ECG Body Surface Mapping (BSM) in Type 1 Diabetic Patients

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Summary
Diabetes mellitus is a risk factor of cardiovascular diseases. ECG of patients with diabetes mellitus type 1 (DM 1) shows tachycardia (block of parasympathetic innervation) and abnormal repolarization (increased QT interval and QT dispersion (QTd)) indicating a risk of ventricular tachycardia and sudden death in young people with DM 1. The aim of the present report was to measure 145 parameters of the heart electric field in 22 patients (14 men, 8 women) with DM 1 without complications (mean age 32.8±11.4 years) and in 22 controls (11 men, 11 women, mean age 30.1±3.4 years). The duration of diabetes was 13.9±7.8 years. The parameters were registered by the diagnostic system Cardiag 112.2 and statistically evaluated by the Student and Mann-Whitney test. Tachycardia (86.3±2.7 beats.min⁻¹), shortening of both QRS (79.9±1.6 ms) and QT (349.0±5.9 ms) and increased QT dispersion (115±36 ms) were observed in DM 1 when compared with the controls (75.0±2.1 beats. min.⁻¹, QRS 89.9±2.7 ms, QT 374.0±4.4 ms, QTd 34.0±12.0 ms, p<0.01). The QTc was 415.2±4.1 ms in DM 1 and 401.4±6.6 ms in controls (NS). Other significant findings in DM 1 were: higher maximum of depolarization isopotential maps (DIPMmax) in the initial phase of QRS and less positive in the terminal phase, more negative minimum (DIPMmin) during QRS similarly as the minimum in depolarization isointegral maps (DIIMmin) and the minimum in isointegral map of the Q wave (Q-IIMmin), lower maximum in repolarization isopotential maps (RIPMmax) and less negative minimum (RIPMmin), more negative amplitude of Q wave (Q-IPMAM) and more pronounced spread of depolarization (activation time). Our results confirmed a decreased parasympathetic to sympathetic tone ratio (tachycardia, shortening of the activation time) and revealed different depolarization and repolarization patterns in DM 1. The differences in heart electric field parameters measured by the BSPM method in DM 1 and in the controls indicate the importance of ECG examination of diabetic patients type 1 in the prevention of cardiovascular diseases.

Key words
Diabetes mellitus type 1 • ECG • VCG • Body surface maps

Introduction
Diabetes mellitus is associated with poor cardiovascular prognosis (Kannel et al. 1986, Charvát 2001). The diagnosis of type 1 diabetes mellitus is usually established at a relatively young age. The
development of macrovascular changes therefore takes many years (Alberti and Zimmet 1998, Beckman et al. 2002, Pickup and Williams 2003). Twelve leads resting electrocardiogram is often falsely negative in diabetic patients with coronary artery disease (Zellweger and Pfisterer 2001). Although certain examinations might be of importance (e.g. echocardiography, carotid sonography), the stress test is often necessary for myocardial ischemia detection in asymptomatic patients (Paillole et al. 1995, Charvát et al. 2004). Apart from cardiovascular morbidity type 1 diabetes mellitus is associated with microvascular complications including autonomic neuropathy (Alberti et al. 1978). The lengthening of QTc (QT corrected for heart rate) in the ECG was observed in patients with diabetes mellitus type 1 (DM 1) both with and without autonomic neuropathy suggesting that autonomic dysfunction does not contribute to hypoglycemia-induced QTc prolongation (Heller 2002).

The blood pressure variability in DM 1 patients is lower than in the controls (Ruzicska et al. 2003). The impaired parasympathetic control of heart rate was observed. No differences in vascular sympathetic control were detected (Javorka et al. 2005).

The insulin hypoglycemia in DM 1 patients causes an abnormal electrocardiogram with an increase in the QT interval and its dispersion (Heller 2002). The abnormalities in cardiac repolarization indicate a risk of ventricular tachycardia and sudden death in DM 1 patients (Marques et al. 1997). In the present report, we studied the electrocardiogram, vectorcardiogram and body surface mapping in asymptomatic DM 1 patients with the aspect to prevent cardiovascular diseases. The preliminary results have been presented elsewhere (Štěpánková et al. 2006).

