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

ORIGINAL ARTICLE

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 depress 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 cholesterol can be oxidized to oxysterol that may cause apoptosis in neurons macrophages (Vincent *et al.* 2011). DN, particularly when it involves loss of autonomic control of the cardiovascular system, typically develops after many years of obesity and other components of the metabolic syndrome (Kalupahana *et al.* 2012).

Regardless of the cause, autonomic dysregulation is associated with the higher risk of cardiac events (Palová *et al.* 2010). As our own studies have shown, the most common reason for cardiac arrhythmias is autonomic nerve dysfunction with predominance of the sympathetic activity, being a result of the vagal tone reducing. It was proved that increased sympathetic activation is observed in both states, depression and DM (Janocha 2012).

Body surface potential mapping (BSPM) is useful method in identifying the arrhythmogenic substrates in the heart and stratifying the individual risk of developing arrhythmias. BSPM, owing to the large number of the recording electrodes placed over the all thoracic surface, enables global and precise sampling of the myocardial potentials. The results of BSPM examinations are displayed graphically in the form of so-called heart maps comprising three types: isopotential, isointegral and isochrone.

In the present study, we have used QRST isointegral maps (a sum of depolarization and repolarization potentials in the entire cardiac cycle). BSPM is of advantage over the conventional ECG in relation to selective assessment of the individual portions of the heart and enables a detection of local electrical events unavailable with the standard precordial leads. BSPM method, holding its unique spatial sensitivity to the regional cardiac events, which is achievable by the large number (87) of the exploring electrodes, could be used as a complementary procedure for detecting local electrical events. Non-dipolar distribution of QRST isointegral maps (Int-QRST), contrary to the normal dipolar one, advocate for heterogeneity of myocardial repolarization and can be a specific indicator of the increased risk of severe ventricular arrhythmias in diabetic patients (Abildskov & Greek 1987; Sobieszczańska *et al.* 2007).

MATERIAL AND METHODS

Subjects

The investigations were performed in the following study groups: the group I with 40 patients (25 females and 15 males, mean age 44.6±4.37 years), the group II with 30 patients (19 females and 11 males, mean age 44.4±4.96 years). Groups I and II recruited from Wroclaw Center for Neurosis Treatment. A disease history was obtained from the all patients of the group I and II, and then every patient underwent a detailed clinical examination and basic laboratory parameters assessment. From the clinical point of view, all patients of the group I had definite DM II diagnosed, with the mean duration of DM of 6.45±4.02 year, and most of them

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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.

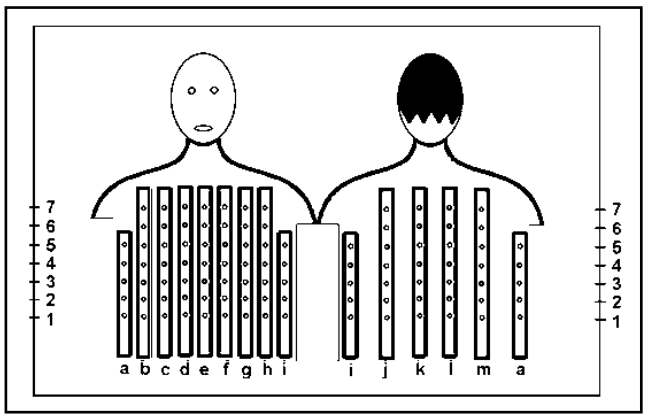

Fig. 1. Scheme of electrodes placement on the thoracic surfaces.

