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## THE RELATIONSHIP OF THE RATIO TAURINE/ALANINE IN SERUM AND INDICATORS OF HEART RATE VARIABILITY IN PATIENTS WITH POSTINFARCTION CARDIOSCLEROSIS AND DIABETES MELLITUS TYPE 2

**Abstract** *The aim of the article : to determine the relationship of the ratio taurine/alanine (Tau/Ala) serum indicators of heart rate variability (HRV) in patients with postinfarction cardiosclerosis (PICS) and diabetes mellitus type 2 (DM 2). Materials and methods: we examined 87 patients with PICS and DM 2 – 50 women and 37 men, median age of the patients was 65.2 years (microtile interval 61-69 years). Amino acids were determined and the ratio between them. According to the results of Holter ECG monitoring (of HMCG) evaluated HRV. Results: in patients with PICS compared with healthy individuals observed a significant decrease in the blood levels of Tau/Ala (at 51.01%,  $p < 0.001$ ). The presence of comorbid diabetes is accompanied by more significant decrease in Tau/Ala (for the accounting period 82.22%,  $p < 0.001$ ) compared to healthy individuals. Between Tau/Ala and SDNN, LF, TP, VLF power of communication has been high, between Tau/Ala and RMSSD, HF, pNN 50.%, ULF, – moderate strength. Conclusions: the lower values of Tau/Ala in the blood of patients Pxs diabetes compared with patients without disorders of carbohydrate metabolism, accompanied by a decrease in spectral and temporal parameters of HRV, but that does not mean a causal relationship, may be associated with pathogenetic mechanisms of disorders of carbohydrate metabolism and requires further research.*

**Keywords:** myocardial infarction, diabetes mellitus type 2, taurine, alanine

**Introduction:** Diabetic autonomic neuropathy is a specific factor of cardiovascular complications in DM. Changes in visceral afferent fibres running from the myocardium, lead to the emergence of less severe forms of myocardial infarction (MI) in DM. According to statistics, in diabetic patients, every third of them is characterized by less severe over (Sessa et al., 2018; Benjamin et al., 2017; Ramirez et al., 2017). Violations of HRV in DM patients develop regardless of the severity of coronary atherosclerosis that is a proven fact (Boos et al., 2017; Ma et al., 2017; Chen, Yang, Liu, & Tang, 2015). In the case of the PICS in DM2 changes of the national Assembly are particularly pronounced. Violation of the activity of afferent and efferent fibers contained NA lead sympatho-vagal imbalance, which is the basis for the emergence of life-threatening arrhythmias, as are accompanied by low HRV.

**The aim of the article:** To determine the relationship of the ratio Tau/Ala serum with indices of HRV in patients with PICS and DM 2.

**Literature review:** Ventricular arrhythmias high gradations are the cause of death in almost half of patients with type 2 diabetes. This figure is almost three times higher than that in the General population and tends to increase, despite the influence of certain traditional risk factors (Kuanf et al., 2017; Triggiani et al., 2017; Huang, Boyle, Vaseghi, 2017). It is therefore particularly important task of the impact on certain specific indicators that should be considered along with the recognized, in the treatment of patients with PICS and of type 2 diabetes (Walker, & Cubbon, 2015; Agarwal, & Singh, 2017; Krishna et al., 2015).

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To date accumulated a significant amount of data regarding the changes of the metabolic benefits of myocardial ischemia in the direction of amino acids and their cardoperating and ameritron properties (Sarapultsev, Yushkov, & Sarapultsev, 2017; Powers et al., 2015; Barman, 2015).

Taurine (Tau) inhibits the release of norepinephrine from the presynaptic endings of adrenergic fibers, reducing the activity of sympathetic nervous system (SNS). The correlation of the low content of Tau and increased SNS tone (Andrikopoulos, Pastromas, & Tzeis, 2015; Page et al., 2016).

The significant role of Tau and formation as ischemic changes of the myocardium, the mechanisms of its antiarrhythmic effect was proved. The increase content of alanine (Ala), which is a competitor of Tau for penetration through the membrane of CMC is associated with increased cardiovascular risk according to the results of previous studies (Page et al., 2016; Bi, & Henry, 2017; Stewart et al., 2018; Piccolo et al., 2015; Zheng et al., 2016).

However, understudied, but promising is the relationship between Tau and Ala, with separate indices of HRV were not developed objective criteria for the appointment of amino acids and diagnostic and therapeutic target post-myocardial infarction patients with diabetes, the above defined need, goals and objectives of the study.

**Materials and method:** There were analyzed the results of a survey of 122 patients with PICS, which, according to the presence of DM2, comprised two groups: a study with concomitant DM2 (n=87): 50 women and 37 men, median age of the patients was 65, 2 years (microtile interval 61-69 years) and a comparison group without disorders of carbohydrate metabolism (n=35): 17 women and 18 men, median age 64.7 years (microtile interval – 64-67 years). The study involved patients with PICS and concomitant type 2 diabetes who gave appropriate informed consent.

