Assessment of body surface potential mapping in diabetic patients with recognized depression

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Abstract

OBJECTIVES: Parameters of body surface potential mapping (BSPM) in DM II patients are significantly different comparing with healthy non-diabetic subjects. Hypothesis that these changes are more pronounced in DM II patients with depression was tested in the present study. For this purpose, analysis of the relationship between the Int-QRST (isointegral) maps distribution and the depressive symptoms intensification, as well interrelation between depressive and diabetic symptoms were performed.

MATERIAL AND METHODS: BSPM registrations were obtained from the three study groups (aged 37–52 years), namely 40 diabetic patients with clinically documented depression, 30 depressive patient without DM and 90 normal subjects. BSPM recordings were displayed in a form of the Int-QRST maps. Examination with BDI and HbA1c test were also performed in all investigated subjects.

RESULTS: Isointegral QRST maps turned out to display abnormal, i.e. non-dipolar distribution. Moreover, extent of Int-QRST maps multipolarity increased in the examined diabetic patients along with DM II duration, BDI scores and HbA1c level.

CONCLUSIONS: Non-dipolar distribution of Int-QRST maps, more pronounced in diabetic patients with depression, can be a specific indicator of the increased risk of severe ventricular arrhythmias occurring prior to abnormalities detectable on the standard 12-lead ECG recordings, which is of great importance especially in prevention of life-threatening arrhythmias.

Abbreviations:
BSPM - body surface potential mapping
DM - diabetes mellitus
DM II - diabetes mellitus type II
ANS - autonomic nervous system
DN - diabetic neuropathy
nAch receptor - nicotinic acetylcholine receptor
ROS - reactive oxygen species
Int-QRST - isointegral QRST maps
BDI - Beck Depression Inventory
HbA1c - glycated hemoglobin
INTRODUCTION

In patients with diabetes mellitus (DM), depression is common and associated with not only worse health-related quality of life, recurrent cardiac events, but also higher mortality. Depression affects one in four individuals with DM and shows a three-fold more frequent incidence with DM of both types, as compared with general population (Cezaretto et al. 2016; Lamers et al. 2008). In our previous study, we stated that depressive patients are more susceptible to DM occurrence than normal subjects (Janocha et al. 2009). Relations between the mentioned two diseases has pathophysiological background, especially concerning autonomic nervous system functioning (ANS). Diabetes mellitus can be complicated by autonomic neuropathy, and, on the other depression, can be complicated by autonomic disorders with relatively increased sympathetic control, as a result of decreased vagal tone (Servant et al. 2009).

Diabetic neuropathy (DN) can affect autonomic nerve fibers in any part of the body, contributing to decreased quality of life in patients with DM. Severity of symptoms increases gradually over time and correlate with the degree of hyperglycemia (Han et al. 2013; Verrotti et al. 2009). Pathogenesis of DN has been widely studied over the past 20 years, nevertheless, the definite pathogenesis remains unclear. Among many factors, two are well-known: metabolic and vascular, and both are involved at all stages of DN.

Microvascular dysfunction in the nerve and decreased endoneurial perfusion with endoneurial hypoxia are thought to contribute to neuropathy. Investigations on biopsy material from patients with DN show structural changes in nerve microvasculature including basement membrane thickening and endothelial cell hyperplasia. Arterio-venous shunting also contributes to reduced endoneurial perfusion. These vascular changes strongly correlate with clinical defects and nerve pathology (Cameron et al. 2011).

Among metabolic factors, hyperglycemia is a very important, but not the only factor influencing a progression of DN. Intracellular hyperglycemia causes excessive reactive oxygen species (ROS) production. Increased ROS depres autonomic ganglion synaptic transmission by oxidizing the nAch receptor α3 subunit, potentially contributing to the increased risk of fatal cardiac arrhythmias associated with diabetic cardiac autonomic neuropathy (Shah & Brownlee 2016). With autonomic neuropathy, also impaired insulin signaling, dyslipidemia, obesity, and growth factor deficiency are correlated (Han et al. 2013). Neurotrophic effects of insulin, promoting neuronal growth and survival. Insulin resistance in type 2 DM, leads to reduced neurotrophic signaling and contributes to the pathogenesis of DN (Kim et al. 2012). Dyslipidemia is linked to DN, e.g. free fatty acids directly cause damage to Schwann cells (in vitro), they also have systemic effects such as promoting inflammatory cytokine release, as well cho-
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BSPM in diabetic patients with depression showed the apparent, reliably documented symptoms and signs of depression varying in degree of severity. Diabetic patients were under treatment with oral hypoglycemic agents or with addition of insulin injections (once a day). In turn, all group II patients had depression but without DM and constituted a specific reference for group I.

