CLINICAL STUDY

The effect of cardiovascular autonomic neuropathy on resting ECG in type 1 diabetic patients

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Abstract

Background: **Cardiovascular autonomic neuropathy (CAN) is a common complication of diabetes mellitus.**
Aim: **To assess the manifestations of CAN on ECG at rest.**
Subjects and methods: **100 type I diabetic patients, mean age 36.5 (range 17—62) years, mean duration of diabetes 14.6 (range 0—49) years were examined. The control group consisted of 88 healthy subjects, mean age 37 (range 15—65) years. Cardiovascular reflexes (respiration sinus arrhythmia, orthostatic test and Valsalva's maneuvre) were examined, and ECG at rest was analysed.**
Results: **In 35 (35 %) diabetics CAN was established. In comparison to diabetic patients without neuropathy, patients with CAN had a higher heart rate (94, 89—99 vs. 79, 75—82 heart beats.min^{-1}, $p<0.001$), higher P wave voltage (0.13, 0.12—0.15 vs 0.11, 0.09—0.12 mV, $p<0.001$), as well as QTc interval length (422, 410—433 vs 396, 388—404 ms, $p<0.001$), but they had a lower voltage of R wave (0.83, 0.72—0.94 vs. 1.0, 0.91—1.09 mV, $p<0.05$) and lower T wave voltage (0.18, 0.15—0.21 vs 0.23, 0.19—0.27 mV, $p<0.05$).**
Conclusions: **The higher voltage of P wave, lower voltage of T wave, shorter PQ interval and prolonged QTc interval with tachycardia may be the manifestation of relative sympatheticotonia. Lower R wave voltage and the prolonged QRS complex are the possible signs of cardiomyopathy.** ***(Tab. 4, Ref. 31.)***
Key words: electrocardiogram, type 1 diabetes mellitus, autonomic neuropathy.

At present, cardiovascular diseases are the main cause of death in diabetic patients. Apart from the coronary disease, the heart of diabetic patients suffers not only from cardiomyopathy but also from autonomic neuropathy (Grossman and Messerli, 1996). Cardiovascular autonomic neuropathy (CAN) is a common complication of diabetes (17 % IDDM patients), although it has mostly an asymptomatic course. Patients suffering from CAN are at risk of intraoperative cardiovascular instability, higher occurrence of silent myocardial ischaemia/infarction, as well as at high risk of sudden death (Ziegler, 1999). They have a relatively poor prognosis in the absence of clinically detectable micro- and macrovascular complications (Rathmann et al, 1993).

Studies dealing with the analysis of ECG at rest in diabetic patients are rather scarce. Kalliomäki et al (1956) attempted to characterize ECG findings in Type 1 diabetic patients without vascular complications and did not find any abnormalities. Other authors have observed higher heart rate and prolonged QTc interval and suggested that CAN is the cause of these abnormalities (Flugelman et al, 1983; Airaksinen, 1985). A detailed investigation of the influence of CAN on ECG at rest has not yet been reported.

Therefore the aim of this study was to analyze ECG at rest in Type 1 diabetic patients in comparison to healthy controls, and to determine the influence of CAN on ECG at rest in Type 1 diabetic patients.

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Subjects and methods

Subjects

We examined 100 Type 1 diabetic patients, 55 men and 45 women, mean age 36.5 (range 17—62 years), mean duration of diabetes 14.6 (range 0—49) years, which were recruited sequentially from patient rosters of our Faculty Hospital outpatient diabetic clinics. The control group consisted of 88 healthy subjects, 50 men and 38 women, mean age 37 (15—65) years. None of the diabetics, nor the control subjects had a history of angina pectoris or myocardial infarction. All were in sinus rhythm and nobody had ST segment changes on ECG at rest. No patient received any drugs that could influence the cardiovascular system and none of the diabetic patients was in ketoacidosis. Further data on the diabetic patients and control subjects are in Table 1.

Methods

The electrocardiograms were recorded with the Multiscriptor EK 22 (Hellige; Germany). The paper speed was 25 mm/s and the following parameters were analyzed:

1) heart rate,

2) variability of R-R intervals on the basis of the difference between the longest and the shortest R-R interval in mm on a 30 cm long strip of the ECG (approximately 15—20 beats) (Airaksinen et al, 1986),

3) amplitude of P and T wave in limb II lead in mV, maximal R wave amplitude in any of the limb leads (Rmax) in mV, as well as the sum of the S wave in V1 and R wave in V5 in mm (Sokolow-Lyon index),

4) length of the PQ interval, QRS complex and QT interval in limb lead II in ms. The QT interval was measured as a mean of 4—5 beats. The end of the T wave was taken as the point where a tangent to the descending limb of the T wave crossed the base-line. The QT interval was corrected for the heart rate by using Bazett's equation: $QT_c = QT/\sqrt{(R\text{-}R)}$ (Ahnve, 1985).

