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# The influence of type 2 diabetes mellitus on the frequency and complexity of ventricular arrhythmias and heart rate variability in patients after myocardial infarction

## Uticaj šećerne bolesti tipa 2 na učestalost i kompleksnost ventrikularnih aritmija i varijabilnost frekvencije srčanog rada kod bolesnika nakon infarkta miokarda

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**Abstract**

**Background/Aim.** After myocardial infarction arrhythmic cardiac deaths are significantly more frequent compared to non-arrhythmic ones. The aim of the study was to investigate the influence of type 2 diabetes mellitus (T2DM) on the frequency and complexity of ventricular arrhythmias after myocardial infarction. **Methods.** The study included 293 patients, mean age 59.5 ± 9.21 years, who were at least six months after acute myocardial infarction with the sinus rhythm, without atrioventricular blocks and branch blocks. In the clinical group 95 (32.42%) patients were with T2DM, while 198 (67.57%) patients were without diabetes. All of the patients were subjected to the following procedures: standard ECG according to which the corrected QT dispersion (QTdc) was calculated, exercise stress test, and 24-hour holter monitoring according to which, the four parameters of time domain of heart rate variability (HRV) were analyzed: standard deviation of all normal RR intervals during 24 hours (SDNN), standard deviation of the averages of normal RR intervals in all five-minute segments during 24 hours (SDANN), the square root of the mean of the sum of the squares of differences between adjacent normal (RMS-SD), and percentage of consequtive RR intervals which differed for more than 50 ms during 24 hours (NN > 50 ms). **Results.** In patients after myocardial infarction, patients with T2DM had significantly higher percentage of frequent and complex ventricular arrhythmias compared to the patients without diabetes ($p < 0.001$). The patients with T2DM had significantly higher percentage of residual ischemia ($p < 0.001$), and arterial hypertension ($p < 0.001$), compared to patients without diabetes. The patients with T2DM had significantly lower values of HRV parameters: SDNN ($p < 0.001$); SDANN ($p < 0.001$); RMS-SD ($p < 0.001$), and NN > 50 ms ($p < 0.001$), and significantly higher values of QTdc ($p < 0.001$) compared to the patients without diabetes. **Conclusion.** The study showed that type 2 diabetes mellitus has significant influence on ventricular arrhythmias, HRV parameters and QT dispersion in patients after myocardial infarction.

**Key words:**
**diabetes melitus type 2; arrhythmias, cardiac; myocardial infarction.**

**Apstrakt**

**Uvod/Cilj.** Nakon infarkta miokarda srčana smrt je, usled razvoja kompleksnih ventrikularnih aritmija, značajno češća od nearitmijske. Cilj studije bio je da se ispita uticaj dijabetesa melitusa tipa 2 (T2DM) na učestalost i kompleksnost ventrikularnih aritmija nakon infarkta miokarda. **Metode.** Studija je obuhvatila 293 bolesnika, prosečne starosti 59,5 ± 9.21 godina, u periodu od najmanje šest meseci nakon akutnog infarkta miokarda. Svi su bili u sinusnom ritmu bez atrioventrikularnih blokova i blokova grana. Sa T2DM bilo je 95 (32,42%) bolesnika, dok je 198 (67,57%) bolesnika bilo bez dijabetesa. Ispitanicima je iz standardnog EKG izračunavana korigovana QT disperzija (QTdc), rađen test fizičkim opterećenjem, ehokardiografski pregled i 24-časovno holter-praćenje, iz koga su analizirana četiri parametra vremenske analize varijabilnosti frekvencije srčanog rada (HRV): standarna devijacija svih normalnih RR intervala registrovanih u toku 24 sata (SDNN), standarna devijacija prosečnih vrednosti svih petominutnih RR intervala u toku 24 sata (SDANN), kvadratni koren prosečne vrednosti kvadriranih

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razlika uzastopnih RR intervala u toku 24 sata (RMS-SD) i procenat uzastopnih RR intervala koji su se razlikovali za više od 50 ms u toku 24 sata (NN > 50 ms). **Rezultati.** Bolesnici sa T2DM imali su učestale i kompleksne ventrikularne aritmije u značajno većem procentu od onih bez dijabetesa ($p < 0,001$). Bolesnici sa T2DM imali su u značajno većem procentu rezidualnu ishemiju ($p < 0,001$) i arterijsku hipertenziju ($p < 0,001$) od bolesnika bez dijabetesa. Bolesnici sa T2DM imali su značajno niže vrednosti parametara varijabilnosti frekvencije srčanog rada: SDNN ($p < 0,001$); SDANN ($p < 0,001$); RMS-SD ($p < 0,001$) i NN > 50 ms ($p < 0,001$) i značajno više vrednosti QTdc ($p < 0,001$) od onih bez dijabetesa. **Zaključak.** Ova studija je pokazala da kod bolesnika nakon infarkta miokarda, dijabetes melitus tipa 2 ima značajan uticaj na pojavu ventrikularnih aritmija, parametre varijabilnosti frekvencije srčanog rada i QT disperziju.