The results of the investigations in the patients group (I, II) were referred to the outcomes obtained from the control group (group III) comprising 90 healthy, age and sex-matched volunteers (55 females and 35 males, mean age 39.89±4.56 years) with no history of DM and no episodes of depression in history.

Methods
In the all study persons, the recordings of BSPM were performed using a specialized HPM-7100 Fukuda Denshi Co. system (Japan) composed of the central unit, microprocessor HP-710, 16-inch screen and preamplifier IB-300. The system performs the simultaneous registrations from the 87 specific mapping leads. A frequency of the ECG signals sampling was 1000 samples/s for each of the used channels (Fukuda Denshi, 1990). The electrode standardized array was applied using one-use electrodes placed on 13 adhesive strips mounted in rows on the anterior and posterior thoracic surfaces (designated on the maps the letters A to M), as displayed in Figure 1.

In this study data, waveforms collected from the 87 ECGs were graphically presented as Int-QRST maps, which represent a resultant of the all instant potentials within the cardiac cycle. This sort of maps reduces significantly an abundant load of the ECG information provided by the basic isopotential maps.

The self-assessment charts, like Beck Depression Inventory (BDI) used in the present study, are considered to be of great usefulness in establishing a diagnosis of depression. The examined subject is requested to complete the questionnaire that consists of 22 issues; for each of the questions one can choose only one answer (yielding 0–3 scores). It is assumed that outcome of the whole test exceeding 12 scores indicates depression.

Also a measurement of glycated hemoglobin (HbA1c), as a most reliable index of diabetic control, was performed.

The investigation protocol was approved by the local Bioethics Committee at Wroclaw Medical University.

Statistical analysis
Standard statistical Student t-test was applied for comparison of the two variables. The values are presented as the mean±SD, and a level of statistical significance was set at p<0.05. Non-parametric data was given as the absolute numbers or percentages.

RESULTS
Diabetic patients (group I) were divided into three subgroups (IA, IB, IC) depending on their HbA1c and the BDI scores. Depressive patients without DM (group II) were divided into two subgroups (IIA, IIB) according to the BDI scores. Characteristics of these groups, subgroups and the control group III are compiled in Table 1 and 2.

![Fig. 1. Scheme of electrodes placements on the thoracic surfaces.](image)

Tab. 1. Characteristics of the diabetic patients from the subgroups IA–IC.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Subgroup IA (N=17)</th>
<th>Subgroup IB (N=13)</th>
<th>Subgroup IC (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c %Hb</td>
<td>6.6±0.33%</td>
<td>8.1±0.6%</td>
<td>12.9±0.71%</td>
</tr>
<tr>
<td>DM type II</td>
<td>1–5 years</td>
<td>&gt;5–10 years</td>
<td>&gt;10 years</td>
</tr>
<tr>
<td>duration</td>
<td>mean 2.58±1.57</td>
<td>mean 7.38±1.54</td>
<td>mean 11.8±1.2</td>
</tr>
<tr>
<td>Depression symptoms</td>
<td>None</td>
<td>Single moderate depressive episodes</td>
<td>Recurrent depressive episodes incl. MDD</td>
</tr>
<tr>
<td>BDI</td>
<td>8.53±1.01 scores</td>
<td>16.8±0.92 scores</td>
<td>27.2±1.56 scores</td>
</tr>
<tr>
<td>Arrhythmias on conventional ECG</td>
<td>Single atrial and/or ventricular extrasystoles</td>
<td>Benign atrial and/or ventricular arrhythmias</td>
<td>Moderate atrial and/or ventricular arrhythmias</td>
</tr>
</tbody>
</table>
Percentage contribution of HbA1c and the mean value of BDI scores showed a clear tendency to increase gradually within the subgroups IA–IC and differences between subgroups were statistically significant ($p<0.001$).

