

Electrocardiographic changes in Diabetes Mellitus

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Short title: ECG in Diabetes Mellitus

Summary

Diabetes mellitus (DM) has been known for many years to be associated with poor cardiovascular prognosis. Due to the sensitive neuropathy, the coronary artery disease in diabetic patients is frequently asymptomatic. Also twelve leads resting ECG can be within normal limits even in an advanced stage of coronary artery disease. Therefore in addition to the standard ECG other electrocardiographic procedures started to be studied in order to find some typical signs of myocardial damages caused by DM. Repeatedly reported results showed in DM patients without cardiovascular complications the tachycardia, shortening of the QRS and QT intervals, increase of the dispersion of QT interval, decreased amplitudes of depolarization waves, shortened activation time of ventricular myocardium and a flattening of T waves confirmed by the lower value of maximum and minimum in repolarization body surface isopotential maps. Most of these changes are even more pronounced in patients with cardiac autonomic neuropathy. Comparison with similar ECG changes in other diseases suggests that the electrocardiographic changes in DM patients are not specific and that they are particularly caused by an increased tone of the sympathetic nervous system what was indirectly confirmed by the heart rate variability findings in these patients.

Key words

Electrocardiography, ECG Body Surface Mapping, Heart rate variability, Diabetes mellitus

Introduction

Diabetes mellitus (DM) has been known for many years to be associated with poor cardiovascular prognosis (Kannel et al. 1986). As the development of macrovascular changes can take a relatively long time, twelve leads resting electrocardiogram (ECG) fails very often in diagnosis of coronary artery disease in diabetic patients suffering from DM of type 1 (Alberti and Zimmet 1998, Beckman et al. 2002, Zellweger and Pfisterer 2001). Therefore in addition to the standard ECG other electrocardiographic procedures started to be studied in order to find some typical signs of myocardial damages caused by DM.

Apart from cardiovascular morbidity DM is also associated with microvascular complications including autonomic neuropathy (Alberti et al. 1978). The impaired parasympathetic control of heart rate was observed but no differences in vascular sympathetic control were detected (Javorka et al. 2005). 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 1998). 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 (Ruttkay-Nedecky 2001, Javorka et al. 2005). Regardless of fact if DM is or is not complicated with autonomic neuropathy some general abnormalities in electrocardiograms were repeatedly reported in DM patients. Typically impairments of ECG parameters associated with the DM were found in QT region of electrocardiogram.

The QT interval on the electrocardiography reflects the total duration of ventricular depolarization and repolarization, and its measurement has been proposed as a simple and noninvasive method for the cardiovascular mortality in various conditions, including DM (Ewing et al. 1991, Rossing et al. 2001, Maser et al. 2003). Since the QT interval differs inversely with heart rate, heart rate-corrected QT (QTc) interval is preferably used. In patients with DM, QTc prolongation and autonomic dysfunction are closely correlated, and QTc prolongation is considered to be a specific sign of autonomic cardiac dysfunction and high mortality risk (Rossing et al. 2001, Khoharo and Halepoto 2012). The lengthening of QTc 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).

Physiologically, QTc interval prolongation reflects prolonged total duration of ventricular myocardial repolarization. It has been reported that not only hypocalcaemia and medication, but also heart failure and ischemic heart disease are involved in QTc interval prolongation (Breidhardt et al. 2007, Brooksby et al. 1999). The abnormalities in cardiac repolarization can indicate an increased risk of ventricular tachycardia or even ventricular fibrillation (Marques et al. 1997) and moreover, a prolonged QTc interval was found to increase the rates of all causes of death (de Bruyne et al. 1999).

An increase in the QT interval and its dispersion were also proved to be caused by the insulin hypoglycemia in DM 1 patients (Heller 2002).

Also women with gestational diabetes mellitus (GDM) are at increased risk for cardiovascular diseases (CVD) events compared with pregnant women without GDM. Gestational diabetes mellitus is defined as carbohydrate intolerance of varying degrees of severity with onset or first recognition during pregnancy (Metzger and Coustan, 1998) ,which spontaneously improves after delivery or until the end of puerperium. The incidence of GDM occurs in about 3-5 % of all pregnancies and it is often associated with maternal risk factors such as overweight, advanced age, positive family history of DM type 2 and a previously complicated obstetric history. GDM is also associated with a high risk of subsequent development of maternal diabetes later in life (Bellamy et al., 2009; Feig et al., 2008; Kim et al., 2002) and cardiovascular disease (Sullivan et al., 2012).

