three conventional cardiovascular reflex tests and a 12-lead ECG were carried out.

Measurement of QT interval

After patients had rested for at least 10 minutes in a supine position, a 12-lead ECG was recorded at a paper speed of 25 mm/s on a 6-channel recorder apparatus (ESAOTE Personal 210 Lap Top, Siemens A/S, Aarhus, Denmark). The ECG was scanned into a personal computer and especially designed software was used to measure the QT interval. On the screen, the ECG was magnified eight times and the PR baseline, the beginning of the QRS complex and the T wave were manually depicted. A tangent to the steepest portion of the downsloping T wave was calculated by the program and the QT interval automatically measured from the onset of the QRS complex to the intersection between the tangent and the PR baseline. The tangent was verified by manual inspection and modified by the operator if necessary. Only leads with well-defined T waves were accepted for measurement and visible U waves were excluded. All analyses were made by one observer blinded to clinical data and treatment modalities. The QT and RR interval were measured in three consecutive cycles and a mean value for each lead was determined. The QT interval was defined as the maximum QT interval measured in the 12-lead ECG. The QT dispersion was defined as the difference between the maximum and the minimum QT interval, with the QT interval corrected for heart rate using Bazett's formula ($QT_c = QT/\text{square root of } RR$). Only leads measurable in the ECGs from all three visits were included in the calculation of the QT parameters.

The mean absolute difference and relative error of the QT measurements have previously been estimated to be 5.7 ms and 1.4% respectively for the QT_c interval and 5.2 ms and 14% respectively for the QT dispersion (for QT_c dispersion 5.4 ms and 14%) [20].

Heart rate variability testing

Bedside tests. Three conventional cardiovascular reflex tests were carried out: (i) heart rate response to standing up (30:15 ratio); (ii) heart rate response to deep breathing (inspiration–expiration difference, average of two measurements); and (iii) blood pressure response to standing up. They were carried out and analysed as previously described [21].

24-hour spectral analysis. Twenty-four-hour ambulatory electrocardiograms were recorded by a Reynolds Tracker two-channel tape recorder (Reynolds Medical, Hertford, UK). Mean RR, distribution of power, and central frequency of low frequency (LF) and high frequency (HF) components were determined, and the coefficient of component variance for HF (CCVHF) was calculated. Results were presented as 24-h, day-time and night-time values. Further details, see [19].

24-hour ambulatory blood pressure. The 24-h AMBP was measured with the Spacelab 90207 (Spacelab, Redmond, Wash., USA) using an oscillometric technique. Readings were obtained every 20 minutes. Day- and night-time blood pressure were calculated on hourly average values based on sleeping times from the Holter analysis.

Urine albumin excretion. Urine albumin was measured by a radioimmunoassay [22]. Patients were provided with three labelled urine collection bottles and collected urine in the day-time, night-time and daytime, according to their sleeping pattern, giving a total of 24 hours. Urine samples were checked for infection (Multistix 8SG, Ames, Stokes Court, UK). Women were instructed not to collect urine during menstruation.

Blood samples. Blood glucose was measured by reflolux II (Boehringer Mannheim, Mannheim, Germany). HbA_{1c} was determined by HPLC (non-diabetic range 4.4–6.4%).

Statistical methods

Variables with skewed distributions were transformed to approximate normal distribution.

We used a compound symmetry model, which has identical correlations between each pair of observations in the same individual. The analysis of each of the response variables was carried out as a linear mixed model. The fixed effects included factors induced by the cross-over design as well as other possible explaining factors/variables (age, smoking etc). The cross-over design with a run-in period was modelled by means of four terms (effects): treatment, period, allocation group and carry-over (period by treatment effect). The possible explaining variables were screened by adding them to the model one at a time, together with their interaction with treatment. Thus the effect of treatment might depend on age, smoking etc. The Bonferroni method was used to adjust the p values. Results are expressed as means $\pm$ SD, UAE is shown as the geometric mean $\times/\div$ tolerance factor. Δ denominates the estimate of the treatment effect $\pm$ SE. A two-tailed p value of less than 0.05 was considered statistically significant.