Body surface heart potential mapping showed a high sensitivity with regard to local changes of the cardio-electrical field. The long-term investigations carried out in Department of Pathophysiology of Wroclaw Medical University were aimed at establishing the patterns of the isopotential maps for normal subjects. Next, the isointegral maps for the entire cardiac cycle (Int-QRST), averaged for this normal subjects, were elaborated. In the group-mean Int-QRST map established for this population, a typical dipolar distribution was observed (Figure 2).

In the control group, the mean value of potential maximum was 82.3 $\mu$V•sec and the mean values of potential minimum was of $-50.3\;\mu$V•sec. In this control group, a dipolar distribution of Int-QRST map was observed, with two extrema: one positive located at G2 and one negative located at E7.

What is of interest, a method of BSPM showed an abnormal potential distribution of Int-QRST maps...
in the subgroups of group I and group II who suffered from a feeling of heart palpitations. Quantitative parameters of Int-QRST maps are compiled in Table 3 and 4.

The subsequent figures show the examplatory multipolar Int-QRST maps obtained from patients in group I (Figure 3) and in group II (Figure 4).

Comparison of qualitative parameters presented on these maps with the pattern map are compiled in Table 5.

Mean numbers of extrema values showed a clear tendency to increase gradually with the BDI scores and percentage of HbA1c. These relationships for groups I and II are presented respectively on Figures 5 and 6.

**DISCUSSION**

Diabetes increases by 2–4-fold the risk of cardiac events, including arrhythmias. A high risk of developing arrhythmias in diabetics results from metabolic disorders and chronic vascular complications. Diabetic heart diseases, especially cardiac autonomic neuropathy, generate within the myocardium arrhythmogenic substrates that could initiate ventricular arrhythmias (Abildskov & Greek 1987; Landsberg & Molitch 2004).
Predominance of the sympathetic activity, being a result of reducing the vagal tone, is observed in depression. Regardless of the cause, autonomic dysregulation is associated with the higher risk of cardiac events (Palová et al. 2010). These events are especially pronounced in diabetic patients simultaneously suffering from depression.

The exact analysis of percentage contribution of HbA1c confirmed DM in all examined subgroups of the group I, but a careful review of the BDI outcomes let us diagnose a depression only in subgroups IB and IC (Tab. 1). These results were referred to the control group III, where BDI (6.9±1.95 scores) and HbA1c (4.8±1.72%) were significantly lower (p<0.001) than in the discussed subgroups. The results of BDI and HbA1c obtained in the control group let us exclude a diagnosis of depression and DM (Table 2). None of the control subjects reported any depressive episode in the past. Like other parameters of group I, the mean DM II duration had a similar growing tendency within the subgroups IA–IC (Tab. 1) and the difference between these subgroups was also statistically significant (p<0.05). However, this parameter could not be assessed with reference to the control group, because there were only healthy subjects there. In the subgroups IIA and IIB, the results of HbA1c enabled to exclude a diagnosis of DM. No statistically significant differences in the percentage of HbA1c were observed between the subgroups IIA and IIB and also between them and the control group. In the mentioned subgroups, the results of BDI let us diagnose a depression (Table 2). In this case, the difference between the two patient subgroups and also between them and control group was statistically significant (p<0.001).

The analysis of results obtained in the present study demonstrated that BSPM method showed a higher sensitivity with regard to local changes of the cardio-electrical field in the diabetic patients (group I), who suffered mainly from a feeling of heart palpitations. In this group, multipolar distribution of Int-QRST map was observed. Recent findings strongly suggested that such multipolar distribution is considered a reflection of the local ventricular repolarization heterogeneity, undetectable on the standard 12-lead ECG, which indicates an increased risk of serious ventricular arrhythmias (Zdárská et al. 2007, Palová et al. 2010, Janocha 2012, Žákovičová et al. 2014). Multipolar distribution occurred even in the early stage of DM II (subgroup IA) with the mean DM duration of 2.58±1.57 years and without arrhythmias detectable on conventional ECG. The similar results were obtained by Palová et al. (2010). In subgroup IA, 64.7% of the analyzed Int-QRST maps revealed the abnormal distribution with the mean value of extrema of 2.82±0.73 (Table 3). These results were significantly higher (p<0.001) than results obtained in the control group, in which only 2.2% of the analyzed Int-QRST maps revealed the multipolar distribution with mean values of extrema of 2.02±0.15 (Table 4), however 97.8% of Int-QRST maps obtained in the control group were normal with a bipolar distribution (Figure 2). In the remaining two subgroups of group I, the abnormal distribution of Int-QRST maps was observed. In subgroup IB, 76.9% of the analyzed maps revealed multipolar distribution, whereas in subgroup IIC 80%, with the mean values of extrema, respectively, 3.46±1.13 and 4.3±1.64 (Table 3). These results were significantly higher than results obtained in the control group (p<0.001).

