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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

The usefulness of sST2 and galectin-3 as novel biomarkers for better risk stratification in hypertrophic cardiomyopathy

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Abstract

Background: Estimation of sudden cardiac death (SCD) risk is an integral part of clinical management of patients with hypertrophic cardiomyopathy (HCM). Identification of novel biomarkers of this disease can provide additional criteria for SCD risk stratification. Soluble suppression of tumourigenicity (sST2) and galectin-3 (Gal-3) are useful biomarkers for prognosis of heart failure (HF). Both of them appear to mediate cardiac fibrosis — an important pathogenetic process in HCM. Data about sST2 and Gal-3 usefulness in patients with HCM are limited.

Aim: The aim of this study was to evaluate sST2 and Gal-3 as potential novel biomarkers for better risk stratification in hypertrophic cardiomyopathy.

Methods: Serum sST2 and serum Gal-3 levels were measured in 57 patients with HCM and in 18 healthy controls. The patients with HCM underwent routine evaluation including medical history, physical examination, blood tests (including N-terminal pro-B-type natriuretic peptide [NT-proBNP] and high-sensitivity cardiac troponin T [hs-cTnT] measurements), 12-lead electrocardiography (ECG), 48-h Holter monitoring and two-dimensional (2D) echocardiography with the assessment of the maximal left ventricular wall thickness, left atrial diameter, maximal left ventricular outflow tract gradient, and left ventricular ejection fraction. Risk of SCD at five years according to HCM SCD-risk calculator was evaluated. The control group underwent ECG, 2D echocardiography, and NT-proBNP measurements to exclude asymptomatic heart disease.

Results: Concentrations of sST2 and Gal-3 were significantly higher in patients with HCM than in controls (14.9 ± 5.8 ng/mL vs. 11.7 ± 3.3 ng/mL, p = 0.03 and 8.4 ng/mL [6.8–10.0] vs. 6.2 ng/mL [5.8–7.7], p = 0.005, respectively). Levels of sST2 and Gal-3 were considerably different in the New York Heart Association (NYHA) groups (p = 0.008, p = 0.009, respectively). Patients who presented non-sustained ventricular tachycardia (nsVT) on 48-h Holter monitoring had higher levels of sST2 (19.1 ng/mL [12.2–24.2] vs. 13.2 ng/mL [10.0–17.1], p = 0.02). There were no significant relationships between sST2 and Gal-3 levels and HCM SCD-risk, history of syncope presence, family history of SCD, and echocardiographic parameters.

Conclusions: Gal-3 levels and sST2 levels were higher in patients with HCM than in the control group. There were significant differences in Gal-3 levels between NYHA classes, but no correlations between Gal-3 levels and other parameters were found. Apart from differences in sST2 levels between NYHA classes, we demonstrated higher levels of sST2 in patients with nsVT. These findings suggest that sST2 may be useful as an additional biomarker for better risk stratification in hypertrophic cardiomyopathy.

Key words: soluble suppression of tumourigenicity (sST2), galectin-3 (Gal-3), hypertrophic cardiomyopathy, biomarker, hypertrophic cardiomyopathy

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INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common of the monogenic heart diseases, with a prevalence in the general population of at least 1/500 and possibly 1/200 [1, 2]. The annual incidence of cardiovascular death among patients with HCM was estimated to be 1–2%, with sudden cardiac death (SCD), heart failure (HF), and less frequently thromboembolic events being the main causes of mortality [3]. Estimation of SCD risk is an integral part of clinical management of patients with HCM. Identification of novel biomarkers of this disease can provide additional criteria for SCD risk stratification. Currently, only two circulating biomarkers, N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT), have significant value in HCM and are mentioned as such in the European Society of Cardiology (ESC) guidelines [3]. Soluble suppression of tumourigenicity 2 (sST2) and galectin-3 (Gal-3) are emerging biomarkers in the field of HF, and both of them have recently gained interest as potential biomarkers in other cardiac diseases [4]. Although sST2 and Gal-3 appear to mediate myocardial fibrosis — an important pathogenetic process in HCM, data about their usefulness in patients with HCM are limited. ST2 is a member of the interleukin-1 (IL-1) receptor/Toll-like receptor superfamily and has two isoforms: a membrane-bound receptor form (ST2L) and a soluble form (sST2). The ST2 gene is upregulated by cardiomyocytes and cardiac fibroblasts in response to mechanical stress. The ligand for ST2 is interleukin-33 (IL-33). IL-33 and its receptor ST2L are part of cardioprotective system that inhibits inflammatory response, and helps to prevent fibrosis and hypertrophy of cardiomyocytes. The soluble form of ST2 acts as a decoy receptor, reverses the beneficial effects of IL-33/ST2L by binding IL-33 and preventing signalling through ST2L. Therefore, it is postulated that sST2 could be a mediator of myocardial fibrosis [4–6]. Gal-3 is a soluble beta-galactoside-binding lectin involved in many pathophysiological processes including inflammation, cardiac fibrosis, and remodelling [6–11]. Based on the information described above and the potential relationship between cardiac fibrosis and SCD, we hypothesised that sST2 and Gal-3 could help better identify patients with HCM at higher risk of SCD and add useful prognostic information. The aim of this study was to evaluate the potential role of sST2 and Gal-3 as biomarkers in HCM.