Standard 12 leads ECG

1. The heart rate

The heart rate was observed to be significantly increased in DM 1 patients in comparison to healthy controls: 86.3 ± 2.7 ms vs. 75.0 ± 2.1 ms (Zdarska et al. 2007). This finding was confirmed later by Palova et al. (2010) who compared electrocardiograms of DM 1 patients with versus without cardiac autonomic neuropathy (CAN). In addition to this finding the study also proved significantly increased heart rate in DM 1 associated with CAN: 92.2 ± 3.0 ms. Increased heart rate in DM 1 patients with CAN have described also Krahulec et al. (2002): 94.9 vs. 79.7 in DM 1 patients without CAN. The significantly increased heart rate was detected from 24 hour Holter ECG also in DM 2 patients in comparison to healthy controls: 80.5 ± 12.7 ms vs. 68.5 ± 10.3 ms (Adebayo et al. 2014). Very similar results were observed in a cohort of patients suffering from DM 2 and CAN monitored by 24 hour Holter

examination by Balcioglu et al. (2007), who found the averaged HR in DM 2 patients with CAN 81.4 ± 8.3 vs 76.0 ± 12.8 in DM 2 patients without CAN.

2. The PQ interval

No changes in the PQ interval were detected in studies focused on the ECG analysis in patients with DM 1, DM 2 or GDM. Neither CAN was reported to have any influence on the duration of the atrioventricular conduction. Slightly higher P wave voltage was reported by Krahulec et al. (2002) in DM 1 patients with CAN compared to DM 1 patients without CAN (0.13 vs 0.11 mV).

3. The QRS complex

Shortening of the QRS complex was reported in DM 1 patients, the average duration of the QRS was detected to be 79.9 ± 1.6 ms only while in the healthy controls it was found to be 89.9 ± 2.7 ms (Zdarska et al. 2007). Even more shortened QRS complex was found in DM 1 patients with CAN (75.5 ± 1.6 ms) what was a significant difference not only in comparison to the healthy controls but also to the DM 1 patients without CAN. On the other hand, controversial results were reported in women suffering from the GDM: while Medova et al. (2012) detected in GDM patients shorter QRS complex (82.0 ± 6.8 ms) in comparison to 89.5 ± 8.2 ms in healthy pregnant women and $90.8 (\pm 7.9)$ ms in the control group of non-pregnant women, Zakovicova et al. (2014) found in GDM patients very similar duration of QRS complex (82.9 ± 15.7 ms) but surprisingly shorter QRS in her cohort of non GDM pregnant women (76.0 ± 7.1 ms). Simultaneously the duration of the QRS complex in the GDM group is correlating according to the same study with echocardiographic findings of posterior wall thickness and interventricular septal thickness.

4. The QT and QTc intervals

The findings regarding the QT and QTc intervals durations use to be also a little bit controversial. While Heller (2002) has detected in DM 1 patients QT and QTc intervals prolongation, Zdarska et al. (2007) have found only non-significant lengthening of the QTc (415.2 ± 4.1 ms vs 401.4 ± 6.1 ms in the healthy controls). The shortening of the QT interval reported by the same authors (374.0 ± 4.4 ms vs. 349.0 ± 5.9 ms) corresponded fully to the accelerated heart rate. Very similar results (shortening of the QT interval and non-significant

prolongation of the QTc interval) were later found in DM 1 patients with CAN (Palova et al., 2010). On the other hand Krahulec et al. (2002) have reported in CAN diabetics extended QTc interval length (422.4 vs 396.3 ms) in comparison to diabetic patients without neuropathy.

On the other hand significantly prolonged duration of the QT interval was found in the group of patients with GDM (400.4 ± 46.3 ms) in comparison to the control group (370.0 ± 49.2 ms). Moreover, positive correlation between QT interval and HbA1C level has been found. But it has to be noted that some ECG findings in pregnant women can be explained by changed spatial arrangement of the chest organs during pregnancy (Lechmanova et al., 2002).

Also animal experiments documented an influence of DM on the QTc: DM was proved to promote a significant prolongation in the QTc interval for instance in streptozotocin-induced diabetes in rats (Erbas et al. 2015).

Body surface ECG maps

ECG body surface isointegral, isopotential and isoarea maps (BSM) are the sensitive indications of local electrical depolarization and repolarization changes (Kittnar and Mlcek 2010). They allow to reveal even very subtle changes of the electrical heart field that cannot be detected by standard twelve lead ECG (Kittnar and Stovicek 1993, Pisvejcova et al. 2002).

1. Depolarization maps

Significantly decreased amplitudes of R waves and on the other hand increased amplitudes of Q and S waves were found in DM 1 patients (Zdarska et al. 2007). Typically the absolute value of maximum in the 50. ms of depolarization was reported to be only 815.8 ± 78.9 μ V in DM 1 patients while in the healthy controls it was 1108.4 ± 108.2 μ V. Regarding the negative waves, the absolute value of minimum at the same time was found to be -1510.0 ± 110.8 μ V comparing to -1160.4 ± 131.3 μ V in the controls.