Patients and Methods

Patients

Twenty-two DM 1 patients examined in 2005 and 22 healthy control subjects have been included in the study (Table 1). The duration of diabetes mellitus type 1 was 13.9±9.8 years. The diagnosis of diabetes mellitus type 1 was based on the WHO criteria (Alberti and Zimmet 1998).

The DM 1 patients were treated with insulin applied either by a continuous subcutaneous injection (CSII) or by insulin applicators in an intensive insulin therapy. They were without any known microvascular or macrovascular complications. Their 12 leads ECGs were within normal limits. Apart from insulin, no medication was applied to the patients and healthy controls. We recorded the duration of type 1 diabetes mellitus and its long-term metabolic compensation. The long-term metabolic compensation of diabetic patients evaluated by HbA1c according to IFCC was 6.5±1.3 %. The average total daily insulin dosage was 46.6±10.4 IU and was applied by CSII in 7 patients and by insulin applicators in intensive insulin therapy in 14 patients.

Measurements

The electrocardiogram (ECG), vectorcardiogram (VCG) and body surface potential maps (BSPM) – isopotential, isointegral and isoarea maps – were registered altogether using the diagnostic system CARDIAG 112.2 (Pišvejcová et al. 2002). All examinations were performed in the morning between 9 to 11 h in order to avoid any influence of circadian rhythms (Švorc et al. 1994, 2000). Heart rate, duration of PQ, QRS, QT and QTc intervals were recorded and evaluated by 12-lead ECG.

In the VCG evaluation the Frank orthogonal lead system was used (Frank 1956). The QRS axis deviation in frontal plane was measured. The QRS-STT angles in the frontal, transversal and left sagittal planes and the shape of QRS loops were registered.

For evaluation of the QT dispersion (QTd) the QT interval was measured by 80 unipolar chest leads used for body surface potential mapping. The QT interval was measured from the start of the Q wave to the end of the T wave. QT dispersion was then defined as the difference between the maximal and minimal QT interval in any of the leads measured.

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 (BSPM). Depolarization isoarea
maps, their maximum and minimum in μVs (isointegral maps from the beginning of QRS until 40 ms – DIAM max 40, DIAM min 40) and depolarization areas and their maximum and minimum in μVs (isointegral maps from the point J to 40th ms – RIAM max 40 and RIAM min 40) were also examined. Isointegral minimum (Q-IIM) and amplitude (IPMAM-Q) of the Q wave as well as QT duration in chest electrodes during BSPM measurement were compared between DM 1 patients and the healthy controls. 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.

Statistical comparison was performed by Student’s t-test and Mann-Whitney test.

Results

The results of 12 leads ECG are shown in Table 2. The heart rate in DM 1 patients was increased (p<0.002), QRS and QT interval shortened (p<0.009; p<0.001) and QTd increased (p<0.001) in comparison with the controls. The Qtc interval (QT corrected for the heart rate) was not significantly prolonged in DM 1 patients.

Significant differences in the parameters of heart electric field between diabetic patients and control subjects during BSPM measurements are presented in Table 3. The absolute value of the maximum (extremum) in depolarization isopotential maps (DIPMmax) from the beginning of Q wave until the 30th ms of the QRS was more positive in DM 1 patients than in the controls (DIPMmax 30). But this parameter was less positive in the later phase of QRS (40th-80th ms of QRS – DIPMmax 50 in Table 3). The minimum (extremum) in DIPM maps (DIPMmin) was more negative in DM 1 patients than in the controls during QRS.

