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sST2 Level at Decompensated Chronic Heart Failure in Patients with Dilated Cardiomyopathy

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Abstract

The purpose of the study was to evaluate the relationship between clinical and functional changes and sST2 levels in patients with dilated cardiomyopathy (DCM) admitted to the hospital due to decompensated chronic heart failure (CHF).

***Methods and Results*:** The study involved 64 DCM patients with clinical signs of decompensated CHF. According to the sST2 level, the patients were divided into two groups. Group 1 included 30 patients with sST2 level <35ng/ml; Group 2 included 34 patients with sST2 level ≥35ng/ml. All patients underwent the following examinations: collection of anamnestic data, physical examination, general clinical and laboratory blood tests, 12-lead ECG, conventional 2D echocardiography in M- and B-modes, the 6MWT, and the assessment of the quality of life according to the Minnesota Living with Heart Failure Questionnaire (MLHFQ). The serum level of sST2 was determined by enzyme immunoassay using the Presage ST2 Assay.

The duration of CHF was significantly longer in Group 2 than in Group 1(48.7±6.5 mth versus 29.6±7 mth $P<0.05$), and the number of hospitalizations per year was more frequent (Table 1). Group 2 patients were characterized by lower blood pressure levels and high heart rate ($P<0.05$). At the same time, the 6MWT value was lower and MLHFQ score was higher in Group 2 than in Group 1 ($P<0.001$ in both cases). In Group 1, LVEF was significantly higher and LVM was significantly lower than in Group 2 ($P<0.001$). All in all, Group 2 patients had more pronounced disorders in LV systolic dysfunction (Table 3). The correlation analysis revealed an inverse correlation between the sST2 level and 6MWT (r=-0.69, $P<0.01$), as well as LVEF (r=-0.26, $P<0.01$). Statistically significant direct correlations were found between the sST2evel and the size and volume of the LV cavities.

Conclusion: sST2 is a clinically relevant biomarker that reflects pathophysiological processes and provides prognostic information in the setting of DCM, especially in patients with HF.(**International Journal of Biomedicine. 2022;12(2):222-226.**)

Key Words: soluble suppression of tumorigenecity 2 • dilated cardiomyopathy • heart failure

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Abbreviations

6MWT, the 6-minute walk test; **CMPs**, cardiomyopathies; **CHF**, chronic heart failure; **DCM**, dilated cardiomyopathy; **DBP**, diastolic blood pressure; **HR**, heart rate; **HF**, heart failure; **LV**, left ventricle; **LVEF**, left ventricular ejection fraction; **LVM**, left ventricular mass; **LVEDD**, left ventricular end-diastolic diameter; **LVEDV**, left ventricular end-diastolic volume; **LVESD**, left ventricular end-systolic diameter; **LVESV**, left ventricular end-systolic volume; **LVPWT**, left ventricular posterior wall thickness; **MLHFQ**, Minnesota Living with Heart Failure Questionnaire; **mPAP**, mean pulmonary artery pressure; **NP**, natriuretic peptide; **sST2**, soluble suppression of tumorigenecity 2. **SBP,** systolic blood pressure.

Introduction

In recent decades, interest in the study of cardiomyopathies (CMPs) has grown. CMPs are a group of often inherited diseases characterized by structural and functional cardiac abnormalities, an unclear etiology, chronic progressive course and, ultimately, cardiomegaly, progressive heart failure (HF), arrhythmic, and thromboembolic syndrome, often resulting in sudden cardiac death.

Dilated cardiomyopathy (DCM), characterized by heterogeneity of clinical manifestations, is inevitably aggravated by the development of severe CHF, which is

associated with a decrease in the quality of life, frequent hospitalizations, and a high mortality rate, reaching 50% per year. Though this condition has been studied for more than half a century, these studies did not contribute to solving a number of issues related to the etiology, pathogenesis, and effective drug therapy. Based on current research data, it can be stated that the vast majority of cases of DCM are genetically determined, although the presence of the disease in close relatives cannot always be detected.[1,2] It is not yet possible to conduct extensive studies to identify genetic mutations before the onset of clinical symptoms or before the incidental detection of myocardial pathology. Moreover, the presence of an established genetic defect in the family is not always accompanied by clinical and/or morphological manifestations.

