

ECG Body Surface Mapping Changes in Type 1 Diabetic Patients with and without Autonomic Neuropathy

S. PALOVÁ¹, K. SZABO¹, J. CHARVÁT¹, J. SLAVÍČEK², E. MEDOVÁ², M. MLČEK², O. KITTNAR²

¹Department of Medicine, Second Medical Faculty, Charles University, Prague, Czech Republic,

²Institute of Physiology, First Medical Faculty, Charles University, Prague, Czech Republic

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Summary

ECG body surface mapping (BSM) parameters in patients with diabetes mellitus Type 1 (DM1) are significantly different comparing to healthy non-diabetic subjects. Hypothesis that these changes are more pronounced in DM1 patients with autonomic neuropathy (AN) was tested. The parameters of BSM were registered by diagnostic system Cardiac 112.2 in 54 DM1 patients including 25 with AN and 30 control subjects. AN was diagnosed according to Ewing criteria when two or more Ewing tests were abnormal. In classic 12-lead ECG the heart rate was increased, QRS and QT shortened ($p < 0.01$) and QT_c prolonged in DM1 patients. The VCG measurement of QRS-STT angles and spatial QRS-STT angle showed non-significant differences. The absolute values of maximum and minimum in depolarization and repolarization isopotential, isointegral, isoarea maps were significantly different in DM1 patients in comparison with controls ($p < 0.01$). The changes were more pronounced in DM1 patients with AN than in DM patients without AN ($p < 0.05$). The QT duration measured in 82 leads of thorax was significantly shortened in 68 leads of both groups of DM 1 patients ($p < 0.01$) when compared with controls. In 34 of them this shortening was more pronounced in DM1 patients with AN than in DM1 patients without AN ($p < 0.05$). The results showed that the method of ECG BSM is capable to confirm the presence of autonomic neuropathy in diabetic patients.

Key words

Diabetes mellitus type 1 • Autonomic neuropathy • ECG Body Surface Mapping

Corresponding author

O. Kittnar, Institute of Physiology, First Medical Faculty, Charles University, Albertov 5, 128 00 Prague 2, Czech Republic. E-mail: otomar.kittnar@lf1.cuni.cz

Introduction

Diabetes mellitus can be complicated by autonomic neuropathy even in young DM1 patients (Alberti *et al.* 1978, Alberti and Zimmet 1989, Beckman *et al.* 2002). The relatively increased sympathetic control in patients with autonomic neuropathy is associated with the higher risk of sudden cardiac death (Alberti *et al.* 1978, Alberti and Zimmet 1989). In these patients the heart rate is accelerated and cardiac response to the different stimuli is pathological as far as autonomic neuropathy produces some abnormalities in heart electrical field (Ruttikay-Nedecky 2001, Javorka *et al.* 2005). In our previous work we found the differences in some parameters of heart electrical field in DM1 patients in comparison with controls (Žďárská *et al.* 2007). In the present study we tested hypothesis that autonomic neuropathy is associated with more pronounced changes on body surface mapping in the DM1 patients. The preliminary results have been published in abstract form (Palová *et al.* 2007).

Methods

The first type diabetic patients (DM1) were recruited in diabetic outpatient department of Medical department of Faculty Hospital Prague Motol. Fifty-four diabetic patients (31 men, 23 women) and 30 controls (11 men, 19 women) participated in the study (Table 1). In DM1 20 men and in DM1 with AN 11 men were present. The parameters of heart electric field were evaluated together for men and women.

Inclusion criteria:

Type 1 diabetes mellitus
 Age: between 18-50 years
 Twelve leads ECG: within normal limits

Exclusion criteria:

Another drug treatment than insulin
 Signs of retinopathy
 Presence of microalbuminuria
 Serum creatinine or urea elevation
 Any 12 lead ECG abnormalities
 Another disease than Type 1 diabetes mellitus

In diabetic patients the duration of DM1 was recorded. DM1 was diagnosed by the increased fasting blood sugar, low C-peptide, and positive findings of glutamic acid decarboxylase 65 (anti-GAD65) or/and to autoantibodies to islet cells (anti-ICA). The long-term metabolic compensation of diabetic patients was evaluated by HbA1c level according to IFCC (Pickup and Williams 2003). The average total daily insulin dosage was also recorded.