For the diagnosis of CAN, the following cardiovascular reflexes were used: respiratory sinus arrhythmia, orthostatic test and Valsalva's manoeuvre. The details of these methods were described previously (Pontuch et al, 1990).

Glycosylated haemoglobin was determined spectrophotometrically with 2-thiobarbituric acid. The blood pressure was measured by the auscultation method using the standard mercury manometer with a cuff fixed to the right arm after 10 minutes of rest in a sitting position.

Tab. 1. Characteristics of clinical and laboratory data of patients suffering from diabetes and of control subjects*.

	Diabetics (n=100)	Controls (n=88)	p
Age (yrs)	37 (34-39)	37 (35-39)	NS
Duration of diabetes (yrs)	15 (13-17)		
Men/Women	55/45	50/38	
GHb (μmol fructose/g Hb)	7,8 (7,5-8,2)		
Systolic BP (mmHg)	139 (136-142)	128 (125-130)	<0,001
Diastolic BP (mmHg)	87 (85-89)	81 (79-83)	<0,001
BMI (kg.m^{-2})	24,1 (23,5-24,5)	23,9 (23,2-24,6)	NS

*data are expressed as means and 95% confidence intervals, GHb—glycosylated haemoglobin, BP—blood pressure, BMI—body mass index

Statistical analysis

Differences in the measured parameters were tested by the non-parametric Mann—Whitney test. Point and interval estimations of the mean value were expressed as arithmetic mean and 95 % confidence intervals. The statistical evaluations were made on the level of significance á=0.05. The lowest normal value for individual indexes of cardiovascular reflexes was established as á quantile of probability distribution of a given parameter in the group of control subjects.

Results

The heart rate was higher and the duration of the QRS complex was longer in diabetic patients than in control subjects. The heights of R and T waves and the length of the PQ interval were reduced in diabetic patients (Tab. 2).

To establish the reference values for the diagnosis of CAN, the control subjects were divided into 3 age groups and for each group the 5 % quantile of distribution of individual indexes were calculated, determining the lower limit of the norm for each test (Krahulec, 1995). CAN was assigned to each diabetic patient who had at least one index in the pathological range (under the lower limit of the normal range).

CAN was established in 35 diabetic patients — 19 men and 16 women (mean age: 43.7 years, age range 21—62 years; mean duration of diabetes: 22.1 years, range 6—49 years). The characteristics of diabetic patients suffering from CAN and comparison of their data with those without CAN are given in Table 3.

The heart rate, height of the P wave and the length of QTc interval were greater in diabetic patients with CAN than in patients without CAN. The heights of R and T-waves were decreased in patients suffering from CAN (Tab. 4).

Discussion

A high heart rate, up to 130 beats per minute, at rest (Page et al, 1977) as well as a low variability of R-R intervals (Spallone and Menzinger, 1997) are the known manifestations of CAN, and were described on rest ECGs of young Type 1 diabetics (Airaksinen, 1985). Together with the shortening of the PQ interval, which has not yet been described in diabetic patients, these may be manifestations of sympatheticotonia (Regan, 1987). Moreover, diabetic patients with CAN exhibited higher voltage of the P-wave and lower voltage of the T-wave. The lower amplitude of the T-wave is in accordance with earlier findings (Karlefors, 1966), as well as its further drop in the course of advanced diabetes (Pesson, 1977). The prolongation of the QT interval,

Tab. 2. Findings in ECG at rest in diabetics and control subjects*.

	Diabetics (n=100)	Controls (n=88)	P
Heart rate (beats.min^{-1})	83 (80-86)	73 (70-75)	<0,001
R-R variation (mm)	1,97 (1,69-2,25)	3,03 (2,69-3,37)	<0,001
P wave (mV)	0,12 (0,11-0,13)	0,11 (0,11-0,12)	NS
R max wave (mV)	0,94 (0,87-1,01)	1,25 (1,16-1,34)	<0,001
S V1+R V5 (Sokolow-Lyon) (mV)	2,12 (1,99-2,25)	2,2 (2,06-2,34)	NS
T wave (mV)	0,21 (0,19-0,24)	0,26 (0,24-0,29)	<0,01
PQ (ms)	143 (139-147)	156 (152-161)	<0.001
QRS (ms)	85 (83-88)	78 (75-81)	<0,001
QTc (ms)	404 (397-411)	398 (390-405)	NS

*data are expressed as means with 95% confidence intervals

Tab. 3. Characteristics of clinical and laboratory data in diabetics with and without cardiovascular autonomic neuropathy*.