The biomarker strategy in diagnosis, risk assessment, and treatment seems to be the most optimal choice due to its high specificity to the main etiopathogenetic mechanisms of disease development and progression, such as inflammation, stress, myocyte injury, extracellular matrix remodeling, oxidative stress, and neurohormonal disorders. Clinical biomarkers such as cardiac troponin and N-terminal pro-BNP (NT-proBNP) are widely used in the diagnosis of heart failure (HF).[3-5] NPs recommended by international communities to diagnose heart failure have firmly entered the toolkit of routine use throughout the world. Meanwhile, in addition to NPs, the potential effectiveness of new biomarkers has been identified, in particular, ST2. For the first time, it has become known as a participant in inflammatory and autoimmune reactions.[3,6-8] ST2 is defined as the IL-33 receptor, as it binds to IL-33.[7,9] ST2 has two main isoforms: transmembrane or cellular (ST2L) and soluble or circulating (sST2) forms.[6,10] The blood sST2 level is increased in inflammatory diseases and in various heart diseases.[11] sST2 is released when cardiomyocytes stretch, neutralizing its ligand IL-33.[4,12] It is also associated with inflammation during myocardial infarction and HF.[13] Recently, sST2 is frequently reported to be associated with HF.[14-16] The 2013 American College of Cardiology and American Heart Association guidelines recommend measurement of ST2 for additive risk stratification in patients with acute or chronic ambulatory HF.[17]

A high risk of rehospitalization and death from HF is observed in the group of patients with decompensated CHF. In this group, mortality rate during the year, according to different authors, ranges from 17.4% to 23.7%, and taking into account hospital mortality rate, it reaches 29%. At the same time, the frequency of repeated hospitalizations during the first 30 days after discharge from the hospital is 20%-25%.

The purpose of the study was to evaluate the relationship between clinical and functional changes and sST2 levels in patients with the DCM admitted to the hospital due to decompensated CHF.

Materials and Methods

The study involved 64 DCM patients with clinical signs of decompensated CHF. The non-inclusion criteria were the presence of bronchopulmonary diseases(including asthma, COPD), chronic kidney disease(3b stages and higher), diabetes mellitus or taking hypoglycemic drugs, permanent atrial fibrillation, anemia, diseases of musculoskeletal system (coxarthrosis, gonarthrosis, etc., reducing motor activity), obesity (2-3 classes) and other severe somatic pathologies.

The study protocol was reviewed and approved by the Ethics Committee of the Republican Specialized Centre of Cardiology. All patients gave informed consent to participate in the study. The diagnosis of CHF was established according to 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure.[18]

According to the sST2 level, the patients were divided into two groups. Group 1 included 30 patients with sST2 level <35ng/ml (mean value of 20.6±5.7 ng/ml); Group 2 included 34 patients with sST2 level ≥35ng/ml (mean value of 77.3±8.8 ng/ml).

All patients underwent the following examinations: collection of anamnestic data, physical examination, general clinical and laboratory blood tests, 12-lead ECG, conventional 2D echocardiography according to the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging (2015) in M- and B-modes, the 6MWT, and the assessment of the quality of life according to the Minnesota Living with Heart Failure Questionnaire (MLHFQ).

The serum level of sST2 was determined by enzyme immunoassay using the Presage ST2 Assay (Critical Diagnostics, San Diego, CA, USA).

Statistical analysis was performed using the statistical software «Statistica» (v6.0, StatSoft, USA). Baseline characteristics were summarized as frequencies and percentages for categorical variables and as mean±standard deviation (SD) for continuous variables. Group comparisons with respect to categorical variables were performed using chi-square tests or, alternatively, Fisher's exact test when expected cell counts were less than 5. A probability value of $P<0.05$ was considered statistically significant.

Results

Our results showed that Group 1 patients were slightly younger than Group 2 patients, and males predominated in both groups (67% and 70%, respectively). The duration of CHF was significantly longer in Group 2 than in Group 1 (48.7±6.5 mth vs. 29.6±7 mth $P<0.05$), and the number of hospitalizations per year was more frequent (Table 1). Group 2 patients were characterized by lower blood pressure levels and high heart rate ($P<0.001$). At the same time, the 6MWT value was lower and MLHFQ score was higher in Group 2 than in Group 1 ($P<0.001$ in both cases) (Table 2). In Group 1, LVEF was significantly higher and LVM was significantly lower than in Group 2 ($P<0.001$). All in all, Group 2 patients had more pronounced disorders in LV systolic dysfunction (Table 3). The correlation analysis revealed an inverse correlation between the sST2 level and 6MWT($r=-0.69$, $P<0.01$), as well as LVEF($r=-0.26$, $P<0.01$). Statistically significant direct correlations were found between the sST2evel and the size and volume of the LV cavities.

Table 1.

Characteristics of patients in both groups

Variable	Group 1, n=30 sST2<35ng/ml	Group 2, n=34 ST2≥35ng/ml	*P*-value
Average age, yrs	36.95±5.38	40.53±5.14	0.0084
Male, n (%)	20 (67)	24 (70)	>0.05
Duration of CHF, months	29.6±7	48.7±6,5	<0.001
Number of hospitalizations per year, n (%): -more than 4 times a year -2-4 times a year -less than 2 times a year	 4 (13.3) 8 (26.7) 18 (60.0)	 14 (41.2) 14(41.2) 6(17.6)	 0.024 0.05 0.002

Table 2.