METHODS

The study complies with the principles outlined in the Declaration of Helsinki and was approved by the Institutional Ethics Committee.

Study population

The study group included 57 consecutive patients with HCM and 18 healthy controls. Informed consent was obtained from each participant. The criteria for diagnosis of HCM, according to ESC guidelines, was the presence of left ventricular (LV) wall thickness of at least 15 mm without any other cause that could lead to ventricular hypertrophy [3]. The exclusion criteria were: prior myocardial infarction, current symptoms suggestive of coronary artery disease, class IV New York Heart Association (NYHA) functional classification of HF, renal dysfunction defined as an estimated glomerular filtration rate < 50 mL/min/1.73 m^2, concomitant neoplasm, infection, and connective tissue disease. Subjects who had a history of alcohol septal ablation or septal myectomy were not included into the present study.

All patients underwent routine evaluation including medical history, physical examination, blood tests (including NT-proBNP, hs-cTnT and creatine kinase [CK] measurements), 12-lead electrocardiography (ECG), 48-h Holter monitoring to detect non-sustained ventricular tachycardia (nsVT) defined as three or more consecutive ventricular beats > 120 bpm, and two-dimensional (2D) echocardiography with the assessment of the maximal LV wall thickness in diastole (MWT), left atrial diameter (LAD), maximal LV outflow tract (LVOT) gradient, and LV ejection fraction (LVEF). All patients underwent standard cardiac magnetic resonance (CMR) imaging on a 1.5 T scanner (Avanto, Siemens, Erlangen, Germany) to calculate MWT. Risk of SCD at five years according to HCM SCD-risk calculator was evaluated [3]. The control group with no significant medical history and with normal physical examination underwent ECG, 2D echocardiography, and NT-proBNP measurements to exclude asymptomatic heart disease.

Measuring sST2 and Gal-3 levels

Venus blood sample was taken without anticoagulants from all participants after overnight fast. Blood samples were centrifuged at 1000 g for 15 min, and the sera were aliquoted and stored at –20°C until analysis. Repeated freeze-thaw cycles were avoided. For the quantitative determination of human ST2 the Quantikine sandwich enzyme-linked immunosorbent assay (ELISA) kit was used. The sensitivity of the assay was 5.1 pg/mL; intra- and inter-assay coefficient of variation (CV) was 5.6% and 7.1%, respectively. For the quantitative determination of human Gal-3 the Quantikine sandwich ELISA kit was applied. The sensitivity of the assay was 0.016 ng/mL; intra- and inter-assay CV was 3.8% and 6.3%, respectively. The immunoassay kits were purchased from R&D Systems, Minneapolis, Minnesota, USA.

Statistical analysis

After checking for normal distribution with the Shapiro-Wilk test, continuous variables were compared using either Student's t-test or the Mann-Whitney test as appropriate. The Kruskal-Wallis test was performed to assess differences between more than two groups. The normally distributed con-

Table 1. Clinical characteristics of patients with hypertrophic cardiomyopathy (HCM) and information about the control group