	Diabetics with CAN (n=35)	Controls without CAN (n=65)	P
Age (yrs)	44 (40-48)	34 (31-36)	<0,001
Duration of diabetes (yrs)	22 (19-25)	11 (8-13)	<0,001
Men/Women	19/16	36/29	
GHb (μmol fructose/g Hb)	8,2 (7,7-8,8)	7,7 (7,2-8,1)	NS
Systolic BP (mmHg)	151 (144-157)	134 (131-136)	<0,005
Diastolic BP (mmHg)	90 (86-95)	86 (84-87)	NS
BMI (kg.m^{-2})	24,4 (23,4-25,4)	23,9 (23,3-24,5)	NS

*data are expressed as means and 95% confidence intervals, CAN—cardiovascular autonomic neuropathy, GHb—glycosylated haemoglobin, BP—blood pressure, BMI—body mass index

lowering of the T-wave voltage as well as tachycardia can be induced by intravenous administration of adrenaline (Struthers et al, 1983). This may demonstrate that in patients with manifestations of CAN, sympatheticotonia is involved, possibly resulting from reduced vagus activity in parasympathetic injury that develops prior to the sympathetic derangement in CAN (Ewing et al, 1985).

The low variation of R-R intervals on the ECG indicating the risk of sudden death is a poor prognostic feature also in people who do not suffer from diabetes mellitus (Hoogenhuyze et al, 1989). Similarly, the prolongation of the QT interval, accompanied with the enhancement of the vulnerable phase of the cardiac cycle (Schwartz and Malliani, 1975) may be associated with poor prognosis as well as with the increased risk of sudden death in diabetic patients with CAN (Kahn et al, 1987; Bellavere et al, 1988). QT interval prolongation is a constant feature of CAN (Ziegler, 1999). The prolonged QT interval can also be a good diagnostic indicator of subclinical autonomic dysfunction, and of increased cardiovascular risk (Whitsel et al, 2000). An increased occurrence of serious ventricular arrythmias is expected in patients with prolonged QT intervals (Ewing et al, 1991) although

Tab. 4. ECG findings in diabetics with and without cardiovascular autonomic neuropathy*.

	Diabetics with CAN (n=35)	Diabetics without CAN (n=65)	P
Heart rate (beats.min^{-1})	94 (89-99)	79 (75-82)	<0,001
R-R variation (mm)	0,94 (0,72-1,15)	2,43 (2,09-3,78)	<0,001
P wave (mV)	0,13 (0,12-0,15)	0,11 (0,09-0,12)	<0,05
R max wave (mV)	0,83 (0,72-0,94)	1,0 (0,91-1,09)	<0,05
S V1+R V5 (Sokolow-Lyon) (mV)	1,93 (1,7-2,16)	2,2 (2,05-2,36)	NS
T wave (mV)	0,18 (0,15-0,21)	0,23 (0,19-0,27)	<0,05
PQ (ms)	150 (140-160)	140 (130-140)	NS
QRS (ms)	83 (78-88)	86 (83-89)	NS
QTc (ms)	422 (410-433)	396 (388-404)	<0,001

*data are expressed as means with 95% confidence intervals; CAN—cardiovascular autonomic neuropathy we failed to establish the increased arrhythmogenicity of the myocardium in type 1 diabetic patients with CAN (Krahulec et al, 1991; Krahulec and Štrbová, 1994). QT interval prolongation was really found in diabetic patient with torsade de pointes (Abo et al, 1996), and is the most predictive factor of increased mortality in Type 1 diabetic patients, even when other variables such as age, duration of disease and blood pressure are taken into account (Veglio et al, 2000). The Framingham's study clearly shows that patients with tachycardia have poor prognosis (Kannel et al, 1987). The ECG of patients suffering from diabetes with CAN showed several indicators of increased cardiovascular risk.

