B-TYPE NATRIURETIC PEPTIDE AS A MARKER OF DIFFERENT FORMS OF SYSTEMIC SCLEROSIS

B-TIP NATRIURETSKOG PEPTIDA KAO MARKER RAZLIČITIH OBLIKA SISTEMSKE SKLEROZE

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Summary

Background: Systemic sclerosis (SSc) is an autoimmune connective tissue disease which affects various tissues and organs, including skin, lungs, kidneys, gastrointestinal tract and cardiovascular system. Cardiac involvement is the most commonly recognized problem and a significant cause of morbidity. The brain natriuretic peptide (BNP) is a previously known marker of elevated cardiovascular risk in SSc, but the levels of BNP in various forms of SSc have not been investigated so far.

Aim: The aim of our study was to evaluate the influence of SSc on the function of the right ventricle and the right atrium using the echocardiographic parameters. Moreover, we examined the levels of BNP in different forms of SSc as well as the association of disease severity with the plasma concentrations of BNP.

Methods: We included 42 patients with newly diagnosed SSc and patients whose disease had been diagnosed earlier. SSc patients and non-SSc control patients were examined by using echocardiography and the concentrations of BNP were determined.

Results: We analyzed differences in the parameters of right ventricle (RV) function and right atrium (RA) function between SSc patients and healthy controls. The two groups
had similar distribution of gender; but SSc patients were significantly older than controls. RV wall thickness was increased in SSc patients \( (p<0.001) \), while right ventricular end-systolic area \( (RV_{ESA}; p=0.408) \) and right ventricular end-diastolic area \( (RV_{EDV}; p=0.368) \) did not differ among the examinees. In contrast, RA minor-axis dimension \( (p=0.001) \) and the tricuspid annular plane systolic excursion \( (TAPSE) \) \( (p=0.001) \) were significantly higher in SSc patients. Also, we analyzed differences in brain natriuretic peptide (BNP) concentrations between diffuse cutaneous systemic sclerosis (DSSc) and limited cutaneous systemic sclerosis (LSSc) patients. DSSc patients had significantly higher concentrations of BNP. We found that levels of BNP were in significant positive correlations with age \( (p=0.007) \), disease duration \( (p=0.023) \), C reactive protein \( (CRP) \) \( (p=0.052) \), right ventricle fractional area change \( (FAC) \) \( (p=0.022) \), pulmonary vascular resistance \( (PVR) \) and Rodnan score \( (p=0.019) \).

**Conclusions:** Given the obtained results, the laboratory determination of BNP could be useful in differentiating different forms of systemic sclerosis as well as in predicting the severity of the disease and future cardiovascular complications.

**Keywords:** systemic sclerosis, right ventricle, right atrium, brain natriuretic peptide (BNP), capillaroscopy, Rodnan score

**Introduction**

Systemic sclerosis (SSc) is an autoimmune connective tissue disease which affects various tissues and organs, including skin, lungs, kidneys, gastrointestinal tract and cardiovascular system (1). There are two subtypes of SSc, i.e., diffuse cutaneous SSc (skin thickening also involves the extremities proximal to elbows and knees, chest, abdomen and back) and limited cutaneous SSc (skin thickening is localized to the face, neck and extremities distal to elbows and knees) (2). Cardiac involvement is the most commonly recognized problem and a significant cause of morbidity (3). The presence of cardiac events is a bad prognostic sign and is one of the leading causes of mortality in patients with SSc (4–6). The brain natriuretic peptide (BNP) is a previously known marker of elevated cardiovascular risk in SSc, but the levels of BNP in various forms of SSc have not been investigated so far.

Cardiac involvement can be primary and secondary. Primary cardiac involvement, which develops as a direct consequence of SSc, may manifest as myocardial involvement, fibrosis of the conduction system, pericardial and less frequently, as valvular disease (2). Secondary cardiac involvement may manifest as a consequence of pulmonary arterial hypertension (PAH), interstitial lung disease and kidney disease (7, 8).

For the detection of myocardial damage in patients with SSc, in everyday clinical work a large number of noninvasive methods is used, but the most accessible are electrocardiography and echocardiography (9, 10). For many years, the right ventricle (RV) has been considered less relevant in cardiac diseases than the left ventricle (11). Nowadays, it is considered that the RV function markers can be used for management and prognosis of many cardiac diseases, such as congestive heart failure, arrhythmia and sudden cardiac death (12, 13). Echocardiography is an available, noninvasive technique, less expensive than the other techniques and is used for evaluation of RV function. Upon the recommendation of The European Heart Association, echocardiography should be done annually for asymptomatic SSc patients and patients with symptomatic connective tissue disease (14).