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

Groups	Group I (N=40; mean age: 44.6±4.37 years)		
	Subgroup IA (N=17)	**Subgroup IB** (N=13)	**Subgroup IC** (N=10)
HbA1c %Hb	6.6±0.33%	8.1±0.6%	12.9±0.71%
DM type II duration	1–5 years mean 2.58±1.57	>5–10 years mean 7.38±1.54	>10 years mean 11.8±1.2
Depression symptoms	None	Single moderate depressive episodes	Recurrent depressive episodes incl. MDD
BDI	8.53±1.01 scores	16.8±0.92 scores	27.2±1.56 scores
Arrhythmias on conventional ECG	Single atrial and/or ventricular extrasystoles	Benign atrial and/or ventricular arrhythmias	Moderate atrial and/or ventricular arrhythmias

Tab. 2. Characteristics of the depressive patients from the subgroups IIA, IIB and the control group II.

Groups	Group II (N=30; mean age: 44.6±4.37 years)		Group III (N=90; mean age: 39.89±4.56 years)
	Subgroup IA (N=16)	Subgroup IB (N=14)	
HbA1c %Hb	4.7±1.26%	4.9±1.93%	4.8±1.72%
DM duration	Healthy	Healthy	Healthy
Depression symptoms	Single moderate depressive episodes	Recurrent depressive episodes incl. MDD	None
BDI	16.2±1.03 scores	27.8±1.82 scores	6.9±1.95 scores
Arrhythmias on conventional ECG	Single atrial and/or ventricular extrasystoles	Benign atrial and/or ventricular arrhythmias	Single atrial and/or ventricular extrasystoles

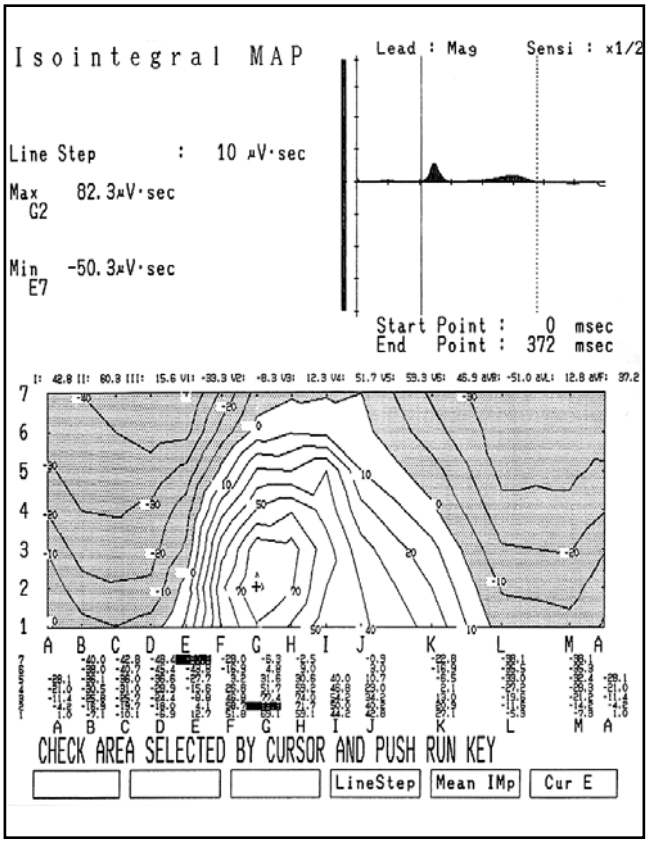

Fig. 2. Int-QRST group-mean map established for the control group.