Parameter	Patients with HCM (n = 57)	Control group (n = 18)	p
Gender (female)	20 (35.1%)	8 (44.4%)	0.48
Age [years]	52.0 [39.0–59.0]	41.5 [34.0–47.0]	0.057
sST2 [ng/mL]	14.9 ± 5.8	11.7 ± 3.3	**0.030**
Galectin-3 [ng/mL]	8.4 [6.8–10.0]	6.2 [5.8–7.7]	**0.005**
NT-proBNP [pg/mL]	861.1 [472.0–1821.0]	39 [18.2–50.6]	**< 0.0001**
hs-cTnT [ng/L]	13.3 [7.8–24.9]		
Creatine kinase [U/L]	116 [89.5–163.0]		
NYHA class	2 [1.0–2.0]		
NYHA I	23 (40.3%)		
NYHA II	30 (52.6%)		
NYHA III	4 (7.0%)		
Unexplained syncope	13 (22.8%)		
Family history of sudden death	9 (15.8%)		
nsVT	16 (28.1%)		
Paroxysmal AF	8 (14.0%)		
SVT	24 (42.1%)		
MWT [mm]	22 [20.0–25.0]		
MWT ≥ 30 mm	5 (8.8%)		
LAD [mm]	47.4 ± 6.6		
SAM	38 (66.7%)		
Resting LVOT gradient ≥ 30 mm Hg	27 (47.4%)		
Maximal LVOT gradient [mm Hg]	57 [4–100]		
LVEF	60 [60.0–65.0]		
Asymmetric hypertrophy	56 (98.2%)		
Mid-cavity obstruction	5 (8.8%)		
Apical hypertrophy	1 (1.8%)		
HCM SCD-risk	4.15 [2.8–7.2]		
HCM SCD-risk ≥ 6%	18 (31.6%)		

Data are presented as numbers and percentages, means ± standard deviations or medians [interquartile ranges]. Student's t-test was performed for normally distributed continuous variables. Mann-Whitney test was performed for non-parametrically distributed variables; NYHA — New York Heart Association classification of heart failure; nsVT — non-sustained ventricular tachycardia; AF — atrial fibrillation; SVT — supraventricular tachycardia; MWT — maximal left ventricular wall thickness; LAD — left atrial diameter; SAM — systolic anterior motion of the mitral valve; LVOT — left ventricular outflow tract; LVEF — left ventricular ejection fraction; HCM SCD-risk — risk of sudden cardiac death at five years according to HCM SCD-risk calculator; NT-proBNP — N-terminal pro-B-type natriuretic peptide; hs-cTnT — high-sensitivity cardiac troponin T

tinuous variables were shown as mean ± standard deviation, and non-parametrically distributed were shown as median [interquartile range]. Categorical variables were expressed as frequency (percentage) of patients and were compared using the χ^2 test or the Fisher exact test. Correlation was performed between two continuous variables by Spearman test. A two-side p value of less than 0.05 was considered statistically significant. Logistic regression was performed to identify potential predictors of the presence of nsVT. Variables with p values of less than 0.10 in the univariate analysis were supposed to be included into the multivariate regression model. All statistical analyses were performed using MedCalc 12.1.4.0 software (MedCalc; Mariakerke, Belgium).

RESULTS

The clinical data of the patients with HCM and a comparison of characteristics of patients with HCM versus the control group is outlined in Table 1. There was no significant difference between the groups in terms of sex. Considering age, the difference was of borderline statistical significance: p = 0.057. Concentrations of sST2, Gal-3, and NT-proBNP were significantly higher in patients with HCM than in the control group

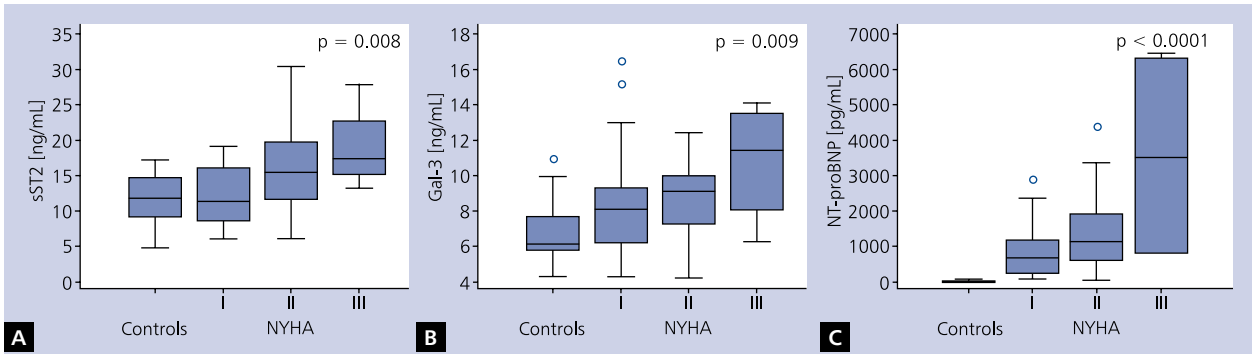

Figure 1. Levels of suppression of tumourigenicity (sST2) (**A**), galectin-3 (Gal-3) (**B**), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) (**C**) in the control group and in groups of patients with hypertrophic cardiomyopathy, according to New York Heart Association (NYHA) functional classification (Kruskal-Wallis test)

