SERBIAN ARCHIVES OF MEDICINE Est.1872

Address: 1 Kraljice Natalije Street, 11000 Belgrade, Serbia
☎ +381 11 4092 776, Fax: +381 11 3348 653
E-mail: office@srpskiarhiv.rs, Web address: www.srpskiarhiv.rs

Paper Accepted* **ISSN Online 2406-0895**

Original Article / Оригинални рад

Snežana Vujošević[1], Nemanja Radojević[2], Nataša Belada[3], Nevena Mijajlović[4], Valentina Kalinić[5], Sanja Borozan[1], Sanja Medenica[1,†]

Cardiovascular diabetic autonomic neuropathy as a risk factor for electrical complications in acute myocardial ischemia

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

[1] Department of Endocrinology, Internal Medicine Clinic, Clinical Center of Montenegro, Faculty of Medicine, University of Montenegro, Podgorica, Montenegro;
[2] Center for Pathology and Forensic Medicine, Clinical Center of Montenegro, Faculty of Medicine University of Montenegro, Podgorica, Montenegro;
[3] Private Specialist Internal Medicine Clinic 'Cardio Lab', Podgorica, Montenegro;
[4] Faculty of Mathematics and Natural Sciences, University of Montenegro, Podgorica, Montenegro;
[5] Department of Internal Medicine, Hospital "Blazo Orlandic", Bar, Montenegro

Received: November 22, 2017
Revised: February 24, 2018
Accepted: February 26, 2018
Online First: March 6, 2018
DOI: https://doi.org/10.2298/SARH171122020V

† **Correspondence to:**
Sanja MEDENICA
Internal Clinic, Clinical Center of Montenegro, Ljubljanska 1, 81000 Podgorica, Montenegro
E-mail: **medenicasanja@gmail.com**

Cardiovascular diabetic autonomic neuropathy as a risk factor for electrical complications in acute myocardial ischemia

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

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 76 patients suffering from type 2 diabetes mellitus were divided in 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 in 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

САЖЕТАК

Увод/Циљ Кардиоваскуларна дијабетесна аутономна полинеуропатија (КДАН) утиче на поремећај срчаног рима путем симпатиковагалне неравнотеже.
Циљ студије је да се одреди могући ризик за КДАН који се односи на електричне компликације акутне миокардне исхемије (АМИ), укључујући и вредности профила гликемије на пријему (ПГП).
Методе У две групе је подељено 76 болесника са типом 2 дијабетес мелитуса зависно од присуства КДАН и сврстани по старости.. Процењен је утицај ПГП на настанак електричних компликација. Јуингови тестови су примењени за постављање дијагнозе КДАН.
Резултати Пацијенти без КДАН имају 42,86% ризик за развој електричних компликација у раном периоду након АМИ. Уколико је стање већ постојало, ризик је виши-63,64% (*n.s.*). Ако је ПГП изнад 12,25 ммол/л, предиктивна вриједност за развој електричних компликација у периоду након АМИ, код пацијената са КДАН расте до 73,68%. Пацијенти са КДАН који имају ПГП изнад граничне вриједности имају статистички значајан виши ризик за развој електричних компликација од оних са нижим вредностима гликемије ($З=2.58$, $p<0,01$). С друге стране, пацијенти КДАН и са ПГП испод 12,25 ммол/л имају низак ризик за развој електричних комоликација који износи 23,08%.
Закључак КДАН је могући важан независни фактор ризика за развој електричних компликација у периоду након акутне миокардне исхемије.
Кључне речи: кардиоваскуларна аутономна неуропатија; профил гликемије на пријему; дијабетес; миокардна исхемија

INTRODUCTION

As it has been already mentioned many times, type 2 diabetes mellitus (DM) is highly linked with cardiovascular deaths [1], mainly due to coronary heart disease, congestive heart failure and cardiomyopathy. These pathological heart conditions in patients with DM who sustained AMI lead to the increased incidence of post-AMI complications [2,3], and higher mortality rate as well [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 predispose 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 strong need for earlier and regular evaluation of autonomic nervous system in type 2 diabetics to prevent further complications [9]. Having in mind basic physiological mechanisms of the heart, it is certainly expected that pre-existing CDAN would have some influence to the development of electrical complications (EC) in post-AMI period.

Vujosevic 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) ≥7.0 mmol/L(126 mg/dL), or 75g oral glucose tolerance test (OGTT) with FPG ≥7.0 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 classical diabetes symptoms [11].