Results

All patients completed the trial. Patient compliance was high as assessed by tablet counting, as $95.9 \pm 4.5\%$ of the delivered tablets were taken. Metabolic control was not optimal at inclusion and remained unchanged during the study period ($HbA_{1c_{\text{run-in}}}$ $9.2 \pm 1.0\%$, $HbA_{1c_{\text{placebo}}}$ $9.2 \pm 1.2\%$, $HbA_{1c_{\text{metoprolol}}}$ $9.3 \pm 0.9\%$, NS). Serum potassium was not influenced by beta blocker treatment (serum potassium_{run-in} 4.6 ± 0.4 mmol/l, serum potassium_{placebo} 4.5 ± 0.4 mmol/l, serum potassium_{metoprolol} 4.5 ± 0.3 mmol/l, NS).

Although none of the patients reported symptoms of diabetic neuropathy, an abnormal/borderline deep-breathing test result was present in 14 patients. Six patients had an abnormal/borderline 30:15 ratio (cut points according to [21]), and five patients showed abnormal/borderline results in both tests.

All patients had a sinus rhythm without signs of left ventricular hypertrophy or bundle branch block, and for all patients it was possible to measure the QT interval in at least four frontal and four precordial leads in each ECG.

The supplementary beta blocker treatment caused no change in systolic AMBP (daytime_{run-in} 134 ± 11 mm Hg, daytime_{placebo} 135 ± 12 mm Hg, daytime_{metoprolol} 133 ± 10 mm Hg, $p = \text{NS}$) but did cause a decrease in day-time diastolic AMBP (daytime_{run-in} 82 ± 9 mm Hg, daytime_{placebo} 83 ± 8 mm Hg, daytime_{metoprolol} 80 ± 8 mm Hg, $p = 0.04$) and an improvement in HRV parameters reflecting parasympathetic modulation (for details, see [19]).

Table 2. Effect of metoprolol on QT interval, QTc interval, QT dispersion and QTc dispersion

Parameter	Run-in	Placebo	Metoprolol	Δ	<i>p</i> value
Mean RR (ms)	841±101	872±111	966±124	109±19	<0.0001
QT interval (ms)	379.90±28.97	382.20±29.89	397.15±31.38	16.1±3.87	0.0001
QTc interval (ms)	415.55±31.47	410.55±27.23	405.35±24.44	7.70±3.52	0.035
QT dispersion (ms)	42.25±21.32	39.90±14.80	43.60±21.35	2.53±4.11	NS (0.54)
QTc dispersion (ms)	47.05±25.75	42.95±16.74	45.10±23.89	0.10±4.47	NS (0.98)

Values are means ± SD. Δ , estimated treatment effect ± SE; mean RR, mean of all normal RR intervals; QTc dispersion, heart-rate-corrected QT interval dispersion; QTc interval, heart-rate-corrected QT interval

The baseline values and effects of metoprolol treatment on QTc interval and QTc dispersion are shown in Table 2. The QTc interval was significantly reduced by metoprolol treatment (approximately 2%). No difference in QTc dispersion was observed following metoprolol treatment.

Correlations between QTc interval and QTc dispersion on the one hand, and blood pressure, UAE and measures of heart rate variability on the other, are shown in Table 3. We found strong correlations between both daytime and night-time blood pressure and QTc dispersion. Heart rate variability parameters indicating sympathetic and parasympathetic modulation showed strong correlations both with QTc interval and QTc dispersion. No correlation between age, diabetes duration and QT measurements (data not shown) were found.

To rule out a possible confounding effect of the heart rate correction, we also analysed the data using QT dispersion without correction for heart rate; the results and associations were similar.

QTc interval and QTc dispersion in the five patients with two abnormal/borderline bedside tests did not differ from patients with normal bedside test ($n=15$) results (QTc interval: 426.4±33.1 ms vs 411.9±31.2 ms, $p=NS$; QTc dispersion: 51.4±24.1 ms vs 45.6±26.9 ms, $p=NS$). Four patients presented with a prolonged QTc interval (>440 ms). Patients with a QTc interval greater than 440 ms did not differ in their response to metoprolol treatment from patients with a QTc interval below 440 ms.