Autonomic diabetic neuropathy (AN) was diagnosed according to Ewing tests examined and evaluated according to previously published protocols (Alberti *et al.* 1978, Alberti and Zimmet 1989). Cardiovascular tests have been developed which indicate the presence or absence of autonomic neuropathy.

Table 1. The characteristics of controls and diabetic patients Type 1 (DM1) with or without autonomic neuropathy (mean \pm S.D.).

	Controls (n=30)	DM1 without AN (n=29)	DM1 with AN (n=25)	p
Age (years)	29.60 \pm 3.22	32.59 \pm 5.55	32.24 \pm 5.77	NS
DM1 duration (years)	–	13.23 \pm 7.82	13.82 \pm 6.64	NS
HbA1c (%)	–	6.41 \pm 1.28	6.96 \pm 1.11	NS
Insulin dosage (units/day)	–	42.44 \pm 10.71	46.18 \pm 11.47	NS
BMI (kg/m ²)	24.30 \pm 2.98	23.44 \pm 2.80	24.40 \pm 2.32	NS

AN – autonomic neuropathy, DM1 – Type 1 diabetes mellitus, HbA1c – glycolated hemoglobin, BMI – body mass index.

The following five autonomic function tests have been performed. The patients with at least two abnormal tests were labeled to suffer from AN (Alberti *et al.* 1978, Alberti and Zimmet 1989).

Ewing autonomic function tests:

- 1) Heart rate variation of deep breathing – abnormal < 10 beats/min
- 2) Heart rate increase on standing at 15 s – abnormal < 12 beats/min
- 3) Heart rate increase on standing, 30:15 ratio – abnormal < 1.00
- 4) Valsalva ratio – abnormal < 1.2
- 5) Postural systolic pressure fall at 2 min – abnormal > 30 mm Hg

The electrocardiogram (ECG), vectorcardiogram (VCG) and body surface isopotential, isointegral and isoarea maps (BSM) were registered altogether using the diagnostic system CARDIAG 112.2 (Slaviček *et al.* 2001, Kittnar and Šťovíček 1993) one hour after a light breakfast and an insulin application in diabetic patients in the morning hours. Healthy control subjects were also examined one hour after breakfast. 201 parameters of heart electrical field were registered in controls, DM1 patients without and with AN.

Heart rate, duration of PQ, QRS, QT and QTc intervals were recorded and evaluated by 12 leads ECG.

In the VCG evaluation, the Frank orthogonal lead system was used (Frank 1956). The depolarization, repolarization isopotential maps (DIPM, RIMP), isointegral depolarization and repolarization maps (DIIM, RIIM) and their maximum and minimum were recorded and evaluated by ECG body surface potential maps (BSM). Depolarization isoarea maps, their maximum and minimum in μ Vs (isointegral maps from the beginning of QRS until 40 ms – DIAM max 40, DIAM min 40) and repolarization areas and their maximum and minimum in μ Vs (isointegral maps from the point J to 40 ms – RIAM max 40 and RIAM min 40) were examined as well as isointegral minimum (Q-IIM), amplitude (IPMAM-Q) of Q wave as and QT duration in the chest electrodes. Activation time (ICHVAT in ms) was measured between the beginning of depolarization in an orthogonal lead and the R wave in the individual chest leads. The QT duration was measured in 85 thoracic leads.

All diabetic patients and control subjects signed informed consent forms prior to their inclusion in the study. The local ethical committee accepted the study

Table 2. Heart rate, PQ, QRS, QT, QTc and R/R duration in controls and DM1 patients with or without autonomic neuropathy measured by classic 12-leads ECG.

