SUMMARY
Introduction/Objective
Cardiovascular diabetic autonomic neuropathy (CDAN) mainly affects heart rhythm through sympathovagal imbalance. The objective of the study is to determine CDAN risk potential regarding electrical complications of acute myocardial ischemia (AMI), including admission glucose profile levels (AGP).

Methods
Seventy-six patients suffering from type 2 diabetes mellitus were divided into two age-matched groups related to the presence of CDAN, and the influence of AGP on electrical complications was estimated. Ewing's tests were used for diagnosis of CDAN.

Results
Patients without CDAN have 42.86% risk for developing electrical complication into early post-AMI period. If it is a pre-existing condition, the risk is 63.64%, which is obvious, but not statistically significant. Considering the AGP, levels above 12.25 mmol/L as predictive for post-AMI electrical complications, in CDAN-positive patients with AGP levels above that cut-off value, the risk for electrical complications is raising up to 73.68%. The patients with CDAN who have AGP levels above the cut-off value have statistically higher risk for development electrical complications than those with lower levels (Z = 2.58, p < 0.01). On the other side, those without CDAN and with level of AGP lower than 12.25 mmol/L, the risk for electrical complications developing is as low as 23.08%.

Conclusion
CDAN may be an important independent risk factor for electrical complications in post-myocardial ischemia period.

Keywords: cardiovascular autonomic neuropathy; admission glucose profile; diabetes mellitus; myocardial ischemia

INTRODUCTION
As it has already been mentioned many times, type 2 diabetes mellitus (DM) is strongly linked with cardiovascular deaths, mainly due to coronary heart disease, congestive heart failure and cardiomyopathy [1]. These pathological heart conditions in patients with DM who sustained acute myocardial ischemia (AMI) lead to the increased incidence of post-AMI complications, and higher mortality rate as well [2, 3, 4]. Cardiovascular diabetic autonomic neuropathy (CDAN) mainly affects heart rhythm through the sympathovagal imbalance, and that dysautonomia has been shown to lead to sudden cardiac death in people with DM due to the decrease in heart rate variability [5, 6, 7]. Cardiovascular autonomic neuropathy may result in orthostatic hypotension, persistent sinus tachycardia, and asymptomatic myocardial infarction, which may cause sudden death [8]. The presence of symptoms and involvement of both components of the autonomic nervous system suggest that dysfunction has been present for a while in these diabetics, and there is a dire need for earlier and regular evaluation of autonomic nervous system in type 2 diabetics to prevent further complications [9]. Having in mind the basic physiological mechanisms of the heart, it is certainly expected that pre-existing CDAN would have some influence on the development of electrical complications (EC) in post-AMI period.

Vujošević et al. [10], showed that admission glucose profile (AGP) level higher than 12.25 mmol/L was associated with higher risk (p = 0.001) for the development of EC (sensitivity 77.3%; specificity 64.5%), while there were no significant relations between higher AGP levels and mechanical complications, as well as between glycosylated haemoglobin A1c and any type of post-AMI complications.

The aim of the study is to determine the risk potential of CDAN on EC in early (intra-hospital) post-AMI period, including AGP levels, too.
**METHODS**

The study was performed on 76 patients suffering from type 2 DM, who were hospitalized with the first-ever AMI. The diagnosis of DM was based on the medical records or diabetes diagnosed during the event according to 2012 International Diabetes Global Guideline following World Health Organization (WHO) criteria: fasting plasma glucose (FPG) ≥ 7 mmol/L (126 mg/dL), or 75 g oral glucose tolerance test (OGTT) with FPG ≥ 7 mmol/L (126 mg/dL) and/or 2 hour plasma glucose ≥ 11.1 mmol/L (200 mg/dL) or glycated haemoglobin (HbA1c) ≥ 6.5% / 48 mmol/mol, or random plasma glucose ≥ 11.1 mmol/L (200 mg/dL) in the presence of common diabetes symptoms [11].

The diagnosis of a heart attack was based on patient’s subjective symptoms related to the pain, ECG changes typical for AMI, and the level of troponin I (greater than 0.033 μg/L). AGP was estimated as mean value of the first six separate blood glucose levels, obtained before each of the three daily meals, and two hours after them. HbA1c was measured from the blood samples taken on the first morning after hospital admission.