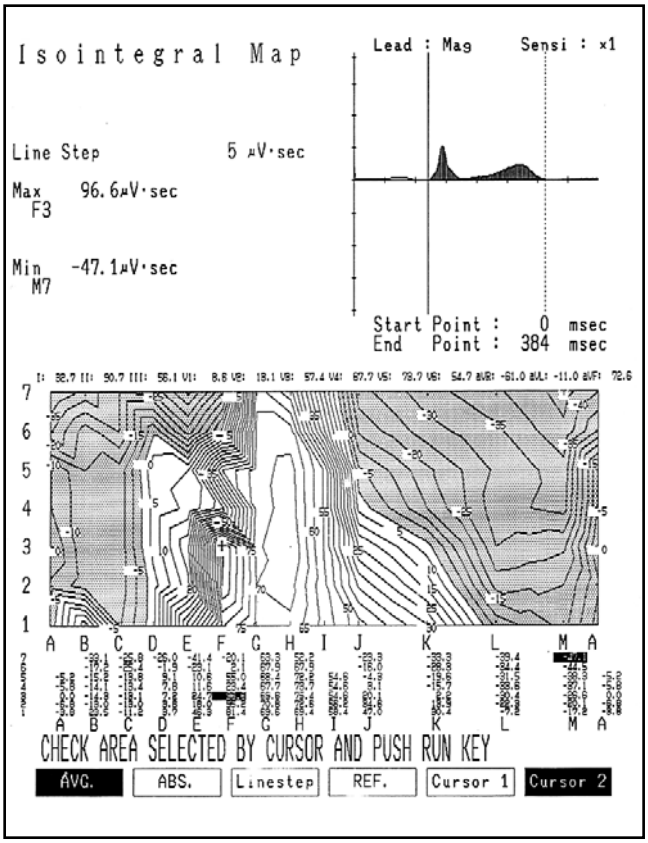

Fig. 3. Multipolar Int-QRST map obtained in group I (6 extrema: 3 positive and 3 negative).

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 cardioelectrical 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 μV•sec and the mean values of potential minimum was of –50.3 μV•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

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Tab. 3. Quantitative parameters of Int-QRST maps obtained in the subgroups IA–IC.

Groups	Group I (N=40)		
	Subgroup IA (N=17)	**Subgroup IB** (N=13)	**Subgroup IC** (N=10)
Number of extrema*	2.82±0.73 (2–4)	3.46±1.13 (2–5)	4.3±1.64 (2–7)
Percentage of multipolar maps	64.7 %	76.9 %	80 %
Mean value of potential max	85.91±11.48 μV•sec	92.68±18.34 μV•sec	98.12±21.57 μV•sec
Mean value of potential min	–45.23±12.21 μV•sec	–39.9±10.86 μV•sec	–37.9±9.87 μV•sec

*Statistical differences between subgroups: IA and IB $p<0.04$; IA and IC $p<0.002$; IB and IC $p<0.08$.

Tab. 4. Quantitative parameters of Int-QRST maps obtained in the subgroups IIA and IIB vs. control group.

Groups	Group II (N=30)		Mean pattern-map established for the control group (N=90)
	Subgroup IIA (N=16)	**Subgroup IIB** (N=14)	
Number of extrema*	2.87±0.72 (2–4)	3.14±1.03 (2–5)	2.02±0.15 (2–3)
Percentage of multipolar maps	68.7 %	78.6 %	2.2 %
Mean value of potential max	85.12±10.89 μV•sec	89.96±12.01 μV•sec	82.3 μV•sec
Mean value of potential min	–47.34±9.12 μV•sec	–42.9±8.64 μV•sec	–50.3 μV•sec

*Statistical differences between subgroups: IIA and IIB $p<0.2$.

Tab. 5. Qualitative parameters of Int-QRST maps obtained in group I, group II vs. reference Int-QRST map.

Location	Group I	Group II	Control group
Potential max	F3	H3	G2
Potential min	C7	D7	E7

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.