Parameter	Controls (n=30)	DM1 without AN (n=29)	DM1 with AN (n=25)	p M-W	p K-W
Heart rate (min^{-1})	73.97 \pm 1.79	82.24 \pm 2.54*	92.24 \pm 3.00**	<0.01	0.000
PQ (ms)	153.93 \pm 5.81	142.82 \pm 3.59	154.08 \pm 10.08	NS	0.743
QRS (ms)	87.60 \pm 2.28	78.62 \pm 1.51*	75.52 \pm 1.63**	<0.01	0.001
QT (ms)	376.53 \pm 4.05	352.24 \pm 5.90**	350.72 \pm 10.08**	<0.01	0.000
QTc (ms)	404.53 \pm 12.08	424.03 \pm 16.31	431.40 \pm 12.66	NS	0.241
RR (ms)	753.29 \pm 22.28	751.48 \pm 23.05	668.09 \pm 25.89*	<0.05	0.014

DM1 – type 1 diabetes mellitus, AN – autonomic neuropathy, * $p < 0.05$; ** $p < 0.01$ in comparison of controls and diabetic patients; comparison of heart rate and QRS duration in DM 1 patients with or without AN (second and third column) – $p < 0.05$; p M-W – Mann-Whitney test; p K-W – test Kruskal-Wallis for all three groups. Data are means \pm S.E.M.

Table 3. VCG QRS-STT angles (expressed in degrees) in frontal, transversal, left sagittal planes and the spatial QRS-STT angle.

Parameter	Controls (n=30)	DM1 without AN (n=29)	DM1 with AN (n=25)	p K-W
QRS-STT angle (frontal plane)	-1.03 \pm 8.25	-3.00 \pm 6.11	-0.52 \pm 4.33	0.923
QRS-STT angle (transversal plane)	-48.77 \pm 7.93	-68.38 \pm 7.95	-48.00 \pm 7.75	0.128
QRS-STT angle (left sagittal plane)	-43.77 \pm 4.13	-62.34 \pm 15.26	-64.60 \pm 9.27	0.092
QRS-STT spatial angle	44.10 \pm 6.33	59.24 \pm 6.17	49.12 \pm 5.02	0.094
QRS axis in frontal plane	38.30 \pm 6.84	37.66 \pm 5.89	38.12 \pm 5.41	0.833

For more detailed description see Table 2. Data are means \pm S.E.M.

protocol with respect to the 1964 Declaration of Helsinki.

Statistical evaluation

The mean value, standard deviation (S.D.) and standard error of mean (S.E.M.) of the measured parameters were calculated. T-test and χ^2 test were used for evaluation of basal characteristics. Kruskal-Wallis test was used for comparison of 12-leads ECG, vectorcardiogram and BSM parameters of all three studied groups (diabetic patients with or without AN and healthy control subjects). The non-parametric Mann-Whitney test was used for separate comparison of 12-leads ECG, vectorcardiogram and BSM parameters of 2 diabetic groups. $p < 0.05$ value was considered to be significant.

Results

The number of controls and diabetic patients with or without AN as well as the parameters of the compensation and treatment of DM1 are summarized in Table 1. No significant changes in these characteristics were present among the groups. Out of twenty-five patients with diagnosis of AN, twenty-one presented a score of 2 and the remaining four patients a score of 3 in pathological Ewing tests.

The results of 12 leads ECG are shown in Table 2. Comparing only two groups of patients with DM1, the significant difference was detected for heart rate which was faster in patients with AN ($p < 0.05$) and R-R shortened ($p < 0.05$). The duration of QRS was

Table 4. The selected parameters of BSM, the significant differences between DM1 patients with or without AN, and control subjects.