**Ključne reči:**
**dijabetes melitus, insulin nezavisni; aritmija; infarkt miokarda.**

## Introduction

Patients with diabetes mellitus (DM) are at a high risk for cardiovascular morbidity and mortality. Patients with type 2 DM (T2DM) are 2–3 times more likely to develop cardiovascular diseases than the ones without this type of diabetes [1]. During post infarction period, patients with T2DM have two times higher mortality rate than non-diabetic ones [2].

Ventricular arrhythmias are the most common cause of death in coronary patients. During the first two years after recovering from myocardial infarction, cardiac deaths caused by arrhythmias are more frequent than non-arrhythmic deaths [3]. It was documented that 55% of total mortality in patients during post infarction period has been caused by malignant ventricular arrhythmias [4].

Many studies report that approximately 8.1% of the world population are patients with DM [5], and among patients with acute coronary syndromes, there are about 20–37% of patients with DM [6].

Considering the fact that in the post-infarction period the mortality rate in T2DM patients is much higher than in non-diabetic ones and that arrhythmic cardiac death is significantly more frequent than non-arrhythmic, the aim of the study was to investigate the influence of T2DM on the frequency and complexity of ventricular arrhythmias, and heart rate variability in patients six months after acute myocardial infarction.

## Methods

The patients (n = 293), at least six months after acute myocardial infarction, were recruited from the Clinic for Cardiovascular Diseases, between 2009 and 2013, at the Institute for Treatment and Rehabilitation "Niška Banja" in Niška Banja. There were 91 females and 202 males, mean age 59.5 ± 9.21 years. The clinical group was divided into two subgroups, according to the presence of T2DM. Among the patients, 95 (32.42%) of them were with 2TDM, mean age 60.1 ± 8.2, while 198 (67.57%) patients were without DM, mean age 59.5 ± 8.9 (they were observed as the control group). In the first clinical subgroup of the patients with T2DM, 50 (52%) patients were smokers and 56 (58.9%) of them had hypertension (or had an antihypertensive therapy); in the group of the patients without diabetes, 53 (26.8%) of them were smokers, and 86 (43.4%) patients had hypertension.

A fasting blood sample was collected from each participant and biochemical measurements were obtained using standard clinical laboratory methods. All analyses were performed on a Human Star 600, Germany.

The patients after myocardial infarction were monitored during the period of at least six months from the diagnosed acute myocardial infarction. All of them had sinus rhythm without atrioventricular and branch blocks.

All the patients were subjected to the procedures as follows: standard ECG according to which QT intervals were calculated, exercise testing, that was used to assess residual ischemia, which was performed on treadmill according to Bruce protocol [7], and 24-hour ambulatory ECG monitoring.

QT interval was determined according to ECG, from the starting point of the Q- or R-peak to the end of the T-wave where the down-slope of the T-wave merged with isoelectric line. The QT interval was determined in each offset from three consecutive sinus cycles as mean value. The values of QT intervals were corrected for the frequency of heart rate according to Bazett's formula [8]. QT dispersion was determined as the difference derived from maximal and minimal value of QT interval found in any of the 12 offsets. Out of the corrected value of QT interval, where the minimal value was subtracted from the maximum value found in any of the ECG offsets, the corrected value for QT dispersion (QT dc) was obtained.

The 24-hour ambulatory ECG monitoring was performed with the system Del Mar Avionics model 5268-505 MPA/R-ACQ: 2.15; Irvine, California, USA. The system included analysis of classic monitoring and determining heart rate variability (HRV). Analysis included the total number of ventricular premature complexes (VPCs) during 24 hours, the number of couples, triplets, bigeminies, the number of multiform VPCs, and the number of non-sustained and sustained ventricular tachycardia (VT). Further evaluation of ventricular arrhythmias was performed according to Lown and Wolf's classification [9]. Ambulatory monitoring results were used for software HRV analysis. The following four parameters of HRV analysis were analyzed: standard deviation of all normal RR intervals during 24 hours (SDNN); standard deviation of the averages of normal RR intervals in all five-minute segments during 24 hours (SDANN); the square root of the mean of the sum of the squares of differences between adjacent normal RR intervals during 24 hours (RMS-SD); percentage of consequtive RR intervals which differed for more than 50 ms during 24 hours (NN > 50 ms).