Furthermore, all 76 patients were divided into two groups related to the presence of CDAN, and the influence of AGP on electrical complications was again estimated. The first group consisted of 21 patients without CDAN and other 55 CDAN-positive patients represented the second one. The other known causes of autonomic neuropathy (ureaemia, alcoholism, amyloidosis, Guillain-Barré syndrome) were excluded.

Standard battery function tests for the estimation of CDAN (also called Ewing’s tests) were used: the heart rate reacts to the Valsalva manoeuvre, standing up and deep breathing; and the blood pressure reacts to standing up, and sustained handgrip [12]. All factors that could influence the test results were excluded before the tests were performed. In brief, autonomic involvement was categorized as follows:
- normal (all tests normal);
- early (one heart rate test abnormal);
- definite (two or more heart rate tests abnormal);
- severe (abnormal heart rate tests plus one or both blood pressure tests abnormal);
- atypical (any other combination of abnormalities).

Ventricular tachycardia, ventricular fibrillation, ventricular extrasystole (trigeminia, quadrigeminia, couplets, triplets, multifocal extrasystole), atrial fibrillation and conduction system disorders: the second and the third atrioventricular block were considered to be post-AMI electrical complications. Only AMI complications developed during the initial hospitalization (early complications) were taken into consideration. EC were diagnosed by standard six-channel ECG, 12 lead ECG was recorded.

The statistical evaluation of results was performed by the SPSS version 12 for Win Software package (SPSS Inc., Chicago, IL, USA). As far as the risk estimation is concerned, its likelihood ratios were calculated in groups. Differences between the risks were statistically analysed using nonparametric Z-test for the comparison of the proportions. P-values below 0.05 were considered significant, since those below 0.01 were highly significant [13].

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethical Committee of School of Medicine, University of Belgrade, Serbia, approved the research.

**RESULTS**

The groups were homogenous by gender, serum lipid level, body mass index, tobacco smoking, and hypertension as the risk factors (Table 1). The study enrolled 76 patients, 43 males and 33 females, with the mean type 2 DM duration 8.4 ± 5.6 years, and the mean age 64.08 ± 9.06 years. Patients from the first group (without CDAN) had 42.86% risk for the development of EC in early post-AMI period. If CDAN is the pre-existing condition, the EC risk is more than doubled, up to 63.64%. Considering the AGP level above the cut-off value of 12.25 mmol/L as statistically highly associated with post-AMI EC [10], for the CDAN-positive patients with higher AGP levels, the risk for EC rises up to 73.68%. For those with CDAN and lower levels of AGP, the risk of developing EC is equal to those without CDAN (about 42%). Patients without CDAN and with lower AGP levels are on the lowest risk for EC (23.08%) in early post-AMI period. Setting the cut-off value on 14.85 mmol/L, which has been considered as highly predictive for EC, similar risks were taken [10] (Figure 1).

Comparing the risks between the groups regarding the development of EC related to pre-existing CDAN, the statistical significance was not reached (Z = 1.64, p = 0.11), even the risk is obviously higher in CDAN-positive ones. The patients with CDAN who have AGP levels above the cut-off value (12.25 mmol/L) are statistically higher at risk for developing EC than those with lower AGP levels (Z = 2.58, p < 0.01).

**Table 1. Risk factors in type 2 diabetic patients with acute myocardial ischemia according to Ewing’s tests**

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>A1*</th>
<th>A2**</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serum lipid level</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>6.12 ± 1.42</td>
<td>6.29 ± 1.75</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>0.96 ± 0.26</td>
<td>1.02 ± 0.14</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>3.80 ± 1.25</td>
<td>3.84 ± 1.27</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>2.06 ± 0.94</td>
<td>2.64 ± 2.12</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 24.9 kg/m²</td>
<td>21.6%</td>
<td>35%</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>25–29.9 kg/m²</td>
<td>58.8%</td>
<td>40%</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>&gt; 30 kg/m²</td>
<td>19.6%</td>
<td>25%</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td><strong>Tobacco smoking</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>35.3</td>
<td>50</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>No</td>
<td>64.7</td>
<td>50</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td><strong>Hypertension (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>70.6</td>
<td>70</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>No</td>
<td>29.4</td>
<td>30</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

BMI – body mass index;
*patients with CDAN;
**patients without CDAN
Out of 55 patients who had pre-existing CDAN, 45 had definitive, severe or atypical form of CDAN, and the others were in the early stage.