Parameter	Controls (n=30)	DM1 without AN (n=29)	DM1 with AN (n=25)	p K-W
<i>DIPMmax10</i> (μV)	100.67±10.92	147.21±10.95**	145.24±21.73	0.001
<i>DIPMmax30</i> (μV)	716.60±55.41	1016.20±68.17**	993.60±45.80	0.005
<i>DIPMmax50</i> (μV)	1051.17±98.93	747.52±69.36	679.64±83.16*	0.015
<i>DIPMmin10</i> (μV)	-48.50±4.06	-66.24±7.04*	-65.40±5.64	0.020
<i>DIPMmin20</i> (μV)	-150.80±21.27	-239.03±41.11	-238.10±38.31*	0.017
<i>DIPMmin30</i> (μV)	-370.13±61.07	-791.86±123.92**	-801.04±113.40**	0.000
<i>DIPMmin40</i> (μV)	-792.43±102.80	-1502.14±158.60**	-1382.67±155.70**	0.000
<i>DIIMmin</i> (μVs)	-31.48±2.71	-46.21±4.28*	-38.17±3.61	0.026
<i>DIAMmax40</i> (μVs)	14.11±1.05	19.84±1.31*	19.14±1.94**	0.004
<i>DIAMmin40</i> (μVs)	-6.96±0.98	-14.15±2.13**	-12.75±2.16**	0.000
<i>RIPMmax10</i> (μV)	144.67±21.09	114.45±16.46	84.6±18.65*	0.004
<i>RIPMmin50</i> (μV)	-278.10±131.14	-127.26±11.64	-100.38±9.48*	0.026
<i>RIPMmin60</i> (μV)	-316.67±120.94	-156.12±13.31	-130.00±11.56**	0.004
<i>RIPMmin70</i> (μV)	-354.80±110.53	-188.52±16.19*	-157.62±12.63**	0.001
<i>RIPMmin80</i> (μV)	-326.13±103.28	-178.50±16.02	-157.80±11.76**	0.005
<i>Q-IPMAM min</i> (μV)	-625.50±12.80	-850.34±17.85	-866.83±19.29*	0.023
<i>ICHVAT</i> (ms)	68.90±1.69	62.72±1.25*	59.70±1.35**	0.001
<i>Q-IIM min</i> (μVs)	-14.86±1.04	-21.96±2.63	-24.02±2.58*	0.016
<i>QS-IPMAM min</i> (μV)	-557.12±50.60	-772.17±98.92	-843.08±82.30*	0.036

DIPMmax, DIPMmin – maximum, minimum in depolarization isopotential map (μV), DIIMmin – minimum in depolarization isointegral map (μVs), DIAMmax 40, DIAMmin 40 – maximum, minimum in depolarization isoarea map from the beginning of QRS to 40th ms of depolarization (μVs), RIPMmax, RIPMmin – maximum, minimum in repolarization isopotential map (μV), Q-IPMAM – amplitude of Q wave (μV), ICHVAT – activation time between the onset of electrical activation registered by orthogonal leads x, y, z and the thoracic surface ECG (ms), Q-IIM – minimum in isointegral map of Q-wave (μVs), QS-IPMAM – amplitude of Q and S wave (μV), * $p < 0.05$, ** $p < 0.01$ in comparison with controls; p K-W – Kruskal-Wallis test for all three group. Data are means \pm S.E.M.

significantly shortened in DM1 patients with AN patients compared to controls ($p < 0.01$). The shortening of QRS was more pronounced in DM1 patients with AN ($p < 0.01$) than in DM1 patients without AN ($p < 0.05$) when compared with controls. The duration of QT was shortened in both groups of diabetic patients due to the increase of heart rate. The QT_C was prolonged in both groups of diabetic patients, but non-significantly (probably due to the wide range of variation in DM1 patients).

The planar QRS-STT angles in VCG changed in a different way in both DM1 groups of patients (Table 3). The QRS axis in frontal plane was unchanged in comparison with controls, similarly as the QRS-STT angle in frontal plane.

The QRS-STT angle in transversal (horizontal) plane was more opened only in DM1 patients without AN, while in left sagittal plane the angle was opened in

both groups. The spatial angle was opened by in a more pronounced way in DM1 without AN than in DM1 with AN. The differences were not statistically significant (Mann-Whitney), the result of Kruskal-Wallis test was significant for the value of left sagittal plane angle and spatial angle (Table 3).