Characteristics of the study and the control group were expressed as mean ± SD (continuous variables), with the

numbers and percentages in brackets (categorical variables). We compared clinical and biochemical data of patients and control group using Student's *t*-test for normally distributed data (expressed as mean ± SD). All analyses were performed with SPSS statistical analysis software, version 10.0 (SPSS, Chicago, IL, United States) at the level of significance set at $p < 0.05$.

## Results

Clinical and biochemical data of the clinical group are presented in Table 1. Significant differences were found between the patients with T2DM and without T2DM in all the evaluated parameters: glycemia ($p = 0.001$), total cholesterol ($p = 0.001$), HDL cholesterol ($p = 0.02$), LDL cholesterol ($p = 0.001$), and triglycerides ($p = 0,001$), all presented in Table 1. The gender of patients with T2DM after myocardial infarction did not significantly influence the frequency and complexity of ventricular arrhythmias. The patients with T2DM, 83 (87.4%) of them, had significantly higher rate of residual ischemia compared to the patients without diabetes, 112 (56.6%), ($p = 0.001$).

Among the patients after myocardial infarction, the ones with T2DM had significantly higher rate of frequent and complex ventricular arrhythmias, classified by Lown and Wolf, compared to patients without diabetes mellitus: Lown 0 ($p = 0.001$), Lown I ($p = 0.001$), Lown II ($p = 0.025$), Lown III ($p = 0.001$), Lown IVa ($p = 0.005$), and Lown IVb ($p = 0.05$), all data presented in Table 2. Analyzing data on ventricular arrhythmias classified as Lown IVb, in the patients with T2DM there were 5 (5.3%) patients with triplets of ventricular extrasystoles, and 3 (3.2%) had non sustained ventricular tachycardia, while in the patients without T2DM there were 3 (1.5%) patients with triplets of ventricular extrasystoles, and one patient (0.5%) had non sustained ventricular tachycardia. Comparing the basic electrocardiographic parameters between these groups of patients we found differences in all evaluated parameters: SDNN (ms) ($p = 0.001$), SDANN (ms) ($p = 0.001$), RMS-SD (ms) ($p = 0.001$), NN > 50 (ms) ($p = 0.001$), RR (ms) ($p = 0.001$), and QTdc (ms) ($p = 0.001$), all data presented in Table 3.

## Discussion

The results of our study show that among the patients six months after myocardial infarction, those with T2DM had significantly higher rate of frequent and complex arrhythmias, compared to the patients without diabetes. It is documented that beside metabolic disorders and scar tissue originating from myocardial infarction, the patients with T2DM have fibrous changes in the interstitium included in the pathogenesis of the diabetic cardiomyopathy, as well as the damages of small blood vessels [10]. Those fibrous changes of the myocardium create anatomical substrate for the occurrence of macro- and micro-reentry ventricular tachycardia [11]. Furthermore, patients without DM, have scar tissue origina-

**Table 1**

**Comparison of biochemical and clinical parameters of the patients after myocardial infarction with and without type 2 diabetes mellitus (T2DM)**

| Parameter | Patients with T2DM | Patients without T2DM | *p* |
|---|---|---|---|
| Number (%) of patient | 95 (32.42) | 198 (67.57) | - |
| Age (years), $\bar{x} \pm SD$ | 60.1 ± 8.2 | 59.5 ± 8.9 | - |
| Glycemia (mmol/L), $\bar{x} \pm SD$ | 10.9 ± 3.9 | 5.5 ± 0.7 | 0.001 |
| Cholesterol ( mmol/L), $\bar{x} \pm SD$ | 6.8 ± 1.2 | 6.0 ± 1.3 | 0.001 |
| Tryglicerides (mmol/L), $\bar{x} \pm SD$ | 2.6 ± 1.9 | 1.9 ± 0.9 | 0.001 |
| HDL cholesterol (mmol/L), $\bar{x} \pm SD$ | 0.9 ± 0.2 | 1.1 ± 0.8 | 0.02 |
| LDL cholesterol (mmol/L), $\bar{x} \pm SD$ | 4.3 ± 0.4 | 4.1 ± 0.7 | 0.005 |
| Hypertension (mm/Hg), n (%) | 56 (58.94) | 86 (43.43) | 0.001 |
| Smoking, n (%) | 50 (52.63) | 53 (26.76) | 0.001 |