**DISCUSSION**

The pathogenesis of CDAN is complex and involves a cascade of pathways activated by hyperglycaemia resulting in neuronal ischaemia and cellular death and, in addition, autoimmune and genetic factors [14]. CDAN has been linked to resting tachycardia, postural hypotension, orthostatic bradycardia and orthostatic tachycardia, exercise intolerance, decreased hypoxia-induced respiratory drive, loss of baroreceptor sensitivity, enhanced intraoperative or perioperative cardiovascular lability, increased incidence of asymptomatic ischemia, myocardial infarction, and decreased rate of survival after myocardial infarction and congestive heart failure [15].

Since CDAN is accompanied by many other pathological conditions in DM (mainly, coronary artery disease) and depends on the duration of DM, severity of hyperglycaemia, the exact contribution of CDAN to the mortality risk of DM has been difficult to quantify. Pop-Busui et al, in a large characterized cohort trial (ACCORD trial) showed that the presence of CDAN reliably predicts all-cause (HR = 2.14; 95% CI, 1.37–3.37) and cardiovascular mortality (HR = 2.62; 95% CI, 1.4–4.91) independently of cardiovascular baseline, diabetes duration, multiple traditional cardiovascular risk factors and medication [16].

Since similar risks for EC are taken with two different cut-off values of AGP (12.25 mmol/L and 14.85 mmol/L), it seems that CDAN may be an independent risk factor for EC in post-AMI period. Further studies may try to prove this idea on a bigger sample, and may try to prove CDAN's influence on different types of EC, bearing in mind data that CDAN dominantly affects the heart rate [17].

Another fact should be emphasised. Since CDAN also affects sensitive innervation, a silent myocardial infarction is consistently associated with CDAN [18]. On the other hand, CDAN has a strong relationship with high mortality risk (up to 50% for a five-year rate), with high percentage of sudden cardiac deaths [19].

The limitation of the study is the size of the sample. Since it was small, the statistical analysis would not be representative for the comparison of risks between group with CDAN and without or between four CDAN-positive patient subgroups.

**CONCLUSION**

Our study showed that patients with CDAN and AGP levels above cut-off value of 12.25 mmol/L have more than two times higher EC development risk in post-AMI period than those without CDAN, so it could be considered as an important independent risk factor.

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Кардиоваскуларна дијабетесна аутономна невропатија као фактор ризика за електричне компликације у акутној исхемији миокарда

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САЖЕТАК
Увод/Циљ Кардиоваскуларна дијабетесна аутономна невропатија (КДАН) утиче на поремећај срчаног ритма путем симпатиковагалне неравнотеже. Циљ студије је да се одреди могући ризик за КДАН који се односи на електричне компликације акутне миокардне исхемије (АМИ).

Методе У две групе, сврстане по старости, подељено је 76 болесника са дијабетесом тип 2, од којих 38 брд为一体的, 38 него. Изменење је утицаја ПГП на настанак електричних компликација. Јужноги тестови су примењени за постављање дијагнозе КДАН.

Резултати Болесници без КДАН имају низак ризик за развој електричних компликација у периоду после АМИ (n.s.). Ако је ПГП изнад 12,25 mmol/l, предиктивна вредност за развој електричних компликација у периоду после АМИ код болесника са КДАН расте до 73,68%. Болесници са КДАН који имају ПГП изнад граничне вредности имају статистички значајан виши ризик за развој електричних компликација од оних са нижим вредностима гликемије (Z = 2,58, p < 0,01). С друге стране, болесници са КДАН и са ПГП испод 12,25 mmol/l имају низак ризик за развој електричних компликација, који износи 23,08%.

Закључак КДАН је могући важан независни фактор ризика за развој електричних компликација у периоду после акутне миокардне исхемије.

Кључне речи: кардиоваскуларна дијабетесна невропатија; профил гликемије на пријему; дијабетес мелитус; миокардна исхемија

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