The parameters of heart electric field in the diabetic patients (both without or with AN) and control subjects during BSM measurement are summarized in Table 4. The maximum in depolarization of isopotential maps (DIPMmax) was more positive until the 30th ms and more negative from the 50th ms. The minimum (DIPMmin) was more negative until the 40th ms of the QRS. The repolarization isopotential map maximum (RIPMmax) was less positive in the 10th ms and minimum (RIPMmin) less negative from 50th to 80th ms from the beginning of the point J (terminal part of the QRS). The changes in DIPM maps were confirmed by

measurement of depolarization isointegral and isoarea maps maximum and minimum (DIIM, DIAM). The amplitude of Q and S wave were more negative (Q-IPMAMmin, QS-IPMAMmin) similarly as the minimum in the isointegral map of the Q wave (Q-IIMmin) in DM patients than in controls. The activation time (ICHVAT) was faster in DM1 patients due to the increased heart rate (Table 4).

In 12 out of 19 parameters (DIPMmax50, DIPMmin20, DIAMmax40, RIPMmax10, RIPMmin 50, 60, 70, 80, Q-IPMAMmin, Q-IIMmin, QS-IPMAMmin, ICHVAT) the DM1 patients with AN showed the more pronounced changes ($p < 0.01$), than DM1 patients without AN ($p < 0.05$) in comparison with controls. On the other hand, the changes of four parameters (DIPMmax10, 30, DIPMmin10, DIIMmin) were more pronounced in DM1 without AN than in DM1 patients with AN ($p < 0.05$, Table 4). The values of three parameters (DIPMmin30, 40, DIPMmin40) were non-significantly different in both groups of DM patients (Table 4), but significantly different in comparison with controls ($p < 0.01$).

In 68 thoracic surface leads out of 82 measured the QT duration was significantly shortened in the both groups of DM1 patients when compared with controls. In 34 leads the QT shortening was more pronounced in DM1 patients with AN ($p < 0.01$) than in DM1 patients without AN ($p < 0.05$). In 34 other leads the shortening of QT duration was not different in the DM1 patients with and without AN in comparison with controls. In the resting 14 leads the significant shortening of the QT duration ($p < 0.01$) was observed only in DM1 patients with AN and not in DM 1 patients without AN (data not shown).

Discussion

The present work showed the differences in parameters of heart electric field in DM1 patients in comparison with the controls: acceleration of heart rate, shortening of RR, QRS and QT intervals. Depolarization and repolarization isopotential, isointegral, isoarea maps (the absolute values of maximum and minimum) were significantly changed. Fourteen parameters were different in comparison of controls and DM1 patients without AN, and twenty parameters were significantly different in comparison of controls and DM1 AN patients. The duration of QT measured in 80 surface thoracic leads was shortened in 68 of them in DM1 patients without AN, but in all 82 places in DM1 patients with AN. Comparison of

two DM1 patient groups showed the more pronounced changes of some heart electric field parameters in DM1 AN patients than in patients without AN (Table 4). The present work confirmed our previous results in DM1 without AN (Žďárská *et al.* 2007).

The statistically significant changes in localization of depolarization isopotential map minimum in 40th and 50th ms (DIPMmin40, 50) were found. The values of minimum were placed two intercostal spaces lower in DM1 AN patients than in controls ($p < 0.05$).