Exclusion criteria from the study : chronic heart failure IIB – III stage according to the classification of Strazhesko-Vasilenko, acute coronary syndrome within the last 12 months, congenital and acquired heart defects, the presence of complete blockade LNPG, implanted pacemaker, AV blockade II-III grade, atrial fibrillation, autoimmune diseases, malignant cancers, expressed in kidney, liver, respiratory failure, endocrine diseases (except type 2 diabetes).

Amino acid spectrum of the blood of patients is determined by the method of chromatography (analyzer MicrotechnaT339). The normative value of AMC obtained based on a survey of 22 practically healthy persons of the control group (CG) matched for age and gender of examined patients: 10 men and 12 women, median age – 65, 3 years (microtile interval – 58-65, 5 years). Daily Holter ECG monitoring (of HMCG) was performed on the "Cardiosense".

In the process of data analysis HMM ECG determined the temporal and spectral indices of heart rate variability (HRV). Determined by the following time parameters: SDNN (MS) – standard deviation intervals R-R, RMSSD (MS) – standard deviation of the difference of successive NN intervals, pNN 50,% – % adjacent NN intervals, the difference between them exceeds 50 msec. Spectral parameters included: VLF (MS2) – power waves of very low frequency; ULF (MS2) – power of the waves ultra-low frequency; HF (MS2) high frequency component of the spectrum in the frequency range of 0.15-0.5 Hz; LF (MS2) low – frequency part of the spectrum in the frequency range from 0.04 to 0.15 Hz; TP, MS2 – total frequency range. The statistical analysis was performed using the statistical packages SPSS, MedStat, EZR.

**Results and discussion:** In the study, we found that blood content of Tau in patients with FHD without DM was significantly ( $p<0.001$ ) lower than in CG, and in patients with PICS and DM2 was lower ( $p<0.05$ ) than in patients with FHD without diabetes. Blood levels of Ala in patients with PICS without DM2 was significantly ( $p<0.001$ ) higher than in KG, and patients with FHD and SD higher ( $p<0.001$ ) than in patients with PICS without diabetes. Determined that Tau/Ala in patients with PICS without diabetes is significantly ( $p<0.001$ ) lower compared to the CG, and patients with PICS and DM2 lower ( $p<0.05$ ), compared with patients with PICS without diabetes (Table 1).

Table 1.

Indicators Tau/Ala, Ala, Tau in patients with PIX and type 2 diabetes, with PEAKS without carbohydrate metabolism abnormalities and those of the control group

Index	Patients with PICS and DM2 (n=87)	Patients with PICS (n=30)	Control group (n=22)
Tau, mg/100 ml	0.186 (0.145-0.290)*	0.229 (0.212-0.262)#	0,351(0.311-0.397)
Tau/Ala	0.031 (0.021-0.040) *#	0.412(0.23-0.046)#	0,841(0.822-0.983)

Notes: \*- p<0.001 – in comparison with patients CG

# – p<0.05 – in comparison with patients from the comparison group

So, we found a decrease in Tau and Tau ratio/Ala, in the blood of patients with PICS compared with persons KG. Moreover, a more significant decrease in Tau and Tau/Ala is observed in patients with PICS and type DM2. The decrease in the taurine content in the blood of patients with diabetes was determined. It can be explained by the accumulation of sorbitol in the tissues upon activation of the polyol channel of glucose oxidation under conditions of hyperglycemia. On the one hand, this leads to a decrease in Tau synthesis in cells, and on the other hand, to a decrease in the activity of glutathione reductase, and, consequently, to a decrease in the reduction of oxidized glutathione. As a result, oxidative stress occurs (Geidenstam, Danielsson, Spéjel, & Ridderstråle, 2016; Boulet et al., 2015; Avetisyan et al., 2017; Hosford, Millar, & Ramage, 2015).

As a result of comparing the time parameters of HRV, we found that in the groups of patients with PICS, the indicators were significantly lower compared with the CG individuals (p<0.05). Moreover, the group of patients with concomitant diabetes was characterized by a more pronounced decrease in these indicators when compared with a group of patients without impaired carbohydrate metabolism (p<0.05) (Tables 2, 3).

Table 2.

HRV indices in patients with PICS and DM2, with PICS without impaired carbohydrate metabolism

Index	Patients with PICS and DM2 (n=87)	Patients with PICS (n=30)	Control group (n=22)
SDNN, mc	88.7 (87.1-100.4)**#	97.2 (87.8-119.3)	125.6 (117.3-126.8)
RMSSD, mc	20.1 (17.3-22.4)**#	23.8 (21.6-24.8)#	33.1 (27.8-35.4)
pNN 50.%	2.74 (1.85-2.78)*	3.29 (2.99-5.1)#	9.22 (8.67-9.57)

Notes: \*- p<0.01, \*\* p<0.001 – in comparison with patients CG

# – p<0.001 – in comparison with patients from the comparison group.

Table 3.