The more negative minimum of depolarization isoarea map maximum from the beginning of Q wave until the 40th ms of depolarization (DIAMmax 40) was higher in DM 1 patients (18.9±1.5 μVs) than in controls (14.3±0.9 μVs, p<0.01). This finding has well corresponded to the DIPMmax values. The depolarization isoarea map minimum (DIAMmin 40) was more negative in DM 1 patients (−11.6±2.2 μVs) than in controls (−6.5±4.6 μVs, p<0.001) similarly as the DIPMmax and DIIMmax. The minimum in isointegral map of Q wave (Q-IIMmin) was more negative in DM 1 patients (−22.8±2.9 μVs) than in controls (−15.1±1.2 μVs, p<0.03) similarly as the minimum in DIPM and DIIM maps. The amplitude of the Q wave (Q-IPMAM) was more negative in DM 1 patients (−861.0±92.1 μV) than in controls (−634.0±49.2 μV, p<0.03). The activation time (ICHVAT), the speed of activation of the heart measured on the surface of thorax, was faster in DM 1 patients (63.2±1.2 ms) when compared to controls (70.5±2.0 ms, p<0.01 in Table 3).

Table 2. Heart rate, PQ, QRS, QT, QTd and QTc in controls and DM 1 patients

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Mean ± S.E.M.</th>
<th>Mann-Whitney</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart rate (min.⁻¹)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>controls</td>
<td>22</td>
<td>75±2.11</td>
<td>113</td>
<td>0.002</td>
</tr>
<tr>
<td>DM 1</td>
<td>22</td>
<td>86.32±2.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PQ (ms)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>controls</td>
<td>22</td>
<td>158.3±7.09</td>
<td>219</td>
<td>NS</td>
</tr>
<tr>
<td>DM 1</td>
<td>22</td>
<td>147.9±3.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>QRS (ms)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>controls</td>
<td>22</td>
<td>89.9±2.67</td>
<td>131</td>
<td>0.009</td>
</tr>
<tr>
<td>DM 1</td>
<td>22</td>
<td>79.9±1.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>QT (ms)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>controls</td>
<td>22</td>
<td>374.0±4.4</td>
<td>101.5</td>
<td>0.001</td>
</tr>
<tr>
<td>DM 1</td>
<td>22</td>
<td>349.0±5.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>QTc (ms)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>controls</td>
<td>22</td>
<td>415.2±4.1</td>
<td>234.5</td>
<td>NS</td>
</tr>
<tr>
<td>DM 1</td>
<td>22</td>
<td>34±12</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>QTd (ms)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>controls</td>
<td>22</td>
<td>115±36</td>
<td>104</td>
<td>0.001</td>
</tr>
<tr>
<td>DM 1</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are means ± S.E.M.
This could well be explained by an activation of the sympathetic nervous system.

The repolarization isopotential map maximum (RIPMmax) was less positive and minimum (RIPMmin) less negative in DM 1 patients than in the controls (Table 3) showing the different rate of repolarization in DM 1 patients during the T wave.

The QT interval was significantly shortened in all 96 thorax leads in DM 1 patients than in the controls thus confirming the activation of the sympathetic nervous system (data not shown).

**Discussion**

Our results showed the tachycardia, shortening of the QRS and QT intervals and increase of the dispersion of QT interval (Table 2) in DM 1 patients without cardiovascular complications. The prolongation of QTc was nonsignificant probably due to the small number of diabetic patients. Our work confirmed the previous findings registered by the classic 12-leads ECG (Pilati et al. 1981, Krahulec et al. 2002). The decrease in T wave amplitude in DM 1 patients (Krahulec et al. 2002) was confirmed in our results by the lower value of maximum and minimum in repolarization isopotential maps (RIPMmax, RIPMmin) in DM 1 patients in comparison with controls (Table 3). Unfortunately, we have no possibility to compare our present results obtained by measuring of heart electric field parameters using the BSPM method in DM 1 patients with another work in the literature (except of the 12-leads ECG) as we were the first who used this method for evaluating heart electric field in DM 1 patients.