In the group I, the statistically significant differences in the number of potential extrema were ascertained between subgroups IA and IB (p<0.04), and subgroups IA and IC (p<0.002). The difference between subgroup IA and subgroups IB and IC was that the subjects of subgroups IB and IC suffered from depression apart from DM II. The results presented suggest that depression should be considered as another significant risk factor for the local heart ventricular repolarization dispersion. Moreover, depression had a negative influ-
ence on the glycaemia self-control quality in diabetic patients (Table 1). In the subgroups IA-IC, the mean numbers of extrema values showed a clear tendency to increase gradually with the BDI scores and percentage of HbA1c (Figure 5) and revealed statistically significant positive correlation with BDI and HbA1c (with p<0.001). It should be noticed that poor glycaemia control and presence of additional aggravating factors, such as depression (BDI scores) or DM mean duration, may cause mutual interactions leading to multipolarity of Int-QRST maps even in an early stage of DM.

In the subgroups of group II (IIA and IIB), the mean numbers of extrema values also showed a clear tendency to increase gradually with the BDI scores and percentage of HbA1c (Figure 6), but positive correlation was statistically significant only with BDI scores (with p<0.001).

The most number of extrema, meaning the largest susceptibility to arrhythmia, was found in the patients of subgroup IC – with a diagnosis of DM II coupled with depression (Table 3). These individuals reported the most intensive heart palpitations and moderate atrial and/or ventricular arrhythmias on standard 12-lead ECGs (Table 1). Multipolarity of Int-QRST maps but with the significantly smaller extrema number was also observed in the patients of subgroups IA and IB. In these subjects, heart palpitations were not a serious complaint and only in subgroup IB, benign atrial and/or ventricular arrhythmias were observed in standard ECGs (Table 1). Finally, in the persons with DM II and without depression (subgroup IA), standard ECGs presented normal recordings.

In the diabetic patients, as compared with the control map, the statistically significant differences were found concerning the values of extrema. In the subgroups IA–IC, higher maxima and less negative minima were observed, which also suggested an increased arrhythmogenicity in these subgroups (Table 3). Also other authors emphasized that fact (Zdárská et al. 2000, Piszvejcová et al. 2002, Palová et al. 2010). Similar outcomes were observed in the subgroups IIA and IIB (Table 4). Nevertheless, the highest maxima and the least negative minima were observed in the subgroup IA.

The results presented above clearly show that concomitance of DM II and depression may cause mutual interaction leading to non-dipolar distribution of Int-QRST maps. What more, both DM II and depression cause autonomic disorders with relatively increased sympathetic control (Servant et al. 2009). Non-dipolar distribution of QRST isointegral maps can be a specific indicator of increased risk of severe ventricular arrhythmias occurring prior to abnormalities detectable on standard 12-lead ECG recordings, which is of great importance especially in prevention of malignant life-threatening arrhythmias. Analysis of qualitative parameters showed that in group I and II, the extremum locations of Int-QRTS maps were different from the reference map (Figures 2–4; Table 5). This phenomenon reflects a heterogeneity of the refractory periods of the ventricles, which is supposed to account for creating a substrate for life threatening arrhythmias. Similar results were noticed by Palová et al. (2010).

Results obtained in the present study revealed different depolarization and repolarization patterns in DM II, especially in the patients with concomitant depression. The differences in heart electric field parameters measured by the BSPM method in diabetic patients and in the controls indicate importance of BSPM examination in the prevention of arrhythmia events.

Authors of this paper also emphasized the importance of correctly conducted glycemic control. The present study probably does not cover all aspects of the problem, nevertheless, a widening of knowledge on emotional factors acting as triggers for the ventricular arrhythmias can contribute to searching new therapeutic solutions and better prevention of the cardiovascular disease. Holistic care of the patients, taking into account somatic and psychiatric aspects of diseases, can avail through improving both health state and quality of life of persons with depression as well of numerous patients with organic diseases.

REFERENCES