Cirkulirajuće razine katestatina su značajno više u ishemijskoj u odnosu na neishemijsku etiologiju kardiomiopatije u bolesnika sa zatajivanjem srca: uloga katestatina kao kompenzatornog biljega neurohumoralne aktivacije

Circulating levels of catestatin are significantly higher in heart failure patients with ischemic vs. non-ischemic cardiomyopathy: the role of catestatin as a compensatory marker of neurohumoral activation

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Uvod: Zatajivanje srca (ZS) je sindrom koji je karakteriziran aktivacijom kompleksne kaskade neurohumoralnih mehanizama kojima nastoji održati srčani minutni volumen.[1] Neka istraživanja su pokazala da je aktivacija simpatičkog živčanog sustava (SŽS) izraženija u kardiomiopatiji ishemijske (IK) u odnosu na neishemijsku (NIK) etiologiju.[2,3] S druge strane, katestatin je pleiotropni endogeni peptid koji inhibira nikotinskim receptorima posredovano otpuštanje katekolamina u cirkulaciju i na taj način djeluje supresivno na aktivnost SŽS-a. Stoga je glavni cilj studije bio utvrditi i usporediti cirkulirajuće razine katestatina u bolesnika sa ishemijskom i neishemijskom etiologijom ZS.

Pacijenti i metode: Ova studija je uključila ukupno 38 bolesnika s akutnom dekompenzacijom ZS utvrđenom prema važećim dijagnostičkim kriterijima Europskog kardiološkog društva za ZS iz 2016. godine, a koji su bili hospitalizirani u Kliničkom bolničkom centru Split od ožujka do lipnja 2018. godine. Bolesnici s akutnim koronarnim sindromom i/ili infekcijom su isključeni. Serumske razine katestatina određene su metodom dvostrukog enzim-imunoadsorpcijskog testa (ELISA).

Rezultati: U opisanom uzorku bolesnika, 21 (55%) je pripadalo IK, a 17 (45%) NIK skupini. Navedene skupine se nisu značajno razlikovale u osnovnim antropometrijskim, kliničkim i ehokardiografskim parametrima te uporabi lijekova (**tablica 1**). Gotovo svi bolesnici su imali NYHA III ili IV stupanj funkcionalne klasifikacije (N=36, 95%). Bolesnici s IK su imali značajno veći prosječni NYHA stupanj u odnosu na bolesnike s NIK (3,4±0,6 vs. 3,1±0,4, p=0.039). Serumske razine katestatina se nisu značajno razlikovale između žena i muškaraca (18,9 vs. 15,7 ng/mL, p=0.570). Bolesnici s IK su imali više nego dvostruko veću prosječnu razinu katestatina u serumu u odnosu na bolesnike s NIK (22,8±20 vs. 10,6±8,5 ng/mL, p=0.025) (**slika 1**). Katestatin je značajno pozitivno korelirao s NT-proBNP-om u ukupnom uzorku bolesnika, neovisno o spolu, dobi, indeksu tjelesne mase i procijenjenoj glomerularnoj filtraciji (r=0.516, p<0.001).

Zaključak: Značajno povišene cirkulirajuće razine katestatina u populaciji bolesnika s ishemijskom etiologijom ZS mogle bi posredno ukazivati na pojačanu neurohumoralnu aktivaciju u toj populaciji, ali i na pojačano tlačno opterećenje ventrikula.

Introduction: Heart failure (HF) is a syndrome characterized by the activation of the complex cascade of neurohumoral mechanisms in order to maintain cardiac output.[1] Previous studies have shown that activation of a sympathetic nervous system (SNS) is more pronounced in patients with ischemic cardiomyopathy (IC) compared to those with non-ischemic cardiomyopathy (NIC).[2,3] On the other hand, catestatin is a pleiotropic endogenous peptide that inhibits nicotinic receptor-mediated catecholamine release into the circulation and, therefore, exhibits inhibitory action on SNS activity. The main goal of the study was to determine and compare circulating catestatin levels among HF patients with IC and NIC.

Patients and Methods: This study included a total of 38 patients admitted to the University Hospital Centre Split during the March-June of 2018 with an acute decompensation of HF determined by the current diagnostic criteria for HF laid out in the European Society of Cardiology guidelines from 2016. Patients with the acute coronary syndrome and/or infectious disease were excluded. Serum levels of catestatin were determined by the enzyme-linked immunosorbent assay (ELISA).