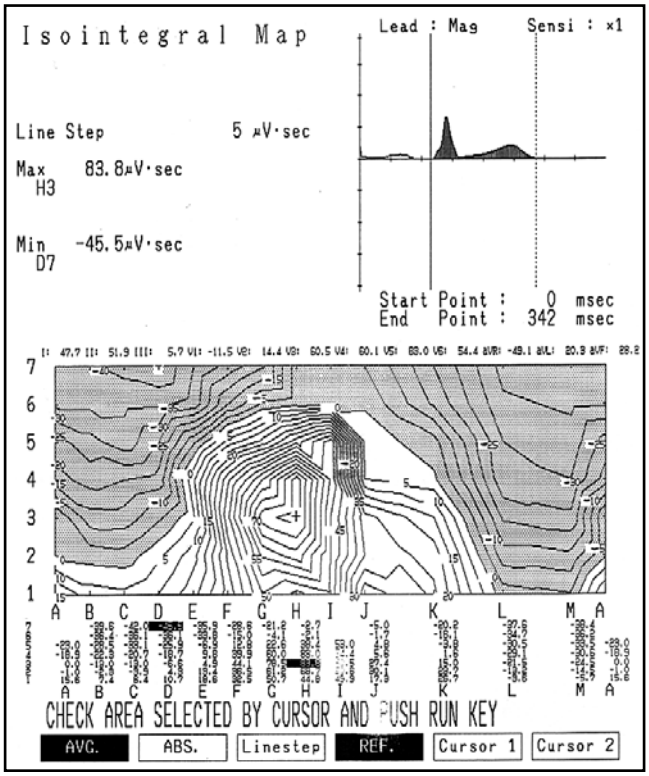

Fig. 4. Multipolar Int-QRST map obtained in group II (4 extrema: 2 positive and 2 negative).

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).

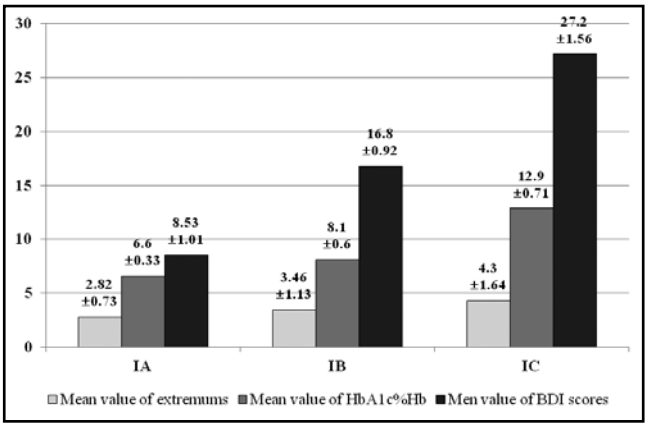

Fig 5. Relationship between the mean numbers of extrema values, BDI scores and percentage of HbA1c in the subgroups IA–IC of the group I. Correlation coefficient between presented data was statistically significant (p<0.001).

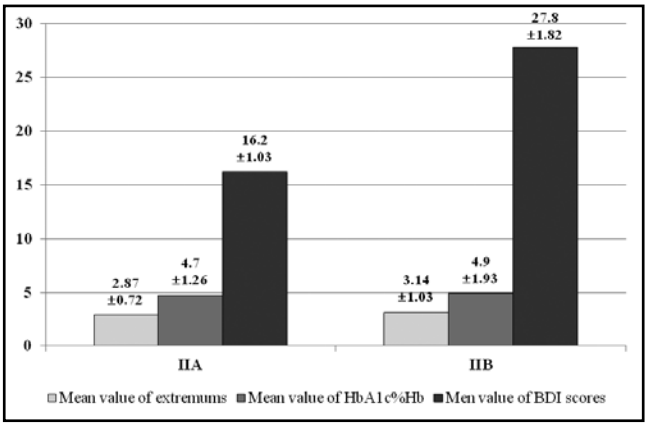

Fig 6. Relationship between the mean numbers of extremum values, BDI scores and percentage of HbA1c in the subgroups IIA and IIB. Correlation coefficient was statistically significant (p<0.001) only between the mean value of extrema and BDI scores.

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 (Table 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 cardioelectrical 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 occured 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-

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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 arrhythmogeneity in these subgroups (Table 3). Also other authors emphasized that fact (Zdárská *et al.* 2000, Pisvejcová *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 concurrence 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 glycaemic 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 psychic 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.

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