**Results compared with Student's-*t* test; LDL – low density lipoprotein; HDL – high density lipoprotein.**

**Table 2**

**Comparison of ventricular arrhythmias, classified by Lown and Wolf in the patients after myocardial infarction with and without type 2 diabetes mellitus (T2DM)**

| Parameter | Patients with T2DM | Patients without T2DM | *t* | *p* |
|---|---|---|---|---|
| Number of patients, n (%) | 95 (32.42) | 198 (67.57) | - | - |
| Age (years), $\bar{x} \pm SD$ | 60.1 ± 8.2 | 59.5 ± 8.9 | - | - |
| Lown 0, n (%) | 9 (9.5) | 43 (21.7) | 4.46 | 0.001 |
| Lown I, n (%) | 21 (22.1) | 109 (55.1) | 4.46 | 0.001 |
| Lown II, n (%) | 15 (15.8) | 11 (5.6) | 2.90 | 0.025 |
| Lown III, n (%) | 28 (29.5) | 25 (12.6) | 4.92 | 0.001 |
| Lown IVa, n (%) | 11 (11.6) | 4 (2.0) | 3.33 | 0.005 |
| Lown IVb, n (%) | 8 (8.4) | 4 (2.0) | 2.12 | 0.05 |
| Lown V, n (%) | 3 (3.2) | 2 (1.0) | 0.53 | NS |

**Results compared with Student's *t*-test; NS – non significant.**

**Table 3**

**Comparison of basic electrocardiographic parameters in the patients after myocardial infarction with and without type 2 diabetes mellitus (T2DM)**

| Parameters | Patients with T2DM | Patients without T2DM | *p* |
|---|---|---|---|
| Number of patiens | 95 | 198 | - |
| SDNN (ms), $\bar{x} \pm SD$ | 79.0 ± 20.5 | 101.5 ± 30.9 | 0.001 |
| SDANN (ms), $\bar{x} \pm SD$ | 68.0 ± 18.7 | 85.3 ± 29.5 | 0.001 |
| RMS-SD (ms), $\bar{x} \pm SD$ | 25.1 ± 10.5 | 35.3 ± 15.2 | 0.001 |
| NN>50 (ms), $\bar{x} \pm SD$ | 5.9 ± 5.7 | 12.0 ± 10.4 | 0.001 |
| RR (ms), $\bar{x} \pm SD$ | 0.78 ± 0.11 | 0.90 ± 0.10 | 0.001 |
| QTdc (ms), $\bar{x} \pm SD$ | 88.0 ± 22.7 | 66.2 ± 26.5 | 0.001 |

**Results compared with Student's *t*-test.**
**SDNN – standard deviation of all normal RR intervals during 24 hours;**
**SDANN – standard deviation of the averages of normal RR intervals in all five-minute segments during 24 hours; RMS-SD – the square root of the mean of the sum of the squares of differences between adjacent normal RR intervals during 24 hour); NN > 50 ms, percentage of consequtive RR intervals which differed for more than 50 ms during 24 hours; RR – RR interval; QTdc – corrected QT dispersion.**

ting from myocardial infarction, represented only as one fibrous island. Contrary to that, in patients with T2DM, beside the scar tissue, there are also diffuse fibrous changes in the interstitium, so there is a greater possibility for the occurrence of ventricular arrhythmias, what was confirmed in our study. These changes in the myocardium of the left ventricle lead to its dilatation, and therefore sustain further development of ventricular arrhythmias [12, 13].