Diabetes mellitus can be considered as a vascular disease because it causes both microvascular and macrovascular complications (Alberti *et al.* 1978, Kannel *et al.* 1986, Alberti and Zimmet 1989, Beckman *et al.* 2002, Pickup and Williams 2003). Cardiovascular disease accounts for at least 66 % of deaths in diabetic patients. Due to the sensitive neuropathy, the coronary artery disease in diabetic patients is frequently asymptomatic (Alberti and Zimmet 1989, Langer *et al.* 1991, Paillole *et al.* 1995, Wackers *et al.* 2004). This fact underlines the importance of the sophisticated laboratory testing in diabetic patients, mainly stress myocardial SPECT and stress echocardiography, for diagnosis evaluation (Langer *et al.* 1991, Paillole *et al.* 1995, Wackers *et al.* 2004). Twelve leads resting ECG can be within normal limits even in an advanced stage of coronary artery disease (Alberti and Zimmet 1989, Pickup and Williams 2003). In this respect, BSM might be useful tool in coronary ischemia detection (Green *et al.* 1985, Kittnar *et al.* 1993, Valouch *et al.* 2004) in asymptomatic diabetic patients. However, the changes due to diabetes itself must be defined first before the specific abnormalities for silent coronary ischemia are looked for on BSM in diabetic patients.

In our present study therefore the young first type diabetic patients with normal resting 12 leads ECG and without any clinically evident macrovascular complications have been evaluated. These patients represent group of subjects with very low probability of asymptomatic coronary artery disease (Alberti *et al.* 1978, Alberti and Zimmet 1989, Pickup and Williams 2003).

The parameters of VCG, QRS-STT angles, the spatial angle and QRS axis in frontal plane were non-significantly different in comparison with controls probably due to a small number of patients (Table 3). However, Kruskal-Wallis test showed the value near to the 5 % signification level in spatial QRS-STT angle and in QRS-STT angle of frontal and left sagittal plane

opening angle. Similarly the height level of SD in Table 3 is due to the small number of patients. On the other hand, the similar results were obtained in frontal plane, i.e. no change in QRS axis deviation and small change in QRS-STT angle in both groups of DM 1 patients in comparison with controls (Table 3).

We have shown the significant changes in heart depolarization and repolarization as well as in activation time and amplitude of Q wave in the young DM1 patients comparing to healthy non-diabetic controls. As far as no diabetic patient was known to suffer from coronary artery disease and only some of them fulfilled the criteria for autonomic neuropathy the body surface mapping changes could be attributed to the specific influence of diabetes. Diabetic patients have fasting as well as postprandial hyperglycemia (Alberti *et al.* 1978, Alberti and Zimmet 1989, Pickup and Williams 2003). They are using more fatty acids and less glucose for cardiac muscle energy metabolism comparing to non-diabetic subjects (Pickup and Williams 2003). This could lead to some changes in cardiomyocyte membranes.

The comparison of DM1 patients with and without AN showed some different results in heart electric field parameters. The heart rate was significantly faster in DM1 patients with AN than in DM1 patients without AN, the R-R, QRS and QT intervals shortened more in DM1 with AN than in DM1 without AN.

DM1 patients with and without AN presented the similar changes of some parameters of heart electric field on BSM. However, several parameters of heart electric field on BSM were more significantly changed in DM1 patients with AN patients than without AN in comparison with controls.

The significant changes of depolarization and repolarization in body surface mapping seen in our young DM1 patients could be explained by the activation of adrenergic system. The changes of these parameters were more pronounced in DM1 patients with AN. The absence

of any statistically significant differences of BSM when only two diabetic groups have been considered could be attributed to limited number of diabetic patients included into study. As far as autonomic neuropathy is associated with significantly increased sympathetic activity (Ruttkey-Nedecky 2001, Javorka *et al.* 2005), the results of our study are in favor of the idea that body surface changes in Type 1 diabetic patients are related to power of adrenergic activation.

The similar results of heart electric field parameters on body surface mapping were observed in depressive patients treated with the tricyclic antidepressants (Slavíček *et al.* 1998, Paclt *et al.* 2003). This observation could be important as far as it is known that among diabetic patients there is high incidence of depressive subjects (Pickup and Williams 2003).

In summary, our results confirmed the significance of body surface mapping changes in young DM1 patients. The presence of more pronounced changes in the heart electric field parameters in DM1 patients with AN than without AN when compared with controls, supports hypothesis that BSM changes in DM1 patients are associated with the augmentation of the adrenergic activation.

Conflict of Interest

There is no conflict of interest.

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