The role of clinical chemistry laboratory in diagnosis and monitoring of SSc is largely underestimated. However, recently brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) were proposed as the latest useful markers in the prediction of cardiovascular outcome in SSc (15–17). Brain natriuretic peptide (BNP) is a natriuretic hormone that is initially secreted from ventricles.
toms and the signs of heart failure and mortality. The right atrium size is correlated with the cardiac involvement in pulmonary arterial hypertension (PAH) (4–6, 9). Yet, it is still unclear whether BNP has any potential in clustering patients according to the form and severity of SSC.

The aim of our study was to evaluate the influence of SSC on the function of the right ventricle and right atrium using the echocardiographic parameters. Moreover, we examined the levels of BNP in different forms of SSC as well as the association of disease severity with the BNP plasma concentration.

Materials and Methods

We included 42 patients with the newly diagnosed SSC and patients whose disease had been diagnosed earlier. The testing was conducted in the Clinic for Emergency Internal Medicine and Clinic for Rheumatology of the Military Medical Academy in 2016. A total of 42 patients with SSC were diagnosed as SSC according to the American College of Rheumatology (ACR) classification criteria for SSC (18). The exclusion criteria were asthma, chronic obstructive bronchitis, patients without known cardiovascular and pulmonary disease.

SSC patients and non-SSC control patients were examined by using echocardiography performed by a single cardiologist. Conventional echocardiographic examinations were performed using a Phillips iE-33 system. All parameters were measured according to the published recommendations.

The following parameters were investigated:

- Measurement of the RV dimensions: RV wall thickness, right ventricular end-systolic area (RVESA) and right ventricular end-diastolic area (RVEDA) and 2D fractional area change (FAC),
- Analysis of blood flow through the tricuspid valve during diastole: early diastolic filling velocity (E\text{LV}), late diastolic filling velocity (A\text{LV}), E\text{LV} to A\text{LV} ratio, deceleration time (DT),
- TAPSE (the tricuspid annular plane systolic excursion), right ventricular systolic pressure (RVSP) based on peak tricuspid regurgitant velocity (TRVmax),
- Inferior vena cava diameter (VCI),
- Pulmonary vascular resistance (PVR) was noninvasively estimated utilizing the Abbas equation: (tricuspid regurgitant velocity/ time velocity integral of the RV outflow tract×10+0.16) with an abnormal value defined as > 2.0 Wood Units (WU) (19).
- The tricuspid annular velocities were determined by pulsed wave Doppler tissue: peak early velocity (e'), peak late diastolic velocity (a'), e'/a'

- The TEI index or myocardial performance index (MPI) is an indicator of RV myocardial contractility. It is defined as the ratio of total isovolumic time divided by ejection time (ET) (19). It is calculated using the following formula: MPI=(IVRT + IVCT)/ET.

Capillaroscopy is a simple, safe and painless method for evaluating small vessels of the microcirculation (20). The importance of capillaroscopy as a noninvasive diagnostic method is in early detection of abnormalities in capillary morphology, monitoring the progression of systemic disease and involvement of internal organs. The abnormalities can be observed long before the onset of clinical symptoms (21). In most SSC patients, peripheral microangiopathy follows a typical scleroderma pattern, consisting of 'early', 'active' and 'late' phases (22). The 'early' pattern can be detected many years before the complete clinical manifestation of SSC, and the progression to 'active' and 'late' patterns corresponds to internal organ involvement (23). Capillaroscopy as a diagnostic method is significant because it is included in the EULAR classification criteria of SSC (24).

Plasma levels of BNP were determined by a commercially available immunoassay on an automated platform (ADVIA Centaur BNP assay; Siemens Healthcare Diagnostics Inc, Tarrytown, NY, USA). The Advia Centaur BNP assay measures BNP concentrations up to 5000 pg/ml (1445 pmol/L) with a minimum detectable concentration (analytical sensitivity) of < 2.0 pg/ml (0.58 pmol). The functional sensitivity is defined as the lowest BNP concentration determined at a coefficient of variation of 20%. The ADVIA Centaur BNP assay functional sensitivity was determined to be 2.5 pg/ml (0.72 pmol/L). The intra-assay coefficient of variation is 4.3% »within-run« and 1.9% »run-to-run« at 29.4 pg/ml, 2.5% »within-run« and 2.1% »run-to-run« at 48.5 pg/ml, 1.8% »within-run« and 1.9% »run-to-run« at 410 pg/ml, 2.0% »within-run« and 1.5% »run-to-run« at 458 pg/ml, 2.0% »within-run« and 0.5% »run-to-run« at 1452 pg/ml and 2.1% »within-run« and 1.7% »run-to-run« at 1736 pg/ml. A reference range for BNP is defined as the interval between 2.00 and 32.80 pg/ml.