Spectral indicators of HRV in patients with PICS and DM 2, with PICS without impaired carbohydrate metabolism

Notes: \*- p<0.001 – in comparison with patients CG

Index	Patients with PICS and DM2 (n=87)		Patients with PICS (n=30)		Control group (n=22)	
	Day	Night	Day	Night	Day	Night
HF, mc <sup>2</sup>	110.12*# (98.61-115.63)	201.43*## (178.6-215.65)	173.54# (148.61-215.6)	271.32# (208.61-315.3)	365.43 (328-417,3)	515.3 (428-517.3)
LF mc <sup>2</sup>	220.76 (198.61-235.6)	421.49# (376.6-515.03)	280.34# (248.6-315.53)	465.11# (398.1-515.3)	650.12 (608-715.3)	702.13 (628-717.1)
LF/HF	2.91* (1.61-10.68)	2.46* (1.61-3.63)	2.39## (1.71-3.23)	1.9## (1.11-2.23)	2.1 (1.61-2.53)	1.72 (1.65-2.2)
TP, mc <sup>2</sup>	1522.54 (1487.6-1525)	1870.81*# (1756.1-1223)	1822.43 (1788-2015.3)	2223.41 (1898.6-2235)	3421.15 (3345-3571)	3120.11 (3045-3341)
ULF, mc <sup>2</sup>	552.68# (478-565.6)	407.31# (398.61-415.8)	627.41# (607.5-715.63)	446.42## (434.61-515.1)	984.13 (981.1-997)	557.12 (481.1-607)
VLF, mc <sup>2</sup>	43.76 (42.2-45.75)	951.52 * # (881-1015.67)	45.11 (38.41-55.62)	992.47 (928.61-1021)	48.14 (45.1-52.63)	1345.14 (1281-1397)

# – p<0.05, # – p<0.001 – in comparison with patients from the comparison group

The data obtained indicate the rigidity of HRV, more pronounced in patients with PICS and DM 2, compared with patients with PICS without impaired carbohydrate metabolism. An analysis of the spectral parameters of HRV revealed a significant ( $p < 0.05$ ) decrease in power in the low-frequency range (LF) in both groups of PICS patients compared with CG, and in the group of patients with diabetes this decrease was more significant in comparison with patients without impaired carbohydrate metabolism ( $p < 0.05$ ). Changes in the spectrum power in the high frequency range (HF) turned out to be similar to changes in the spectrum power in the low frequency range.

The decrease in HF in the groups of patients with PICS without diabetes was less pronounced than in the group of patients with PICS and diabetes ( $p < 0.05$ ). Moreover, the ratio of LF/HF in patients with concomitant diabetes was within normal limits (Tables 4, 5).

Table 4.

Correlation between Tau / Ala Indicators and HRV Timing in Patients with PICS and DM 2

Index	SDNN, mc	RMSSD, mc	pNN 50.%
Tau/Ala	$r=0.65$ $p < 0.05$	$r=0.69$ $p < 0.05$	$r=0.51$ $p < 0.05$

Table 5.

Correlation relationships between Tau / Ala and HRV spectral indices in patients with PICS and DM 2,  $p < 0.05$

Index	HF, $mc^2$	LF, $mc^2$	LF/HF	TP, $mc^2$	ULF, $mc^2$	VLF, $mc^2$
Tau/Ala	$r=0.62$	$r=0.77$	$r=0.52$	$r=0.82$	$r=0.55$	$r=0.79$

## Conclusion

1. In patients with PICS compared with healthy individuals observed a significant decrease in the blood levels of Tau (at 34.75%,  $p < 0.001$ ) and Tau/Ala (at 51.01%,  $p < 0.001$ ). The presence of comorbid diabetes is accompanied by more significant decrease in these parameters Tau (by 46.72%,  $p < 0.001$ ) and Tau/Ala (for the accounting period 82.22%,  $p < 0.001$ ) compared with healthy individuals, which may be associated with pathogenetic mechanisms of disorders of carbohydrate metabolism.

2. The decrease in the value of the content ratio Taurine/Alanine in the blood of patients PICS with concomitant diabetes compared with patients without disorders of carbohydrate metabolism, accompanied by a reduction of the spectral indices of heart rate variability. Between Tau/Ala and SDNN, LF, TP, VLF revealed strong positive between Tau/Ala and RMSSD, HF, pNN 50.%, ULF, – moderate strength positive correlation, which however does not mean causal relationship and further research.

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