The diagnosis of the heart attack was based on patient's subjective symptoms related to the pain, ECG changes typical for AMI, and the level of troponin I (higher that 0.033μg/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 sampled in the first morning after the hospital admission.

Furthermore, all 76 patients were divided in 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 (uraemia, alcoholism, amyloidosis, Guillain-Barré syndrome 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), or 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 electrocardiogram was recorded.

The statistical evaluation of results was performed by the SPSSver. 12 for Winsoftware 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 as 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 male and 33 female, 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

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

Risk factors		Patients with CDAN	Patients without CDAN	*p*
Serum lipid level	Cholesterol (mmol/l)	6.12±1.42	6.29±1.75	> 0.05
	HDL-cholesterol (mmol/l)	0.96±0.26	1.02±0.14	> 0.05
	LDL-cholesterol (mmol/l)	3.80±1.25	3.84 ± 1.27	> 0.05
	Triglyceride (mmol/l)	2.06±0.94	2.64 ± 2.12	> 0.05
Body mass index	< 24.9 kg/m²	21.6 %	35 %	> 0.05
	25-29.9 kg/m²	58.8 %	40 %	> 0.05
	> 30 kg/m²	19.6 %	25 %	> 0.05
Tobacco smoking	Yes	35.3	50	> 0.05
	No	64.7	50	> 0.05
Hypertension (mmHg)	Yes	70.6	70	> 0.05
	No	29.1	30	> 0.05

levels of AGP, the risk for developing EC is equal to those without CDAN (circa 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 [10], almost the same risks were obtained (Figure 1).

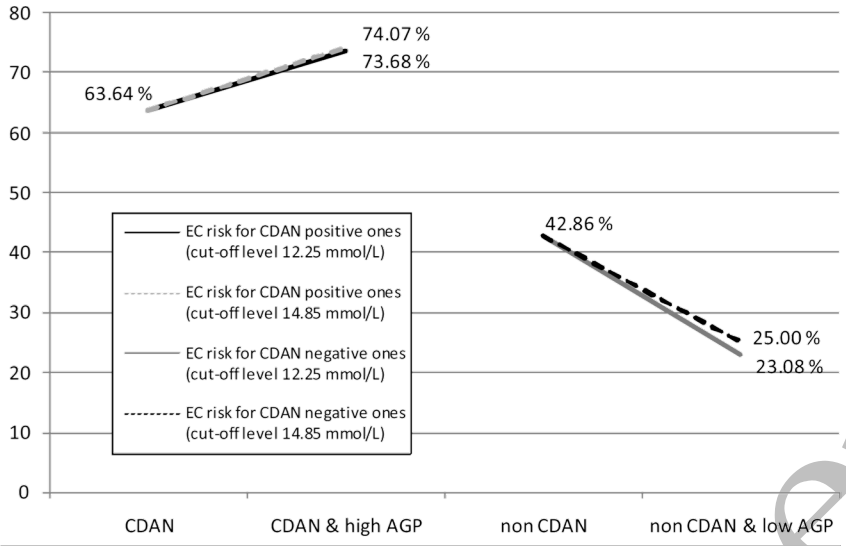

Figure 1. Electrical complications (EC) risk for patients with or without cardiovascular diabetic autonomic neuropathy (CDAN) and different cut-off values of admission glucose profile (AGP) set on 12.25 mmol/L and 14.85 mmol/L.

Comparing the risks between the groups regarding the development of EC related to preexisting 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 on statistically higher risk for the development of EC than those with lower AGP levels ($Z=2.58$, $p<0.01$).

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 strongly 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].

The results presented in the paper under review here, clearly show a higher incidence of EC in early post-AMI period in patients with pre-existing CDAN. Borderline statistical insignificance is strongly believed to be the consequence of the small sample, especially when it comes to the first group (only 21 patients). Moreover, our sample consisted of patients with non-silent AMI only; a high pool of CDAN-positive patients died suddenly [12], with no evidence of complication manifested.

Since almost the same risks for EC are obtained with two different cut-off values of AGP (12.25 mmol/L and 14.48 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 5-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.

ACKNOWLEDGEMENT

Authors wish to thank Miroslava Zamaklar MD PhD, for providing the professional assistance.