The activation time (ICHVAT), the speed of activation of the heart measured on the surface of thorax measured between the beginning of depolarization in an orthogonal lead and the R wave in the individual chest leads, was faster in DM 1 patients (63.2 ± 1.2 ms) when compared to controls (70.5 ± 2.0 ms), what could be well explained by an activation of the sympathetic

nervous system. Fully corresponding results were reported also in DM 1 patients with CAN (Palova et al. 2010).

Pronounced differences were also found in the duration of myocardial activation time in pregnant patients with GDM. Activation time of the ventricular myocardium in healthy pregnant women (72.8 ± 1.6 ms) was longer than in women with GDM (65.7 ± 1.5 ms). Moreover ICHVAT significantly correlated with the thickness of the interventricular septum and posterior wall diameter in GDM patients (Zakovicova et al. 2014).

2. Repolarization maps

The repolarization isopotential map maximum (RIPMmax) was less positive and minimum (RIPMmin) less negative in DM 1 patients than in the controls showing the different rate of repolarization in DM 1 patients during the T wave resulting in significant general flattening of T waves. Typically the absolute value of maximum in the 100. ms of repolarization in DM 1 patients was reported to be only 142.8 ± 12.69 μ V while in the healthy controls it was 248.3 ± 38.9 μ V. Regarding the regions of a thorax with negative T waves, the absolute value of minimum at the same time was found to be -119.0 ± 23.3 μ V comparing to -289.2 ± 122.7 μ V in the controls. The changes in the repolarization maps does not depend on fact if the DM 1 patients suffers also from the CAN or not.

Dispersion of QT interval

Dispersion of QT interval (QTd) is defined as the difference between the maximal and minimal QT interval in any of the leads measured. QTd should be evaluated from the Body surface ECG mapping as consideration of greater number of leads for determination of QT dispersion appears to determine QTd more accurately than assessment in only 12 or even 6 precordial leads. The use of low number of leads was undoubtedly the main cause of repeatedly suggested poor reproducibility (Kautzner et al. 1994, Day et al. 1990). Enhanced accuracy for QT dispersion assessment from 12-lead ECG in comparison with only 6 precordial leads was reported as well (van de Loo et al. 1994, Higham et Campbell 1994). Our previous results have suggested that the QTd can be changed under pathological conditions (Kittnar et al. 2004) but also physiologically in a late pregnancy (Lechmanova et al. 2002). We have concluded therefore that QTd can reflect not only increased risk of serious

tachyarrhythmias especially due to myocardial ischaemia but it must be interpreted simply just as “an unspecific sign of changed course of repolarization” what seems to offer an explanation of increased QTd under many different circumstances (Masaki et al. 2006, Cafiero et al. 2011, Fauchier et al. 2005).

Dispersion of QT interval was detected to be increased in DM 1 patients: 115 ± 36 ms vs 34 ± 12 ms in the healthy controls (Zdarska et al. 2007) and also in pregnant women suffering from GDM: QTd was proved to be significantly higher (107 ± 25 ms) both than in pregnant women with physiological pregnancy (73 ± 18 ms) and than in the healthy non-pregnant women (34 ± 12 ms).

Increased QTd seems to be resulting from a fact that shortening of the QT interval is not identical on the whole thorax surface but it is more pronounced in some thoracic regions. Zdarska et al. (2007) reported significantly shortened QT interval in all thoracic leads in DM 1 patients. But the study published later from the same laboratory revealed some interesting findings: 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 CAN than in DM1 patients without CAN. In 34 other leads the shortening of QT duration was not different in the DM1 patients with and without CAN in comparison with controls. In the resting 14 leads the significant shortening of the duration of QT interval was observed only in DM1 patients with CAN and not in DM 1 patients without CAN (Palova et al. 2010).

Heart rate variability

Cardiovascular autonomic neuropathy (CAN) is the most studied form of DAN (diabetic autonomic neuropathy) and it's prevalence varies between cohorts of diabetic patients, due to differences in the methodology (O'Brien et al., 1986; Vinik and Ziegler, 2007; Ziegler et al., 1992). Changes in spectral analysis of heart rate variability, such as increased sympathetic activity and reduced parasympathetic activity of the autonomic vegetative system has already been described in the offspring of patients with DM type 2 (De Angelis et al., 2001; Laitinen et al., 1999) or pre-diabetic patients with insulin resistance (Lefrandt et al., 2000). One recent Finnish study (Heiskanen et al., 2010) showed that women with GDM and proper metabolic

control compared with healthy pregnant women, did not have present significant changes in autonomic vegetative system, as it was previously assumed (Poyhonen-Alho et al., 2010).