A division of patients according to the median value for QTc dispersion (39 ms) showed no difference in blood pressure values or any parameter reflecting cardiac autonomic function. Patients with QTc dispersion values above the median had higher UAE (263.6 ×/÷ 222.7 vs 91.5 ×/÷ 57.8 µg/min, $p=0.03$) and higher HbA_{1c} values (9.7±1% vs 8.6±0.6%, $p=0.02$). Patients with QTc dispersion above the median did not differ in response to metoprolol treatment from patients with QTc dispersion below the median (data not shown).

Dividing patients according to the median value for QTc interval (413.5 ms) showed no difference in blood pressure values, HbA_{1c} or UAE, but did show differences in heart rate. Patients with QTc interval above the median had higher night-time heart rates

Table 3. Correlations between QTc interval and QTc dispersion, and blood pressure, heart rate variability parameters and UAE at run-in visit

	QTc interval		QTc dispersion	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
Blood pressure				
Sys daytime	0.274	NS	0.580	0.007
Dia daytime	0.284	NS	0.536	0.015
Sys night-time	0.215	NS	0.482	0.031
Dia night-time	0.290	NS	0.499	0.025
Sys N/D ratio	-0.089	NS	-0.095	NS
Dia N/D ratio	0.009	NS	-0.33	NS
Spectral 24-h				
HFpower (log), total	-0.519	0.019	-0.477	0.033
HFpower (log) daytime	-0.493	0.027	-0.490	0.028
HFpower (log) night-time	-0.498	0.026	-0.423	0.063
LFpower (log), total	-0.450	0.046	-0.531	0.016
LFpower (log) daytime	-0.459	0.042	-0.513	0.021
LFpower (log) night-time	-0.434	0.056	-0.568	0.009
CCVHF (log), total	-0.457	0.043	-0.361	NS
CCVHF (log) daytime	-0.435	0.055	-0.369	NS
CCVHF (log) night-time	-0.432	0.057	-0.302	NS
UAE				
UAE (log) night-time	0.242	NS	0.499	0.030
UAE (log) daytime	0.332	NS	0.615	0.005
UAE (log), total	0.311	NS	0.591	0.008
UAE N/D ratio	-0.297	NS	-0.474	0.040

Dia, diastolic; CCVHF, coefficient of component variance for HF; HF power, power of the high frequency of oscillation; LF power, power of the low frequency of oscillation; N/D, night/day; Sys, systolic; UAE, urin albumin excretion

(76±10 beats per min vs 65±6 beats per min, $p=0.006$). However, this difference is due to the confounding effect of the heart rate correction, as there was no difference in night-time heart rate without the heart rate correction calculation (70±7 beats per min vs 72±13 beats per min, $p=NS$). Daytime heart rate values did not differ between the groups.

Discussion

We have previously shown an association between nocturnal blood pressure and QTc dispersion in normo-

tensive, normoalbuminuric Type 1 diabetic patients, but no correlation between daytime blood pressure and QTc dispersion [20]. In this study, which was of patients with abnormal albuminuria who were receiving ACE-inhibitor treatment, we show strong associations between both daytime and night-time blood pressure and QTc dispersion (Table 3). In non-diabetic hypertensive patients an increased QTc dispersion is presumed to be related to left ventricular hypertrophy [23]. In addition, an association between QTc dispersion and ischaemic heart disease has been shown in non-diabetic [24] and in diabetic [8, 25] patients. Abnormal albuminuria is a strong predictor of cardiovascular disease and although none of the patients in the present study showed symptoms or signs of cardiovascular disease, the difference in test results between patients with normal and abnormal albuminuria may reflect a more pronounced (although subclinical) myocardial ischaemic disease and/or ventricular hypertrophy in the latter group. Invasive tests and measures of ventricular mass were not performed therefore we cannot verify this hypothesis.

No association between blood pressure and QTc interval prolongation were shown. This is in line with results obtained in normoalbuminuric Type 1 diabetic patients [20] using 24-h AMBP, but it contrasts with results from the large EURODIAB IDDM study, where a significant relation was observed between QTc interval prolongation and both systolic and diastolic blood pressure [12]. This discrepancy may be due to different sample sizes. However, blood pressure values in the EURODIAB IDDM study were based on one recording.