The modified Rodnan skin score (MSSS) is a measure of skin thickness and measure of disease severity and mortality in patients with dcSSC (25). An increase in skin thickening is associated with increased risk of the internal organs’ involvement and increased mortality (26).

This observational cross-sectional study was approved by the Ethics Committee of the Institutional Review Board (IRB) of the Military Medical Academy
and written informed consent was given by the patients. This study complies with the World Medical Association’s Declaration of Helsinki.

**Statistical analysis**

Variables that followed normal distribution were presented as mean ± standard deviation (Sd) and compared by the Student-t test or ANOVA. Asymmetrically distributed variables were presented as median (interquartile range) and analyzed by Mann-Whitney U-test. Chi-square test – contingency tables were employed for analysis of categorical variables, presented as absolute frequencies. Correlation analysis was performed by using Spearman’s test. Differences with P<0.05 were considered to be statistically significant. Exploration of differences in BNP levels among patients divided according to the results of capillaroscopy was done by the Kruskal-Wallis test following post hoc Mann-Whitney U-test. The Bonferroni correction was used in order to reduce a likelihood of type I error. According to the Bonferroni adjustment, statistical significance for multiple comparison testing was set at P<0.017. All statistical analyses were done by employing PASW Statistics version 18.0 and MedCalc Software version 11.4.

**Results**

In this study, we included 42 patients with SSc aged 34–71 years (mean: 51.52; Sd: 10.63) and 40 non-SSc control patients aged 21–62 years (mean: 39.40; Sd: 9.95) without known cardiovascular and pulmonary disease. SSc patients were predominantly women. Six patients were men and 36 were women.

*Table I* presented the results of analysis of differences in parameters of RV function between SSc patients and healthy controls.

| Parameter                          | SSc (n=42)          | Controls (n=40) | P     |
|------------------------------------|---------------------|-----------------|-------|
| Age (years)                        | 51.52 ± 10.63       | 39.40 ± 9.95    | <0.001|
| Gender, male (n)                   | 6                   | 11              | 0.177 |
| RV wall thickness (cm)#            | 0.40 (0.40–0.51)    | 0.35 (0.30–0.98)| <0.001|
| RVESA (mm)                         | 5.55 (4.50–8.25)    | 5.90 (4.38–6.90)| 0.408 |
| RVEDA (mm)                         | 10.50 (9.23–13.53)  | 12.20 (9.40–13.08) | 0.368 |
| FAC (%)                            | 49.15 ± 12.87       | 48.80 ± 8.82    | 0.888 |
| RA major-axis dimension (cm)       | 4.45 ± 0.56         | 4.33 ± 0.49     | 0.295 |
| RA minor-axis dimension (cm)       | 3.48 ± 0.42         | 3.19 ± 0.36     | 0.001 |
| TAPSE (cm)                         | 2.47 ± 0.39         | 2.21 ± 0.53     | 0.001 |
| E ′ (cm/s) #                       | 55.90 (46.90–59.55) | 56.80 (53.88–62.40) | 0.021 |
| A ′ (cm/s) #                       | 38.00 (35.08–39.83) | 44.25 (41.53–49.53) | <0.001|
| E ′/A ′ #                          | 1.40 (1.30–1.70)    | 1.30 (1.14–1.38) | 0.001 |
| E ′/e′ #                           | 5.20 (4.19–6.35)    | 4.60 (4.10–4.90) | 0.017 |
| s′ (cm/s) #                        | 12.90 (11.48–15.70) | 12.00 (11.33–12.68) | 0.007 |
| e′ (cm/s) #                        | 10.80 (8.19–14.18)  | 12.10 (10.53–12.70) | 0.148 |
| a′ (cm/s) #                        | 13.20 (11.85–15.80) | 9.35 (8.70–10.10) | <0.001|
| e′/a′ #                            | 0.70 (0.50–0.95)    | 1.10 (0.90–1.30) | <0.001|
| DT (ms) #                          | 193.00 (159.50–252.00) | 204.50 (160.00–216.75) | 0.981 |
| TR Vmax (cm/s) #                   | 2.51 (2.13–2.78)    | 2.02 (1.76–2.32) | 0.001 |
| RVSP (mm Hg)                       | 33.51 ± 8.71        | 28.80 ± 4.42    | 0.003 |
| VCI (cm) #                         | 1.50 (1.13–1.70)    | 1.19 (1.02–1.56) | 0.005 |
| PVR (MPa×s/m3)#                    | 1.56 (1.28–1.99)    | 1.22 (1.14–1.30) | <0.001|
| TEI index #                        | 0.40 (0.30–0.43)    | 0.30 (0.30–0.40) | 0.090 |