Results: Twenty-one (55%) patient had IC while 17 (45%) had NIC. Both groups did not significantly differ in baseline anthropometric, clinical and echocardiographic parameters as well as medication intake (**Table 1**). Almost all patients were in NYHA III or IV class regarding the functional classification of HF (N=36, 95%). Patients with IC had significantly higher mean NYHA degree compared to NIC patients (3.4±0.6 vs. 3.1±0.4, p=0.039). Serum catestatin levels did not significantly differ between women and men (18.9 vs. 15.7 ng/mL, p=0.570). HF patients with IC had more than 2-fold higher catestatin serum levels compared to HF patients with NIC (22.8±20 vs. 10.6±8.5 ng/mL, p=0.025) (**Figure 1**). Catestatin showed positive significant correlation with NT-proBNP in a total sample of patients, independent of sex, age, body mass index and estimated glomerular filtration rate (r=0.516, p<0.001).

Conclusion: Significantly increased circulating catestatin levels in HF patients with ischemic etiology of the disease might indirectly reflect an increased neurohumoral activation in this population, as well as ventricular pressure overload.

TABLE 1. Baseline characteristics of heart failure patients with non-ischemic and ischemic etiology.

Variable	Non-ischemic, N=17	Ischemic, N=21	p-value
Male sex	8 (47.1%)	14 (66.7%)	0.145
Age (years)	67.1 ± 9.3	70.7 ± 12.2	0.310
BMI (kg/m^2)	31.1 ± 5.6	28.9 ± 3.9	0.178
BSA (Mosteller, m^2)	2.1 ± 0.19	2.1 ± 0.18	0.904
Systolic BP (mmHg)	135 ± 24	138.1 ± 26	0.705
Diastolic BP (mmHg)	83.5 ± 10	83.1 ± 12	0.909
Mean NYHA class	3.1 ± 0.4	3.4 ± 0.6	0.039
Urea (mmol/L)	11.6 ± 7.1	13.3 ± 7.4	0.499
eGFR CKD-EPI (mL/min/1.73 m^2)	60.7 ± 26.1	48.4 ± 25	0.145
NT-proBNP (pg/mL)	8205 ± 6638	9858 ± 7783	0.746
CRP (mg/L)	23.4 ± 17.6	18.6 ± 20.4	0.628
Glucose, fasting (mmol/L)	8.4 ± 3.1	10.3 ± 4.4	0.134
LVEF (biplane Simpson, %)	35 ± 15	37 ± 14	0.697
LVEDd (mm)	61.4 ± 8.9	61.1 ± 8.8	0.894
LVESd (mm)	48 ± 11.2	47.1 ± 12.8	0.843
LA diameter (mm)	50.9 ± 8.8	51.3 ± 8.1	0.884
Comorbidities (%)			
Arterial hypertension	15 (88.2%)	21 (100%)	0.106
Diabetes mellitus	4 (23.5%)	10 (47.6%)	0.126
Atrial fibrillation	9 (52.9%)	12 (57.1%)	0.796
Dyslipidemia	12 (70.6%)	13 (61.9%)	0.575
History of stroke or TIA	2 (11.8%)	3 (14.3%)	0.819
Peripheral artery disease	5 (29.4%)	3 (14.3%)	0.255
COPD	4 (23.5%)	2 (9.5%)	0.239
Medication use (%)			
Aspirin	5 (41.2%)	13 (61.9%)	0.393
ACE-I or ARB	14 (82.4%)	15 (71.4%)	0.431
Beta-blocker	15 (88.2%)	19 (90.5%)	0.823
Diuretics	17 (100%)	20 (95.2%)	0.362
Calcium channel blocker	3 (17.6%)	3 (14.3%)	0.778
Statins	6 (35.3%)	10 (47.6%)	0.444

Abbreviations: ACE-I-angiotensin-converting-enzyme inhibitor; **ARB**-angiotensin II receptor blocker; **BMI**-body mass index; **BP**-blood pressure; **BSA**-body surface area; **COPD**-chronic obstructive pulmonary disease; **CRP**-C-reactive protein; **LA**-left atrium; **LVEDd**-left ventricular end-diastolic diameter; **LVEF**-left ventricular ejection fraction; **LVESd**-left ventricular end-systolic diameter; **eGFR**-estimated glomerular filtration rate; **NT-proBNP**-N-terminal prohormone of brain natriuretic peptide; **NYHA**-New York Heart Association functional classification of heart failure; **TIA**-transient ischemic attack.

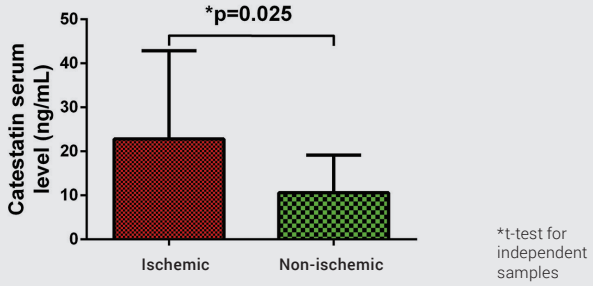

FIGURE 1. Difference in mean catestatin serum level (ng/mL) between heart failure patients with ischemic and non-ischemic cardiomyopathy.

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