Table 2. Associations of biomarkers levels (sST2, Gal-3, NT-proBNP, and hs-cTnT) with clinical features of hypertrophic cardiomyopathy (HCM) patients

	sST2 [ng/mL]	Galectin-3 [ng/mL]	NT-proBNP [pg/mL]	hs-cTnT [ng/L]
Females (n = 20)	11.7 [8.8–16.3]	8.8 [7.1–11.4]	1549 [844–2290]	14.1 [8.0–28.9]
Males (n = 37)	15.9 [11.7–19.0]	8.4 [6.3–9.8]	728 [258–1376]	13.3 [7.3–24.4]
p	**0.047**	0.15	**0.004**	0.81
Unexplained syncope (n = 13)	10.5 [9.1–16.8]	8.1 [6.6–8.7]	1237 [768–1715]	8.8 [5.1–19.1]
No syncope (n = 44)	15.0 [11.1–19.0]	8.9 [7.1–10.0]	844 [306–1823]	14.1 [8.9–25.1]
p	0.14	0.18	0.42	0.09
Family history of SCD (n = 9)	14.8 [10.1–19.5]	8.1 [6.8–9.7]	1488 [1138–2484]	10.2 [6.8–25.9]
No history of SCD (n = 48)	15.0 [9.8–18.7]	8.4 [6.6–10.0]	837 [284–1721]	13.3 [7.5–24.6]
p	0.92	0.72	0.025	0.55
nsVT* (n = 16)	19.1 [12.2–24.2]	8.8 [6.9–9.8]	843 [538–2188]	24.2 [9.1–31.1]
No nsVT (n = 41)	13.2 [10.0–17.1]	8.4 [6.8–10.0]	906 [293–1690]	11.5 [7.4–20.8]
p	**0.02**	0.80	0.57	0.07
Resting LVOT gradient ≥ 30 mm Hg (n = 27)	13.2 [9.8–18.7]	8.1 [6.4–10.1]	1154 [838–1890]	14.6 [8.6–26.4]
Resting LVOT gradient < 30 mm Hg (n = 30)	15.1 [10.2–18.4]	8.7 [6.9–9.9]	665 [242–1311]	10.3 [6.8–24.1]
p	0.70	0.89	**0.027**	0.27
HCM SCD-risk ≥ 6% (n = 18)	15.0 [9.2–22.8]	8.6 [6.8–9.8]	1530 [842–2344]	20.5 [8.8–31.1]
HCM SCD-risk< 6% (n = 39)	14.9 [10.3–18.1]	8.4 [6.6–10.1]	795 [252–1544]	11.5 [7.1–22.9]
p	0.67	0.65	0.005	0.17

Abbreviations are the same as in Table 1. Data are presented as mean and standard deviation or median with interquartile range. Student's t-test was performed for normally distributed continuous variables. Mann-Whitney test was performed for non-parametrically distributed variables.
*37 patients underwent 48-h Holter ECG monitoring and 20 patients underwent 24-h Holter ECG monitoring at least twice

(14.9 ± 5.8 ng/mL vs. 11.7 ± 3.3 ng/mL, p = 0.03; 8.4 ng/mL [6.8–10.0] vs. 6.2 ng/mL [5.8–7.7], p = 0.005; and 861.1 pg/mL [472.0–1821.0] vs. 39 pg/mL [18.2–50.6], p < 0.0001, respectively). Concentrations of sST2 and Gal-3 were compared in the groups according to NYHA classification of HF and in the control group, and their levels were considerably different (p = 0.008, p = 0.009, respectively; Fig. 1), increasing with worse functional status (Jonckheere-Terpstra test for trend: p < 0.001 both for sST2 and Gal-3).

Associations between biomarkers levels: sST2, Gal-3, NT-proBNP, and hs-cTnT and clinical features of HCM patients are summarised in Table 2.

Patients who presented nsVT on 48-h Holter monitoring or had previously documented history of nsVT had

higher levels of sST2 (19.1 ng/mL [12.2–24.2] vs. 13.2 ng/mL [10.0–17.1], p = 0.02). There was no significant difference between the group with nsVT and the group without nsVT in terms of age (48.5 [40.5–59.5] vs. 52.0 [36.0–58.2], p = 0.80). Although no correlations were found between sST2 levels and echocardiographic parameters, there was significant positive correlation between sST2 levels and MWT assessed by CMR (r = 0.32, p = 0.015). We also observed borderline significantly increased sST2 levels in male patients (15.9 ng/mL [11.7–19.0] vs. 11.7 ng/mL [8.8–16.3], p = 0.047). No other relationships between sST2 levels and clinical features of patients were found. There were no significant relationships between Gal-3 levels and HCM SCD-risk, syncope presence, family history of SCD, nsVT, and echocardiographic parameters.