Clinical and systemic hemodynamic parameters of patients in both groups

Variable	Group 1, n=30 sST2 <35 ng/ml	Group 2, n=34 ST2 ≥35 ng/ml	*P*-value
SBP, mmHg	118.3±5.4	101.3±5.5	<0.0001
DBP, mmHg	75.3±3.5	60.3±4.5	<0.0001
HR, bpm	75.3±12.5	85.3±17.5	0.0117
6MWT, m	232.3±29.8	113.3±32.8	<0.0001
MLHFQ, total score	46.4±12.4	58.4±12.4	0.0003

Table 3.

Indicators of intracardiac hemodynamics in patients of both groups

Indicators	Group 1, n=30 ST2<35ng/ml	Group 2, n=34 ST2≥35ng/ml	P-value
LVEDD, mm	61.6±4.5	73.8±3.1	<0.0001
LVESD, mm	52.7±4.8	65.7±4	<0.0001
LBEDV, ml	210.7±20.6	270±21.4	<0.0001
LVESV, мл	131.6±26.2	189±11.5	<0.0001
LVEF, %	33.1±2.1	24.9±3.3	<0.0001
LA, mm	41.5±3.3	46.6±2.2	<0.0001
RV, mm	40±9.2	41.2±6.1	>0.05
LVM, g	273.3±23	345.4±24.5	<0.0001
PWLV, mm	8.15±0.69	9.54±0.75	<0.0001
mPAP, mmHg	45.1±6.2	62±5.7	<0.0001

Discussion

The success of using NT-proBNP as "gold standard" [19] both in practical medicine (as a reference for the diagnosis of CHF) and in scientific research is limited by many factors (impaired renal function, anemia, COPD, obesity) that can affect its level. sST2 has emerged as a new biomarker that may be used to improve management of heart failure patients beyond the diagnostic value of NPs.[10] Recently, sST2 was found to independently predict all-cause mortality and heart failure hospitalization in patients with CHF.[15] Elevated blood sST2 values have also been significantly correlated with LVEF and NYHA class.[20] Ky et al.[21] demonstrated that patients with sST2 higher than 36.6ng/mL have a three times higher risk of death or cardiac transplantation than those with lower values.

Under local inflammation and/or mechanical or biochemical stress, cardiac tissues produce protective cytokines such as IL-33 and growth differentiation factor-15.[22] In experimental models, the interaction between IL-33 and ST2L provided the cardioprotective effects, reducing myocardial fibrosis, cardiomyocyte hypertrophy, and apoptosis, as well as improving myocardial function. sST2 avidly binds to IL-33, competing with ST2L.[10] The interaction of sSH2 with IL-33 blocks the IL-33/ST2L system and, as a result, eliminates the IL-33 cardioprotective effects.[10] sST2 secreted by damaged cardiac tissue acts as a decoy receptor for IL-33, and can completely attenuate the protective effects of IL-33.[7]

The results of our study agrees with several studies that have established a direct correlation between the sST2 levels and the severity of the CHF symptoms, impaired systolic myocardial function,[23,24] as well as the severity of HF.[24-27] In a study performed by You et al.,[28] 94 patients with pediatric DCM were enrolled after admission from two centers in China and followed up for adverse events. Patients in the highest tertile of sST2 levels had increased risk of short-term (<6 months) and long-term adverse events (2 years) than those in lower tertiles. A study by Binas et al.[20] revealed that sST2 predicts all-cause mortality and cardiac mortality in 262 DCM patients with CHF. P Jirak [30] also observed a significant increase in and correlation with disease severity of sST2 in chronic HFrEF patients of both ischemic and non-ischemic origin.

Lupon et al.[31] developed the ST_2-R2 score to predict reverse remodeling in HF with systolic dysfunction; patients with sST_2 values above 48 ng/mL will unlikely experience LV reverse remodeling. In a study performed by Wojciechowska et al.,[32] 107 DCM patients of 39-56 years were followed up for mean 4.8 years. The ROC curve indicated a cut-off value of ST2-17.53 ng/ml, AUC-0.65(0.53-0.76) for prediction of death. In multivariate analysis, ST2 was a predictor of death (HR per unit increase in log ST2 2.705, 95% CI 1.324-5.528, *P*=0.006) and combined endpoint (HR per unit increase in log ST2 2.753, 95% CI 1.542-4.914, *P*<0.001). The authors concluded that sST2 may be useful for predicting adverse outcomes in stable DCM patients.

Therefore, sST2 is a clinically relevant biomarker that reflects pathophysiological processes and provides prognostic information in the setting of DCM, especially in patients with HF.

Competing Interests

The authors declare that they have no competing interests.

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