Data are presented as mean ± Sd for continuous variables, or as absolute frequencies for categorical variables and compared by the Student’s t-test or by the Chi-square test, respectively. #Due to asymmetrical distribution, values are presented as median (interquartile range) and analyzed by the Mann-Whitney U-test.
patients and healthy controls. The two groups had similar distribution of gender, but patients were significantly older than controls. RV wall thickness was increased in patients, while RVESA and RVEDA did not differ among the examinees. Similarly, we found no differences in the FAC, RA major-axis dimension and TAPSE. In contrast, RA minor-axis dimension and TAPSE were significantly higher in SSc patients. Etz/Atz, Etz/e’ ratio, s’ velocity and a’ velocity were significantly higher, while Etz, Atz and e’/a’ ratio were lower in SSc patients than in controls. We found no differences in DT and TEI index, but TR Vmax, VCI, RVSP and PVR were significantly higher in SSc patients.

In addition, we compared the same parameters as in the previous analysis among limited cutaneous systemic sclerosis (LSSc) and diffuse cutaneous systemic sclerosis (DSSc) patients (Table II). Apart from the expected gender differences, all the other examined parameters were uniform between the two groups of SSc patients, with the exception of the e’/a’ ratio which was significantly higher in LSSc patients.

Next, we analyzed differences in the concentrations of the brain natriuretic peptide (BNP) between DSSc and LSSc patients. As it can be seen in the Figure 1, DSSc patients had significantly higher concentrations of the BNP.

Based on the previous findings, we further explored the levels of BNP in SSc patients clustered by the results of capillaroscopy (Figure 2). The obtained results revealed that SSc patients with an early form of the disease had the lowest concentrations of BNP, whereas the levels of this marker increased in parallel with the disease progression. The patients with an early form of SSc had markedly lower concentrations of BNP than subjects with a late
form, although with borderline significance (reached $P=0.020$ vs. $P<0.017$ according to Bonferroni correction).

We found that levels of BNP were in significant positive correlations with age, disease duration, C reactive protein (CRP), fractional area change (FAC), pulmonary vascular resistance (PVR) and Rodnan score, while in negative correlation with $e'/a'$ ratio.

**Discussion**

Cardiac involvement in SSc may be presented with various manifestations and is an indicator of a poor prognosis (2). Recent studies have suggested that the RV and left ventricle (LV) functions are reduced in patients with SSc and are associated with elevated morbidity (27–29). In our study, we compared the examined parameters of RV systolic function in SSc patients and healthy controls. Our results confirmed the previous findings, when it came to the RV wall thickness. Although in both groups the RV had an average wall thickness, the RV wall thickness was significantly higher in SSc patients. Right ventricular end-systolic area (RVESA) and right ventricular end-diastolic area (RVEDA) did not differ among the examinees. We found no differences in the FAC. TAPSE were significantly higher in SSc patients. There were no differences in TEI index among the examinees. $s'$ velocity was significantly higher in SSc patients than in healthy controls (Table I).

It has been proved that measures of RV systolic function such as TAPSE, $S'$ velocity, FAC, and TEI index correlate with decreased survival (27, 29). In our study, we found no differences in the FAC and TEI index, while TAPSE and $s'$ velocity were significantly higher in SSc patients than in healthy controls (Table I).

Parameters of the RV diastolic dysfunction are the $E_tz/A_tz$ ratio, DT, the $E_tz/e'$ ratio, and RA size. In our study, we investigated all these parameters. We found no differences in the RA major-axis dimension. In contrast, RA minor-axis dimensions were significantly higher in SSc patients. The $E_tz/A_tz$ ratio and $e'/a'$ ratio were lower in SSc patients than in controls, while $E_tz/A_tz$ ratio, $E_tz/e'$ ratio, and $a'$ velocity were signifi-
cantly higher. We found no differences in DT and e’ velocity (Table I). It is known that the right atrial and RV chamber enlargement in SSc are directly related with the heart failure symptoms and mortality (30–37). RA size is correlated with clinical outcomes in PAH (28). In our SSc population, the Etz/Atz ratio was significantly higher than in healthy controls (Table I). This can be considered as an index of abnormal right ventricular relaxation. Another explanation is that it is an indicator of diastolic dysfunction, which is a more subtle disorder and occurs earlier.