Levels of NT-proBNP were increased in the group of patients with risk of SCD at five years according to HCM SCD-risk calculator ≥ 6% (1530 pg/mL [842–2344] vs. 795 pg/mL [252–1544], p = 0.005), in the group with resting LVOT gradient ≥ 30 mm Hg (1154 pg/mL [838–1890] vs. 665 pg/mL [242–1311], p = 0.027), and in the group with family history of SCD (1488 pg/mL [1138–2484] vs. 837 pg/mL [284–1721], p = 0.025). Females with HCM also had higher concentrations of NT-proBNP (1549 pg/mL [844–2290] vs. 728 [258–1376], p = 0.004). We confirmed positive correlations between NT-proBNP levels and MWT assessed by echocardiography as well as CMR (r = 0.35, p = 0.008 and r = 0.42, p = 0.001, respectively), LAD (r = 0.3, p = 0.025), and HCM SCD-risk (r = 0.36, p = 0.007). Levels of hs-cTnT were positively correlated with LAD (r = 0.45, p = 0.0004). Similarly to sST2, no correlation was found between hs-cTnT levels and MWT assessed by echocardiography; however, there was significant positive correlation between hs-cTnT levels and MWT assessed by CMR (r = 0.31, p = 0.017). In order to identify independent determinants of the presence of nsVT logistic regression was performed. The included variables were as follows: levels of sST2, Gal-3, hs-cTnT, NT-proBNP, worse functional class (NYHA III), resting LVOT gradient at least 30 mm Hg, and hypertrophy severity (MWT). Variables with p values less than 0.10 in the univariate analysis were supposed to be included into the multivariate regression model, but only sST2 was firmly associated with the occurrence of the ventricular arrhythmia in univariate analysis (OR 1.16, 95% CI 1.04–1.30, p = 0.01).

DISCUSSION

The prediction and prevention of SCD remain a big challenge in the management of patients with HCM. Circulating biomarkers as additional tests to complement currently available tools would be helpful to improve prognostic accuracy and to provide better insight into the pathogenesis of HCM. Although sST2 and Gal-3 were evaluated in a wide range of patient types, and both of them appear to mediate cardiac fibrosis, there are scarce data about their usefulness in patients with HCM. We found that concentrations of sST2 and Gal-3 were significantly higher in patients with HCM than in the control group (p = 0.03 and p = 0.005), but the differences were not as great as in the case of NT-proBNP levels (p < 0.0001). The finding that levels of sST2 and Gal-3 were clearly increased in HCM patients with symptoms of more advanced HF corresponds to literature data suggesting that sST2 and Gal-3 are useful biomarkers for prognosis of HF [12–14]. Soluble ST2 and Gal-3 are predictive for hospitalisation and death in patients with HF and also add additional prognostic value over natriuretic peptides according to American College of Cardiology/American Heart Association guidelines for the management of HF, but neither of these biomarkers are included in the ESC guidelines for the diagnosis and treatment of acute and chronic HF [15, 16].

Considering Gal-3, there is a report that plasma Gal-3 levels positively correlate with the thickness of the interventricular septum and with LV mass index evaluated by transthoracic echocardiography in patients with HCM [17]. However, our findings differ from those of Yakar Tülüce et al. [17]. No correlation was found between Gal-3 levels and clinical features, echocardiographic parameters as well as MWT assessed by CMR in patients with HCM.

Levels of sST2 were increased in the presence of ventricular arrhythmia, while other biomarkers (Gal-3, NT-proBNP, and hs-cTnT) remained unaltered. Although sST2 is a biomarker for prognosis of HF, the group with nsVT on Holter monitoring did not consist of patients with more advanced HF symptoms. Half of them belonged to NYHA class I. These findings suggest that increased levels of sST2 were associated with ventricular arrhythmia irrespective of HF symptoms, and that sST2 may have potential as a biomarker in HCM. There are also reports that sST2 is associated with ventricular arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy and in patients with mildly symptomatic HF, which makes our observations more interesting and suggests further research in this field [18, 19]. On the other hand, no correlation was found between sST2 levels and HCM SCD-risk or other risk factors of SCD except for correlation with LV hypertrophy assessed by CMR. HCM SCD-risk score seem to be more prognostically relevant for managing decisions in a HCM patient than prediction of the nsVT. The relationship between nsVT and higher risk of SCD is observed in young patients with HCM [20]. Our study population consists of more advanced-age individuals (age of the group with nsVT: 48.5 [40.5–59.5] years), and in older patients (over 40 years old) nsVT is more related to a progressive myocyte loss and fibrosis and does not necessarily correlate with increased SCD risk [20].