It has been demonstrated that during dilatation of the left ventricle impulse conduction becomes slower, total block occurs, effective refractive period shortens, dispersion refractivity increases and the difference in refractivity between subepicardial and subendocardial layers also increases [11, 14]. Extension of the left ventricle walls leads to the changes of membrane resting potential and refractive period, which alleviates the occurrence of ventricular arrhythmias [15–17]. When the ventricle myocardium is damaged and electrophysiological remodeling occurs, activation of channels alters, which leads to reduced dispersion of repolarization.[14]

Increased QTd values also appear due to fibrous changes and myocardial ischemia [18–20]. Increased QTd value reflects regional difference in repolarization of the myocardium and is a potential predictor for cardiac mortality.[21,22] Among our patients early after myocardial infarction, those with T2DM had significantly higher percentage of frequent and complex ventricular arrhythmias and significantly higher QTd values, compared to patients without T2DM. Increased QTd value is a marker for electric instability of the ventricular myocardium and is a predictor for complex ventricular arrhythmias, including ventricular tachycardia,[21,23] also found in our patients. According to QTd values, we can identify patients with heart failure, who are at a higher risk for cardiac death.[24]

Most of our patients with T2DM had residual ischemia, which certainly contributed to the occurrence of arrhythmias [25]. In experimental studies, before the occurrence of ischemia, ventricular fibrillation (VF) could not be caused even by premature stimuli, while during ischemia, VF was caused by a single premature stimulus, between the 17th and 32nd minute from the beginning of the ischemia.[26] Ischemia causes intracellular and extracellular acidosis and damages cell membrane, causing potassium to exit and calcium to enter the cell, which leads to decreased membrane resting potential and creates conditions for trigger activity.[11, 27] Slowing or complete blocking of conduction is also caused by increased resistance of gap connection due to acidosis. Besides that, the decrease of action potential creates conditions for the occurrence of arrhythmias based on automatism.[25] These changes are heterogenic in the ischemic region, depending on the level of ischemia.[25] All our patients with T2DM and residual ischemia, had frequent and complex ventricular arrhythmias.

A correlation between increased level of fasting plasma glucose and cardiovascular diseases is well-known [28, 29]. Hyperglycemia causes coronary dysfunction by creating reactive oxygen species, which inactivates nitric oxide produced in the endothelium, and activate protein kinase C, which induces the production of vasoconstrictor prostanoids.[26] It is considered that hyperglycemia is one of the most important causes of the occurrence of myocardial fibrosis, it causes local production of angiotensin II in myocytes, leading to their apoptosis.[30] According to Framingham study, hyperglycemia, including mild hyperglycemia, causes reduced values of HRV parameters. Similar results were recorded in the ARIC study.[5]

Parameters of heart rate variability as markers of the autonomic nervous system state are used for evaluation of the influence of both, sympathetic and parasympathetic effect on the heart function, and for the identification of patients who are at higher risk for cardiovascular events [31–33]. It has been recorded that there is a significantly higher mortality rate in patients with reduced SDNN values [34]. Many studies have shown that HRV is an independent predictor for sudden cardiac death in patients after myocardial infarction [4, 31, 33, 35, 36]. It has also been documented that in patients with T2DM after myocardial infarction, reduced HRV values are predictors for cardiac death and sudden cardiac death [5].

Cardiovascular autonomic neuropathy (CAN) is significantly associated with subsequent mortality in people with DM (T1DM and T2DM) in meta-analysis of 15 studies. Probably, in our patients with T2DM, CAN also contributed to significantly higher percentage of registered frequent and

complex ventricular arrhythmias, compared to the patients without T2DM. Patients with T2DM had significantly lower values of HRV parameters, which maintained the vagal tone, as well as RMS – SD and NN > 50 ms, [37, 38] and RR interval values, compared to the patients without T2DM, which was also found in our patients. The presence of tachycardia at rest is an early sign of CAN in patients with T2DM, [39] and we recorded sinus tachycardia which occurred at rest or developed easily at slight effort [30]. Early detection of CAN may help us to detect earlier development of atherosclerosis in patients with T2DM to prevent unfavorable outcomes [39, 40].

Regulation of glycemia, hypertension, myocardial ischemia, increased sympathetic activity and dysfunction of the left ventricle would lead to reduced vulnerability of the myocardium and reduced arrhythmic deaths in patients with T2DM after myocardial infarction. Regulation of these pathological states would reduce arrhythmic deaths and thus improve the prognosis for these patients after myocardial infarction.

## Conclusion

This study showed that in patients after myocardial infarction, type 2 diabetes mellitus has a significant impact on ventricular arrhythmias, heart rate variability, and QT dispersion. We also showed that these patients had a significantly higher percentage of frequent and complex ventricular arrhythmias, compared to non-diabetic patients. Finally, heart rate variability and QT dispersion, may be an easy and helpful tool for easier identification of patients with type 2 diabetes mellitus who are at greater risk for further cardiovascular events.

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