Our results have not shown a correlation of the disease severity with the echocardiogram assessment of systolic function of the RV, which is not in accordance with the results of previous studies. In our study, RVSP and PVR were significantly higher in SSc patients, although values were in the normal range. This can be explained as an increased risk in these patients for the occurrence of PAH.

In a recent study, it has been shown that non-invasive measurements of PVR predict pulmonary arterial hypertension (PAH) in SSc (19). Guazzi et al. (32) reported that the TAPSE/systolic pulmonary artery pressure (SPAP) ratio improves the prognostic risk stratification in heart failure patients when compared to TAPSE alone and a ratio, 0.36 mm/mmHg predicts higher mortality in such patients (32). The inferior vena cava was significantly higher in SSc patients. It is known that dilated IVC usually denotes elevated RA pressures, and the results in our study could be explained by the fact that the SSc patients have a higher risk for PAH.

In the next step, we compared parameters of RV function among subjects with limited and diffuse forms of scleroderma (Table II). According to our results, echocardiographic parameters were similar in SSc patients and healthy controls (38–40). Some studies have found that cardiac manifestations occur in both diffuse and limited cutaneous forms of SSc, whereas according to others, the prevalence is greater in the diffuse cutaneous form of the disease and the DSSc is associated with significant morbidity and mortality (2, 41).

Although echocardiographic markers failed to detect significant differences between DSSc and LSSc participants in our study, DSSc patients had significantly higher concentrations of BNP (Figure 1). Increased concentration of natriuretic peptides in the plasma may be associated with an increased risk of pulmonary hypertension, which arises as a consequence of RV dysfunction (37, 39). It has been previously demonstrated (15–17) that BNP might be useful in predicting cardiovascular outcome in SSc patients. In this study, we demonstrated that the laboratory determination of BNP can also be used as a tool in differentiating various types of SSc. Furthermore, considering that the parameters of RV did not differ between the two forms of SSc in our study (Table II), the obtained results suggested that BNP might even be more sensitive for estimating possible cardiovascular complications in different forms of SSc. Such results emphasize the role of laboratory analyses in the treatment and follow-up of this particular group of patients.

To further extend our previous findings, we analysed the levels of BNP according to the disease extent and severity. According to our results, measuring of BNP in SSc patients could also be useful in the detection of disease severity (Figure 2). Interestingly, Elishamy et al. (42) demonstrated that NT-proBNP has potential in estimating SSc severity. Our results expand these previous findings by confirming that BNP can also be used for the same purposes. Such researches highlight the importance of cooperative activities in the diagnostics and follow-up of complex diseases.

Additionally (Table III), we found that BNP correlates with age and disease duration but also with Rodnan score, which is used as a sign of disease severity and mortality in DSSc patients (41). These results provide further strength to the proposed hypothesis regarding the role of BNP as SSc type and severity marker. It is known that the BNP is in negative correlation with FAC. In our study, levels of BNP were in significant positive correlations with FAC (Table III). Right ventricle is the main source of circulating BNP, and our results can be explained by the fact that the right heart failure has not developed in our patients.

Our study had several limitations. First, the number of patients included in the study was small. The reason for this is that SSc is a rare disease. Another potential limitation of our study was that it included the majority of patients with newly diagnosed SSc, but still there was no development of RV myocardial dysfunction. Moreover, the data on BNP levels in the control group are missing, so we could not compare BNP concentrations between the SSc patients and healthy individuals.

**Conclusion**

Notwithstanding the great progress in the treatment of patients with systemic sclerosis, the percentage of cardiovascular involvement in these patients is still relatively high.

Early detection of SSc in the period before significant manifestation to certain organs or systems is in the focus of many researchers. SSc is a lifelong disease and cannot be cured, but knowing that cardiac dysfunction significantly worsens the prognosis, early detection of cardiac complications and appropriate therapy can influence its progress and improve the
quality of life for patients. Our findings that BNP is associated with the severity of the disease might suggest that BNP is a more sensitive marker than echocardiographic parameters for the evaluation of systolic function.

Given the obtained results, the laboratory determination of BNP could be useful in differentiating different forms of systemic sclerosis as well as in predicting the severity of the disease and future cardiovascular complications.

**Conflict of interest statement**

The authors stated that they have no conflicts of interest regarding the publication of this article.

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