The correlation between sST2 levels and MWT assessed by CMR was similar to the correlation between hs-cTnT levels and MWT assessed by CMR, but weaker than the correlation

between NT-proBNP levels and MWT. These results correspond to previous data, showing that cardiac troponins and NT-proBNP are associated with the extent of LV hypertrophy [21–23]. In contrast to sST2, Gal-3, and hs-cTnT, levels of NT-proBNP were also increased in the group of patients with risk of SCD at five years according to HCM SCD-risk calculator at least 6%, in the group with resting LVOT gradient at least 30 mm Hg and in the group with family history of SCD. We confirmed positive correlations between NT-proBNP levels and HCM SCD-risk and LAD. Our results, which are consistent with previous data, show that NT-proBNP levels in patients with HCM correlate positively with hypertrophy severity and LVOT gradient, and predict death and HF-related events, making NT-proBNP a more valuable biomarker for prognosis of HCM than sST2 [24, 25].

Limitations of the study

There are some limitations related with the present study: the study population was relatively small and the difference, of borderline statistical significance, in terms of age between group of patients with HCM and controls might have introduced a bias.

CONCLUSIONS

The results of this study confirm that NT-proBNP and hs-cTnT are valuable biomarkers in HCM. Particularly, NT-proBNP was better correlated to risk factors for SCD in HCM than either Gal-3 or sST2. There was no correlation between Gal-3 levels and assessed parameters. Apart from elevated levels of sST2 in HCM patients compared to controls, and differences in sST2 levels between NYHA classes, we demonstrated that higher levels of sST2 were independently associated with ventricular arrhythmias. Our results suggest that sST2 may provide some information about disease severity, in addition to those obtained from NT-proBNP and hs-cTnT measurements, but further research is needed to verify these results and to assess whether sST2 can be used as a reliable biomarker for better risk stratification in patients with HCM.

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References

1. Maron BJ, Gardin JM, Flack JM, et al. Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA Study. Coronary Artery Risk Development in (Young) Adults. Circulation. 1995; 92(4): 785–789, indexed in Pubmed: 7641357.
2. Semsarian C, Ingles J, Maron MS, et al. New perspectives on the prevalence of hypertrophic cardiomyopathy. J Am Coll Cardiol. 2015; 65(12): 1249–1254, doi: 10.1016/j.jacc.2015.01.019, indexed in Pubmed: 25814232.
3. Elliott PM, Anastasakis A, Borger MA, et al. Authors/Task Force members. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014; 35(39): 2733–2779, doi: 10.1093/eurheartj/ehu284, indexed in Pubmed: 25173338.
4. Meijers WC, van der Velde AR, de Boer RA. ST2 and Galectin-3: Ready for Prime Time? EJIFCC. 2016; 27(3): 238–252, indexed in Pubmed: 27683537.
5. Zile MR, Baicu CF. Biomarkers of diastolic dysfunction and myocardial fibrosis: application to heart failure with a preserved ejection fraction. J Cardiovasc Transl Res. 2013; 6(4): 501–515, doi: 10.1007/s12265-013-9472-1, indexed in Pubmed: 23716130.
6. Schmitter D, Cotter G, Voors AA. Clinical use of novel biomarkers in heart failure: towards personalized medicine. Heart Fail Rev. 2014; 19(3): 369–381, doi: 10.1007/s10741-013-9396-5, indexed in Pubmed: 23709316.
7. de Boer RA, Yu L, van Veldhuisen DJ. Galectin-3 in cardiac remodeling and heart failure. Curr Heart Fail Rep. 2010; 7(1): 1–8, doi: 10.1007/s11897-010-0004-x, indexed in Pubmed: 20425490.
8. Szadkowska I, Wlazeł RN, Migała M, et al. The association between galectin-3 and clinical parameters in patients with first acute myocardial infarction treated with primary percutaneous coronary angioplasty. Cardiol J. 2013; 20(6): 577–582, doi: 10.5603/CJ.2013.0157, indexed in Pubmed: 24338533.
9. Yin QS, Shi B, Dong L, et al. Comparative study of galectin-3 and B-type natriuretic peptide as biomarkers for the diagnosis of heart failure. J Geriatr Cardiol. 2014; 11(1): 79–82, doi: 10.3969/j.issn.1671-5411.2014.01.014, indexed in Pubmed: 24748886.
10. Toprak G, Yüksel H, Demirpençe Ö, et al. Fibrosis in heart failure subtypes. Eur Rev Med Pharmacol Sci. 2013; 17(17): 2302–2309, indexed in Pubmed: 24065222.
11. Liu YH, D'Ambrosio M, Liao Td, et al. N-acetyl-seryl-aspartyl-lysyl-proline prevents cardiac remodeling and dysfunction induced by galectin-3, a mammalian adhesion/growth-regulatory lectin. Am J Physiol Heart Circ Physiol. 2009; 296(2): H404–H412, doi: 10.1152/ajpheart.00747.2008, indexed in Pubmed: 19098114.
12. Aimo A, Vergaro G, Passino C, et al. Prognostic Value of Soluble Suppression of Tumorigenicity-2 in Chronic Heart Failure: A Meta-Analysis. JACC Heart Fail. 2017; 5(4): 280–286, doi: 10.1016/j.jchf.2016.09.010, indexed in Pubmed: 27816512.
13. Mueller T, Gegenhuber A, Leitner I, et al. Diagnostic and prognostic accuracy of galectin-3 and soluble ST2 for acute heart failure. Clin Chim Acta. 2016; 463: 158–164, doi: 10.1016/j.cca.2016.10.034, indexed in Pubmed: 27983996.
14. French B, Wang Le, Ky B, et al. Prognostic Value of Galectin-3 for Adverse Outcomes in Chronic Heart Failure. J Card Fail. 2016; 22(4): 256–262, doi: 10.1016/j.cardfail.2015.10.022, indexed in Pubmed: 26571149.
15. Yancy CW, Jessup M, Bozkurt B, et al. American College of Cardiology Foundation, American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013; 62(16): e147–e239, doi: 10.1016/j.jacc.2013.05.019, indexed in Pubmed: 23747642.
16. Ponikowski P, Voors AA, Anker SD, et al. Authors/Task Force Members, Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Associa-