The BSPM method was used in the ontogeny of healthy humans (Slavíček et al. 2001), in coronary artery disease (Kittnar et al. 1993), in hypertension (Tichý et al. 2001), or in depressive patients treated with antidepressants (Slavíček et al. 1998, Paclt et al. 2003, Kitzlerová et al. 2003, Kittnar et al. 2004), in panic disorder before treatment (Pišvejcová et al. 2002), or in late pregnancy and after delivery (Lechmanová et al. 2002).

The similar results of heart electric field parameters which we have obtained in the present work in DM 1 patients were also observed in the depressive patients treated with the tricyclic antidepressants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls (n=22)</th>
<th>DM 1 (n=22)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIPMmax 10 (µV)</td>
<td>96.09±11.3</td>
<td>122.64±7.9</td>
<td>0.008</td>
</tr>
<tr>
<td>DIPMmax 30 (µV)</td>
<td>722.5±52.6</td>
<td>965.6±79.9</td>
<td>0.023</td>
</tr>
<tr>
<td>DIPMmin 40 (µV)</td>
<td>-829.6±131.3</td>
<td>-1468.7±164.9</td>
<td>0.001</td>
</tr>
<tr>
<td>DIPMmax 50 (µV)</td>
<td>1108.4±108.2</td>
<td>815.8±78.9</td>
<td>0.046</td>
</tr>
<tr>
<td>DIPMmin 50 (µV)</td>
<td>-1160.4±531.9</td>
<td>-1510.0±110.8</td>
<td>0.03</td>
</tr>
<tr>
<td>DIIMmin (µVs)</td>
<td>-33.6±4.3</td>
<td>-48.1±4.</td>
<td>0.01</td>
</tr>
<tr>
<td>RIPMmax 10 (µV)</td>
<td>168.8±26.1</td>
<td>119.14±21.2</td>
<td>0.017</td>
</tr>
<tr>
<td>RIPMmin 30 (µV)</td>
<td>-327.9±193.3</td>
<td>-96.9±11.6</td>
<td>0.041</td>
</tr>
<tr>
<td>RIPMmin 90 (µV)</td>
<td>-313.4±133.2</td>
<td>-143.0±19.8</td>
<td>0.029</td>
</tr>
<tr>
<td>RIPMmax 100 (µV)</td>
<td>248.3±38.9</td>
<td>142.0±12.6</td>
<td>0.013</td>
</tr>
<tr>
<td>RIPMmin 100 (µV)</td>
<td>-289.2±122.7</td>
<td>-119.0±23.3</td>
<td>0.006</td>
</tr>
<tr>
<td>DIAMmax 40 (µVs)</td>
<td>14.2±0.92</td>
<td>18.9±1.51</td>
<td>0.011</td>
</tr>
<tr>
<td>DIAMmin 40 (µVs)</td>
<td>-6.5±1.0</td>
<td>-11.6±2.25</td>
<td>0.001</td>
</tr>
<tr>
<td>Q-IIM (µVs)</td>
<td>-15.0±1.17</td>
<td>-22.8±2.82</td>
<td>0.039</td>
</tr>
<tr>
<td>Q-IPMAM (µV)</td>
<td>-634.2±49.2</td>
<td>-861.2±92.1</td>
<td>0.038</td>
</tr>
<tr>
<td>ICHVAT (ms)</td>
<td>70.4±2.0</td>
<td>63.2±1.5</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Data are mean ± S.E.M. DIPMmax, DIPMmin - maximum, minimum in depolarization isopotential map (µV), RIPMmax, RIPMmin – maximum, minimum in repolarization 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. Q-IPMAM – maximum 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).
(Slaviček et al. 1995, 1998, Paclt et al. 2003, Kitzlerová et al. 2003) or in panic disorder (Pišvejcová et al. 2002) due to activation of the sympathetic nervous system. On the other hand, ontogenic changes of the heart rate (the bradycardia in older healthy humans) have been characterized by different alterations in the parameters of heart electric field (Slaviček et al. 2001) than in the present work. The vectorcardiographic parameters were unchanged in our present work although the effect of dosulepine caused a deviation of the QRS axis (Kitzlerová et al. 2003) due to activation of the sympathetic nervous system.