Four patients with prolonged QTc intervals did not differ from patients with a QTc interval below 440 ms in response to metoprolol treatment. However, the number of patients is small, and the study was not designed to test this hypothesis.

Heart rate variability. The 24-h spectral analysis showed that QTc interval as well as QTc dispersion are correlated with both parameters indicating sympathetic and parasympathetic modulation. Our results are in line with results observed in Type 2 diabetic patients using 24-h spectral analysis testing; there QTc dispersion was correlated with both low- and high-frequency power spectral parameters, although no correlation with bedside tests was observed [26]. Bedside cardiovascular autonomic function tests are less sensitive in detecting impaired sympathovagal function than spectral analysis methods [27, 28]. This may explain the discrepancy in results, as others have found no relation, when using bedside tests, between QTc interval dispersion and autonomic neuropathy measurements [8, 25].

Urine albumin excretion. Despite ongoing ACE-inhibitor treatment, there was a close relation between blood

pressure and UAE. The strong correlations between QTc dispersion and UAE may reflect this relationship.

ACE-inhibitors are known to reduce QTc interval dispersion in congestive heart failure [29, 30] and post-acute myocardial infarction [31]. Participants in our study were on chronic and stable ACE-inhibitor treatment prior to inclusion and during the study period. It therefore seems unlikely that the changes seen in QTc interval and QTc dispersion were caused by the ACE inhibitor treatment. It might even be possible that the changes induced by beta blocker treatment in QT dispersion and QT interval were masked by the ACE-inhibition effect.

This study is the first to address the effect of metoprolol treatment on QTc interval and QTc dispersion in Type 1 diabetic patients. Beta blocker treatment caused a decrease in QTc interval but no change in QTc dispersion. These results are in line with results obtained in healthy subjects [16] and also in line with the theoretical background for the relationship between the cardiac nervous system, QTc interval and QTc interval dispersion [3]. The unaltered QTc dispersion is in contrast with results obtained by beta blocker treatment in patients with dilated cardiomyopathy, where a reduction in QTc dispersion was shown [18]. This discrepancy could be explained by different patient categories, but the restrictions of the QT dispersion measurement must also be kept in mind [2]. As QTc interval prolongation is an independent marker of increased mortality in Type 1 diabetic patients [11], our results are interesting. However, further investigations are necessary to interpret the fact that QTc interval, but not QTc dispersion were affected.

The EURODIAB IDDM study found that increased QTc interval and increased QT dispersion identified different patients, as the former was related to autonomic neuropathy and the latter was associated with ischaemic heart disease and diastolic blood pressure [25]. In studies of patients with hypertension, QT dispersion has been related to left ventricular hypertrophy [23]. In our study we did not perform echocardiography or use other means to estimate left ventricular mass, but we did find a positive relationship between blood pressure and QT dispersion. Assuming that QT dispersion is related to left ventricular mass and ischaemic heart disease, a change in QT dispersion would not be expected through a short-term treatment with a beta blocking agent. On the other hand, autonomic neuropathy is readily affected by beta blockade, resulting in a shortening of the QTc interval. Theoretically, differences in underlying cardiac abnormalities may therefore be the explanation of the different response of the two parameters to beta blocking treatment seen in our study.

Patients with diabetes are noticeably more susceptible, and to an increasingly greater degree, to cardiovascular disease than is the background population. A similar situation pertains with regard to the dead-

in-bed syndrome, i.e. sudden and unexpected death in young people with diabetes. Both these conditions are possibly linked to cardiac autonomic neuropathy and prolonged QT interval. In experimental and in spontaneous nocturnal hypoglycaemia, prolongation in QTc has been demonstrated [32, 33], and pre-treatment with a beta blocker demonstrably prevented abnormal repolarisation during experimental hypoglycaemia [32]. We have previously shown that it is possible to improve heart rate variability parameters by B1-selective beta blockade [19]. This study now shows that it is also possible to reduce the QTc interval by B1-selective beta blockade. These results could partly explain the pronounced cardioprotective effect of beta blocker treatment in diabetic patients with cardiovascular disease.

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