During the research, Dr Radojevic was a fellow of Fogarty International Center of the National Institutes of Health's "Research Ethics Education in the Balkans and Black Sea Countries" (Award Number R25TW008171), provided by Icahn School of Medicine at Mount Sinai New York USA and School of Medicine University of Belgrade Serbia.

REFERENCES

1. Buse JB, Polonsky KS, Burant CF. Type 2 diabetes mellitus. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR. Williams Textbook of Endocrinology. 11th Ed. Philadelphia: Saunders Elsevier; 2008. p. 1329–88.
2. Miettinen H, Lehto S, Salomaa V, Mähönen M, Niemelä M, Haffner SM, et al. Impact of diabetes on mortality after the first myocardial infarction. The FINMONICA myocardial infarction register study group. Diabetes Care. 1998; 21: 69–75.
3. Franklin K, Goldberg RJ, Spencer F, Klein W, Budaj A, Brieger D. et al; GRACE Investigators. Implications of diabetes in patients with acute coronary syndromes. The Global Registry of Acute Coronary Events. Arch Intern Med. 2004; 164: 1457–63.

4. Chun BY, Dobson AJ, Heller RF. The impact of diabetes on survival among patients with first myocardial infarction. Diabetes Care. 1997; 20: 704–8.
5. Vinik AI, Erbas T, Casellini CM. Diabetic cardiac autonomic neuropathy, inflammation and cardiovascular disease. J Diabetes Investig. 2013; 4: 4–18.
6. Karmakar C, Jelinek H, Khandoker A, Tulppo M, Makikallio T, Kiviniemi A, et al. Identifying increased risk of post-infarct people with diabetes using multi-lag Tone-Entropy analysis. Conf Proc IEEE Eng Med Biol Soc. 2012; 012: 25–8.
7. Maser RE, Mitchell BD, Vinik AI, Freeman R. The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a meta-analysis. Diabetes Care. 2003; 26: 1895–901.
8. Chun MY, Park HK, Hwang HS, Han JI, Chee YJ, Lee JS. The Association between Symptoms of Autonomic Neuropathy and the Heart RateVariability in Diabetics. Korean J Fam Med. 2011; 32: 292–8.
9. Sucharita S, Bantwal G, Idiculla J, Ayyar V, Vaz M. Autonomic nervou ssystem function in type 2 diabetes using conventional clinical autonomic tests, heart rate and blood pressure variability measures. Indian J Endocrinol Metab. 2011; 15: 198–203.
10. Vujosevic S, Radojevic N, Belada N. Influence of admission glucose profile and haemoglobin A1c on complications of acute myocardial infarction in diabetic patients. Eur Rev Med Pharmacol Sci. 2013; 17: 1252–7.
11. International Diabeted Federation. Clinical Guidelines Task Force, Global Guideline for Type 2 Diabetes, 2012. Available at : http://www.idf.org/sites/default/files/IDF%20T2DM%20Guideline.pdf
12. Ewing DJ, Campbell IW, Clarke BF. Assessment of cardiovascular effects in diabetic autonomic neuropathy and prognostic implications. Ann Intern Med. 1980; 92: 308–11.
13. Newman TB, Browner WS, Hulley SB. Enhancing Causal Interference in Observational studies. In : Hulley SB, Cummings SR, Browner WS, Grady DG, Newman TB. Desining Clinical Research. 4th Ed. Philadelphia : Wolters Kluwer, Lippincott Williams & Wilkins ; 2013. pp 117–22.
14. Dimitropoulos G, Tahrani AA, Stevens MJ. Cardiac autonomic neuropathy in patients with diabetes mellitus. World J Diabetes. 2014; 5: 17–39.
15. Vinik AI, Erbas T. Diabetic autonomic neuropathy. Handb Clin Neurol. 2013; 117: 279–94.
16. Pop-Busui R, Evans GW, Gerstein HC, Fonseca V, Fleg JL, Hoogwerf BJ, et al. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Diabetes Care. 2010; 33: 1578–84.
17. Lykke JA, Tarnow L, Parving HH, Hilsted J. A combined abnormality in heart rate variation and QT corrected interval is a strong predictor of cardiovascular death in type 1 diabetes. Scand J Clin Lab Invest. 2008; 68: 654–9.
18. Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. Diabetes Care. 2003; 26: 1553–79.
19. O'Brien IA, McFadden JP, Corrall RJ. The influence of autonomic neuropathy on mortality in insulin-dependent diabetes. QJ Med. 1991; 79: 495–502.