QTd was evaluated using the method of BSPM. The decision to use a greater number of leads for the determination of QT dispersion helps to determine the QTd more accurately than the assessment with only 12 or even 6 precordial leads. The use of a low number of leads was undoubtedly the main cause of the repeatedly suggested poor reproducibility (Kautzner et al. 1994, Day et al. 1990). Enhanced accuracy for QT dispersion assessment from a 12-lead ECG in comparison with only 6 precordial leads was also reported (van de Loo et al. 1994, Higham and Campbell 1994).

Measurements performed in the present study indicate that type 1 diabetes causes an increase in the QT dispersion even in diabetic patients without any clinically evident microvascular and/or macrovascular complications. This finding is in agreement with that from our previous study (Lechmanová et al. 2002), where QT dispersion was measured using the same method on healthy female volunteers in a late phase of pregnancy. In the above study, we concluded that QT dispersion can reflect not only an increased risk of serious tachyarrhythmias, especially due to myocardial ischemia, but it can also be increased physiologically by a changed spatial arrangement of the chest organs, including the heart. In the present study, the results are very similar but, in the latter case, we suppose that the increased QT dispersion is a non-specific sign of a changed course of repolarization, which could reflect the changes in the tone of autonomic nervous system.

The non-specificity of QTd is supported by the fact that it corresponds to the dispersion of T wave amplitude (Havránek et al. 2004). We suppose that changed T wave shape does reflect the same abnormality as QTd does, as both of them could be non-specific signs of an attenuated repolarization pattern (and flattening of T wave is well known non-specific sign of a defective course of repolarization).

Diabetes mellitus can be considered as a vascular disease because it causes both microvascular and macrovascular complications. It is one of the most common chronic diseases in the world (Nathan et al. 1997). Cardiovascular diseases account for at least 66 % of deaths in diabetic patients (Zimmet and Alberti 1997). Due to the sensitive neuropathy, the coronary artery disease in diabetic patients is frequently asymptomatic (Langer et al. 1991). This fact underlines the importance of laboratory testing. Twelve ECG leads at rest can be within normal limits even in an advanced stage of coronary artery disease (Wackers et al. 2004). Therefore, the stress test may play an important role in detection of significant coronary stenosis (Bigi et al. 2001, DeLorenzo et al. 2002). In this respect BSPM may be a useful tool in coronary ischemia diagnosis, however, there is not yet any available BSPM in asymptomatic diabetic patients.

In our present study, we have studied DM 1 patients without any clinically evident microvascular and/or macrovascular complications. These patients represent a group of young people with a very low probability of asymptomatic coronary artery disease. ECG changes including BSM results in our diabetic patients should therefore be interpreted carefully. Heart rate acceleration, shortening of QRS and QT intervals, significant changes of depolarization and repolarization in BSPM measurement can be explained by activation of the adrenergic system in diabetic patients and compared to nondiabetic subjects. The augmented sympathetic nervous activity is one of the assumptions for the development of arrhythmias and changes of ventricular repolarization (Abildskov 1985). However, no diabetic patients in our group fulfilled the criteria for autonomic neuropathy defined by the Ewing test or by a heart rate variability study (Alberti and Zimmet 1998).

The influence of autonomic neuropathy and of the left ventricle mass on BSPM should be addressed in future studies because these situations are frequently seen in diabetic patients. Finally the position of BSPM in coronary ischemia detection may be appreciated in asymptomatic diabetic patients with resting 12 leads ECG within normal limits using its association with the stress test (e.g. stress myocardial SPECT) or with coronary angiography.

It could be concluded that our results have confirmed a decreased parasympathetic to sympathetic tone ratio (tachycardia, shortening of the activation time) and revealed different depolarization and repolarization patterns in DM 1 patients. The differences in heart
electric field parameters measured by BSPM method in DM 1 and in the controls show the importance of ECG examination of DM 1 patients in the prevention of cardiovascular diseases.

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