tion (HFA) of the ESC. Eur J Heart Fail. 2016; 18(8): 891–975, doi: 10.1002/ejhf.592, indexed in Pubmed: 27207191.
17. Yakar Tülüce S, Tülüce K, Çil Z, et al. Galectin-3 levels in patients with hypertrophic cardiomyopathy and its relationship with left ventricular mass index and function. Anatol J Cardiol. 2016; 16(5): 344–348, doi: 10.5152/AnatolJCardiol.2015.6191, indexed in Pubmed: 26488381.
18. Broch K, Leren IS, Saberniak J, et al. Soluble ST2 is associated with disease severity in arrhythmogenic right ventricular cardiomyopathy. Biomarkers. 2017; 22(3-4): 367–371, doi: 10.1080/1354750X.2016.1278266, indexed in Pubmed: 28067540.
19. Skali H, Gerwien R, Meyer TE, et al. Soluble ST2 and Risk of Arrhythmias, Heart Failure, or Death in Patients with Mildly Symptomatic Heart Failure: Results from MADIT-CRT. J Cardiovasc Transl Res. 2016; 9(5-6): 421–428, doi: 10.1007/s12265-016-9713-1, indexed in Pubmed: 27798759.
20. Monserrat L, Elliott PM, Gimeno JR, et al. Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients. J Am Coll Cardiol. 2003; 42(5): 873–879, indexed in Pubmed: 12957435.
21. Cramer G, Bakker J, Gommans F, et al. Relation of highly sensitive cardiac troponin T in hypertrophic cardiomyopathy to left ventricular mass and cardiovascular risk. Am J Cardiol. 2014; 113(7): 1240–1245, doi: 10.1016/j.amjcard.2013.12.033, indexed in Pubmed: 24513467.
22. Kubo T, Kitaoka H, Okawa M, et al. Combined measurements of cardiac troponin I and brain natriuretic peptide are useful for predicting adverse outcomes in hypertrophic cardiomyopathy. Circ J. 2011; 75(4): 919–926, indexed in Pubmed: 21304210.
23. Kubo T, Kitaoka H, Yamanaka S, et al. Significance of high-sensitivity cardiac troponin T in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2013; 62(14): 1252–1259, doi: 10.1016/j.jacc.2013.03.055, indexed in Pubmed: 23623916.
24. Coats CJ, Gallagher MJ, Foley M, et al. Relation between serum N-terminal pro-brain natriuretic peptide and prognosis in patients with hypertrophic cardiomyopathy. Eur Heart J. 2013; 34(32): 2529–2537, doi: 10.1093/eurheartj/eht070, indexed in Pubmed: 23455360.
25. D'Amato R, Tomberli B, Castelli G, et al. Prognostic value of N-terminal pro-brain natriuretic Peptide in outpatients with hypertrophic cardiomyopathy. Am J Cardiol. 2013; 112(8): 1190–1196, doi: 10.1016/j.amjcard.2013.06.018, indexed in Pubmed: 23871673.