Adebayo et al. (2014) have analyzed heart rate variability (HRV) in DM 2 patients in comparison to patients with arterial hypertension (AH) and they found standard deviation of normal-to-normal RR intervals (SDNN) average (ms) significantly reduced in DM 2 patients (81.03 ± 26.33) compared to the AH patients without heart failure (119.65 ± 29.86) and with heart failure (107.03 ± 62.50). Similar findings were also noted when the root mean square of successive heartbeat interval differences (RMSSD) average (ms) was used to assess the HRV, with significant reduction in DM 2 patients (36.48 ± 21.10) compared to AH patients without heart failure (103.82 ± 78.91) and with heart failure (99.45 ± 88.14). It is necessary to add that HRV was found to be reduced in hypertensive patients when compared with normotensive individuals (Menezes A et al. 2004). Moreover, using SDNN, Adebayo et al. (2014) have also detected a statistically significant variation between day and night HRV in DM 2 patients.

All HR variability indexes were found to be significantly decreased with CAN (Balcioglu et al. 2007). In patients with CAN, duration of DM 2 was found to be correlated positively with the Ewing score ($r = 0.753$, $p < 0.01$) and negatively with HR variability indexes (SDNN, $r = -0.358$, $p < 0.01$; SDNN index, $r = -0.421$, $p < 0.01$; SDANN (standard deviation of the averages of normal-to-normal RR intervals), $r = -0.294$, $p < 0.01$; square root of the mean squared differences of successive NN intervals, $r = -0.361$, $p < 0.01$; triangular index, $r = -0.468$, $p < 0.01$), turbulence slope ($r = -0.559$, $p < 0.01$), and HR turbulence score ($r = -0.485$, $p < 0.01$).

No changes in HRV were found in pregnant women with GDM (Zakovicova et al. 2014): Parasympathetic activity assessed by spectral power in high frequency (HF) for three consecutive time intervals was 151 ± 155 , 230 ± 343 , 212 ± 280 ms² in the control group, which was comparable to 234 ± 341 , 170 ± 271 , 216 ± 277 ms² (NS) in women with GDM. Sympathetic activity evaluated as a LF / HF ratio (low frequency / high frequency) in three consecutive intervals was 1.9 ± 1.7 , 1.9 ± 1.6 , 1.7 ± 1.9 in the control group, which was comparable to 2.1 ± 1.7 , 3.6 ± 3.9 and 2.1 ± 2.3 (NS) in women with GDM. Total parasympathetic activity evaluated as the sum of all three intervals (HF1 + HF2 + HF3) was 632 ± 511 ms² in the control group and 621 ± 790 ms² in GDM group (NS). Total sympathetic activity evaluated as the sum of LF / HF ratio in all three intervals (LF1/HF1 +

LF2/HF2 + LF3/HF3) was 5.5 ± 4.1 in the control group versus 7.9 ± 6.0 in the group of women with GDM (NS).

Limitations

All studies focused on ECG features that are characteristic for the DM patients have some similar limits derived from a fact that these features can be also modified by several other factors in addition to the DM. These factors include particularly concomitant diseases, different drugs used by the DM patients and obesity. That is why preferably studies in which concomitant diseases and obesity were listed among exclusion criteria were chosen for this review. Consequently with this selection also use of drugs that could influence particularly the heart rate and QT interval was supposed to be unlikely.

Conclusions

Repeatedly reported results showed in DM patients without cardiovascular complications the tachycardia, shortening of the QRS and QT intervals, increase of the dispersion of QT interval and decrease in T wave amplitude confirmed by the lower value of maximum and minimum in repolarization isopotential maps. 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 (Slavicek *et al.* 1995, 1998, Paclt *et al.* 2003, Kittnar *et al.* 2004) or in panic disorder (Pisvejcova *et al.* 2002) due to activation of the sympathetic nervous system. Also shortening of activation time can be explained by an activation of the sympathetic nervous system. It can be therefore concluded that the electrocardiographic changes in DM patients are not specific and that they are particularly caused by an increased tone of the sympathetic nervous system what was indirectly confirmed by the HRV analysis.

Diabetes mellitus can be generally considered as a cardiovascular disease because it causes both microvascular and macrovascular complications (Alberti *et al.* 1978, Kannel *et al.* 1986, Alberti and Zimmet 1998, Beckman *et al.* 2002, Pickup and Williams 2003). Due to the sensitive neuropathy, the coronary artery disease in diabetic patients is frequently asymptomatic (Alberti and Zimmet 1998, Langer *et al.* 1991, Paillole *et al.* 1995, Wackers *et*

al. 2004). Also 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 relatively useful tool in coronary ischemia detection (Green *et al.* 1985, Kittnar *et al.* 1993, Valouch *et al.* 2004) in asymptomatic diabetic patients.

Agnnowledgement

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