Diabetes mellitus leads to collagen accumulation in the interstitium of the cardiac muscle, resulting in diffuse damage of the myocardium (Regan and Weisse, 1992). Such a latent derangement of left ventricular function, as a feature of cardiomyopathy, can be manifested by decreased voltage of the R wave and prolongation of the QRS complex on ECG at rest. A low R wave was observed also by other authors (Airaksinen, 1985; Karlefors, 1966) and in the course of diabetes it was found to diminish further (Persson, 1977). Diabetic patients with CAN have a significantly lower R wave than diabetic patients without the complication. This can be considered as the evidence that the heart of diabetic patients is damaged both by cardioneuropathy and cardiomyopathy. This does reportedly neither involve the manifestation of reduced muscle bulk of the ventricles nor pericardial exudate/transudate (Fisher et al, 1989). Moreover, the Sokolov-Lyon index which is considered to be a highly specific indicator of hypertrophy of the left ventricle of the heart (Deveneux, 1990), did not show any differences in the two groups of patients.

Cardioneuropathy seems to be an important factor involved in the changes in ECG at rest in diabetic patients, partly accounting for the poor prognosis in these patients.

References

Abo K, Ishida Y, Yoshida R, Hozumi T, Ueno H, Shiotani H, Matsunaga K, Kazumi T. Torsade de pointes in NIDDM with long QT intervals. Diabetes Care 1996; 19: 1010.

Airaksinen KEJ. Electrocardiogram of young diabetic subjects. Ann Clin Res 1985; 17: 135—138.

Airaksinen KEJ, Nieminen PJ, Pirttiaho HI, Takkunen JT. Standard ECG: A useful screening method for diabetic autonomic neuropathy. Diabetes Care 1986; 9: 103—104.

Ahnve S. Correction of the QT interval for heart rate: Review of different formulas and the use of Bazett's formula in myocardial infarction. Amer Heart J 1985; 109: 568—574.

Bellavere F, Ferri M, Quarini L, Bax G, Piccoli A, Cardone C, Fedele D. Prolonged QT period in diabetic autonomic neuropathy: a possible role in sudden cardiac death? Brit Heart J 1988; 59: 379—383.

Deveneux RB. Is the electrocardiogram still useful for detection of left ventricular hypertrophy? Circulation 1990; 81; 1144—1146.

Ewing DJ, Boland O, Neilson JMM, Cho CG, Clarke BF. Autonomic neuropathy, QT interval lengthening, and unexpected deaths in male diabetic patients. Diabetologia 1991; 34: 182—185.

Ewing DJ, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. Diabetes Care 1985; 8: 491—498.

Fisher BM, Cleland JGF, Dargie HJ, Frier BM. Non-invasive evaluation of cardiac function in young patients with type 1 diabetes. Diabet Med 1989; 6 677—681.

Flugelman MY, Kanter Y, Abinader EG, Lewis BS, Barzilai D. Electrocardiographic patterns in diabetics without clinical ischemic heart disease. Isr J Med Sci 1983; 19: 252—255.

Grossman E, Messerli FH. Diabetic and hypertensive heart disease. Ann Intern Med 1996; 125: 304—310.

Hoogenhuyze DV, Martin GJ, Weiss JS, Schaad J, Fintel D, Singer DH. Heart rate variability 1989 an update. J Electrocardiol 1989; 22: S204—S208.

Kahn JK, Sisson JC, Vinik AI. QT interval prolongation and sudden cardiac death in diabetic autonomic neuropathy. J Clin Endocrinol Metab 1987; 64: 751—754.

Kalliomaki JL, Mollerstrom J, Sollberger A. Observations on the standard electrocardiogram in diabetics with clinically normal hearts. Acta Med Scand 1956; 156: 211—220.

Kannel WB, Kannel C, Paffenbarger RSJr, Cupples LA. Heart rate and cardiovascular mortality: the Framingham study. Amer Heart J 1987; 113: 1489—1494.

Karlefors T. Exercise tests in male diabetics-electrocardiographic study. Acta Med Scand 1966; 180: 3—18.

Krahulec B. The importance and possibilities of the autonomic nervous system examination of patients with diabetes mellitus. Part 1. Noninvas Cardiol 1995; 4: 154—164.

Krahulec B, Kuka P, Štrbová L. Is a prolonged QT interval really arrhythmogenic in the diabetic patient? Diabetologia 1991; 34: 159 (Abstract).

Krahulec B, Štrbová L. QT dispersion in diabetic autonomic neuropathy. Diabetologia 1994; 37: A8 (Abstract).