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Znaczenie sST2 i galektyny-3 jako nowych biomarkerów w kardiomiopatii przerostowej

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Streszczenie

Wstęp: Oszacowanie ryzyka nagłego zgonu (SCD) jest kluczową częścią oceny klinicznej pacjentów z kardiomiopatią przerostową (HCM). Identyfikacja nowych biomarkerów tej choroby może wnieść wiele cennych informacji, a być może dostarczy także dodatkowe kryteria stratyfikacji ryzyka SCD u osób z HCM. Białko sST2 i galektyna-3 (Gal-3) są przydatnymi biomarkerami prognostycznymi w niewydolności serca. Wydaje się, że oba te biomarkery mają związek z włóknieniem mięśnia sercowego — często obserwowanym i niekorzystnym procesem patogenetycznym w HCM. Dotychczas przydatność kliniczna sST2 i Gal-3 u pacjentów z HCM nie była szerzej badana.

Cel: Celem pracy jest ocena przydatności klinicznej wybranych biochemicznych markerów włóknienia: sST2 i Gal-3 w HCM.

Metody: Stężenia sST2 i Gal-3 zmierzono w surowicy 57 pacjentów z HCM oraz 18 zdrowych ochotników. U każdego chorego z HCM przeprowadzono badania podmiotowe i przedmiotowe, badania laboratoryjne z pomiarem stężeń N-końcowego propeptydu natriuretycznego typu B (NT-proBNP) i troponiny T oznaczonej za pomocą testu o wysokiej czułości (hs-cTnT), EKG, 48-godzinne badanie Holter EKG pod kątem złożonej arytmii komorowej (nsVT), badanie echokardiograficzne z oceną: maksymalnej grubości ściany lewej komory, wymiaru lewego przedsionka, gradientu w drodze odpływu lewej komory oraz frakcji wyrzutowej lewej komory. Ryzyko SCD w ciągu 5 lat zostało wyliczone na podstawie kalkulatora HCM SCD-risk. W grupie kontrolnej złożonej ze zdrowych ochotników wykonano EKG, echokardiografię oraz oznaczono NT-proBNP w celu wykluczenia asymptomatycznej choroby serca.

Wyniki: Stężenia sST2 i Gal-3 były istotnie wyższe w grupie pacjentów z HCM w porównaniu z grupą kontrolą (14,9 ± 5,8 ng/ml *vs*. 11,7 ± 3,3 ng/ml; p = 0,03 i 8,4 ng/ml [6,8–10,0] *vs*. 6,2 ng/ml [5,8–7,7]; p = 0,005, odpowiednio). Stężenia sST2 i Gal-3 różniły się między grupami pacjentów w różnych klasach niewydolności serca wg *New York Heart Association* (NYHA) (p = 0,008; p = 0,009, odpowiednio) i wzrastały wraz z nasileniem objawów niewydolności serca. Pacjenci, u których zarejestrowano nsVT w 48-godzinnym badaniu Holter EKG, charakteryzowali się istotnie wyższym stężeniem sST2 (19,1 ng/ml [12,2–24,2] *vs*. 13,2 ng/ml [10,0–17,1]; p = 0,02). Nie zaobserwowano związku między stężeniami badanych biomarkerów a ryzykiem SCD obliczonym wg kalkulatora HCM SCD-risk, omdleniami, wywiadem SCD w rodzinie oraz parametrami echokardiograficznymi.

Wnioski: Stężenia sST2 i Gal-3 były wyższe u pacjentów z HCM w porównaniu z grupą kontrolną. Stwierdzono także związek między stężeniami sST2 i Gal-3 a zaawansowaniem niewydolności serca u pacjentów z HCM. Nie zaobserwowano żadnych innych zależności pomiędzy stężeniami Gal-3 a klinicznymi cechami pacjentów z HCM. W przypadku sST2 stwierdzono związek między tym biomarkerem a występowaniem złożonej arytmii komorowej, niezależnie od nasilenia objawów niewydolności serca. sST2 może mieć potencjał jako dodatkowy biomarker stratyfikacji ryzyka SCD w HCM.

Słowa kluczowe: białko sST2, galektyna-3, kardiomiopatia przerostowa, biomarker, kardiomiopatia przerostowa

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