Page MMcB, Watkins PJ. The heart in diabetes: Autonomic neuropathy and cardiomyopathy. Clin Endocrin Metab 1977; 6: 377—388.

Persson G. Exercise tests in male diabetics. Acta Med Scand 1977; S605: 7—23.

Pontuch P, Vozár J, Potocký M, Krahulec B. Relationship between nephropathy, retinopathy and autonomic neuropathy in patients with type 1 diabetes. J Diabet Complications 1990; 4: 188—192.

Rathmann W, Ziegler D, Jahnke M, Haastert B, Gries FA. Mortality in diabetic patients with cardiovascular autonomic neuropathy. Diabet Med 1993; 10: 820—824.

Regan TJ. The myocardium in diabetes mellitus. J Appl Cardiol 1987; 2: 379—396.

Regan TJ, Weisse AB. Diabetic cardiomyopathy. J Amer Coll Cardiol 1992; 19: 1165—1166.

Schwartz PJ, Malliani A. Electrical alternation of the T-wave: clinical and experimental evidence of its relationship with the sympathetic nervous system and with the long QT syndrome. Amer Heart J 1975; 89: 45—50.

Spallone V, Menzinger G. Diagnosis of cardiovascular autonomic neuropathy in diabetes. Diabetes 1997; 46: S67—S76.

Struthers AD, Reid JL, Whitesmith R, Rodger JC. Effect of intravenous adrenaline on electrocardiogram, blood pressure and serum potassium. Brit Heart J 1983; 49: 90—93.

Veglio M, Sivieri R, Chinaglia A, Scaglione L, Cavallo-Perin P. QT interval prolongation and mortality in type 1 diabetic patients. Diabetes Care 2000; 23: 1381—1383.

Whitsel EA, Boyko EJ, Siscovick DS. Reassessing the role of QTc in the diagnosis of autonomic failure among patients with diabetes. A meta-analysis. Diabet Care 2000; 23: 241—247.

Ziegler D. Cardiovascular autonomic neuropathy: clinical manifestations and measurement. Diabet Rev 1999; 7: 342—357.

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NEW BOOKS

Mego M. Forensic Medicine I. PSYCHOPROF, Ltd., Nové Zámky 2001. 1st edition, 192 pp., 43 black-and-white figures and photographs, schemes, pen-and-ink drawings, and 24 colour photographs within a colour supplement, ISBN 80-967148-3-X.

After 30 years the textbook of forensic medicine, first part, has been published in Slovak (except a Czech-Slovak schoolbook for facukties of medicine from 1987 where there texts of Slovak contributirs, too). The book shows polygraphically fair aesthetical design.

The dominant feature of the book is its devotion to students of medicine and law, as well. This demanding task has led the author to somewhat essential character and briefness accompanied by using generally acceptable medical terminology, and mainly offers basic knowledge of theory and practice in forensic medicine. It contains the promise of wider information on procedures overcoming a frame of basic orientation in this branch in the future part.

The author's professional curriculum vitae can be found on the back cover of the book. Since his graduation at the Bratislava Faculty of Medicine of the Comenius University he has been engaged at the Bratislava Institute of Forensic Medicine and now is the current head of the Institute. He is one of the most experienced forensic surgeons in Slovakia.

The first part of the textbook consists of 20 standard chapters — concept, meaning and historical frame of forensic medicine, death and the process of dying, death allegation, after-death transformations, death time, dying history, the cadaver as a source of forensic-medical information, autopsy and its documentation, exhumation, categories and kinds of a death, effects of mechanical violence, mechanical injuries, selected head injuries, high-fall casualties, suffocation, imoact of heightened and lowered air pressure, of electric current and lightning, of heightened temperature, as well as transport casualities.

The contents follows the so-called classical forensic medicine. Despite a tendency towards the archaic style, synoptical schemes, drawings, and photographs of high quality contribute to figurativeness of the book.

Bibliography offers all fundamental Slovak and Czech writings on the topic preceding this textbook, significant West-European publications which are mainly represented by those of German provenance (since German legal medicine has reached the top in European context), as well as American sources of the worldly recognized experts. Index helps in orientation markedly. Though the book within its scope is not intended for a postgraduate study in forensic medicine, it brings valid information for practitioners, psychiatrists, psychologists, students at the Pilce Constabulary Academy, police investigators, prsecutors, and judges, as well.

The book undoubtedly contributes to scanty Slovak specialized writing on the item. We hope that following books will cover the whole scope of knowledge in forensic medicine, including current information, so that they will satisfy the recipients.

F. Longauer