Relation of asymmetric dimethylarginine and cardiac involvement in systemıc sclerosis

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ABSTRACT

Objectives: The heart is a commonly involved organ in systemic sclerosis (SSc) and pulmonary hypertension is a commonly observed complication that is associated with poor prognosis in this disease. Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide synthases. In this study, we aimed to contribute to an early diagnosis of cardiac involvement by evaluating ADMA and tissue Doppler echocardiographic findings in patients with SSc.

Methods: 30 SSc patients without clinical cardiac symptoms and 30 controls were included. Plasma ADMA levels were measured and tissue Doppler echocardiography examination was carried out for all participants. Systolic and diastolic functions were assessed; pulmonary arterial systolic pressure and mean pulmonary arterial pressure were measured.

Results: The patient and control groups demonstrated a significant difference with regard to right ventricular free wall tissue Doppler late diastolic wave, pulmonary arterial systolic pressure, right ventricular ejection fraction, and right ventricular diastolic dysfunction values. ADMA levels were significantly higher in SSc patients and also in active patients compared to inactive patients. No significant relationship between ADMA and echocardiographic parameters was found.

Conclusion: Tissue Doppler echocardiography is capable of revealing impaired right ventricular functions and increased pulmonary arterial systolic pressure before the occurrence of any cardiac clinical symptoms in patients with SSc. Serum ADMA levels were increased in SSc and in patients with active disease.

Keywords: Systemic sclerosis; Pulmonary hypertension; Asymmetric dimethylarginine.

INTRODUCTION

SSc is a multisystem disease characterized by collagen deposition in the skin and internal organs as well as microvascular obstruction and small artery involvement, the etiology of which is unknown[1].

Cardiac involvement is a common event in SSc. Pericardial, myocardial and conduction systems are affected from inflammation and fibrosis. Rhythmic and conduction system disorders are more frequently encountered than congestive heart failure and myocardial infarction[2-4]. Many autopsy studies have revealed patch-like myocardial fibrosis in ventricles despite the absence of a serious coronary lesion[5,6].

Pulmonary vascular involvement presents with elevated pulmonary arterial pressure, ventricular dysfunction, and tricuspid insufficiency. Pulmonary artery pressure can either be measured indirectly by Doppler echocardiography using tricuspid insufficiency velocity or directly via cardiac catheterization. Tissue Doppler echocardiography can be used in the evaluation of right and left ventricular functions in SSc patients. This is a recent non-invasive echocardiographic examination method allowing the measurement of myocardial velocity[7].

Asymmetric dimethylarginine (ADMA) is a derivative amino acid that is an analogue of L-arginine guanitidine which is endogenously synthesized via methylation of arginine residues in proteins by the protein arginine methyltransferases (PRMTI). ADMA is an endogenous inhibitor of nitric oxide synthases (NOS)[8,9].

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Since ADMA inhibits NOS activity, it decreases NO levels, which in turn generates endothelial dysfunction. Elevated ADMA concentration indicates endothelial dysfunction and is recognized as an important parameter in determining cardiovascular mortality and morbidity[9,10].

In this study, we aimed to investigate systolic and diastolic functions of the heart by tissue color Doppler echocardiography and estimate pulmonary artery systolic pressure values in order to evaluate cardiac involvement and the relationship of these findings with disease activity and serum ADMA levels.

METHODS

This study was performed as a joint effort between the Department of Physical Medicine and Rehabilitation and the Department of Cardiology, both at the Dicle University School of Medicine. Our trial included 30 patients who were diagnosed with SSc based on the criteria of *American College of Rheumatology* and followed up at the Rheumatology Outpatient Clinic, Department of Physical Medicine and Rehabilitation, along with 30 controls that presented to the same clinic but were found to have no rheumatologic disease[11].

The exclusion criteria for both the patient and the control groups were as follows: presence or history of coronary artery disease, diabetes mellitus, cerebrovascular disease, peripheral arterial disease, aortic aneurysm, chronic renal failure, cardiac arrhythmia, any collagen tissue disease other than SSc, rheumatic valvular disease, prosthetic cardiac valve, Alzheimer's disease, preeclampsia, hemorrhagic shock, use of drugs that may influence ADMA levels (L-Arginine, ACE inhibitors, metformin and thiazolidinediones, estrogens, vitamin D, folic acid, all-trans retinoic acid, fenofibrates), and absence of consent.

A total of 60 subjects, 30 patients and 30 controls, wich did not display any of the exclusion criteria were enrolled in our study after obtaining their written informed consent. The study protocol was approved by the Local Ethics Committee at the Dicle University School of Medicine.

In all participants, venous blood samples were collected from the brachial vein of the antecubital fossa for the assessment of serum ADMA levels and routine biochemical parameters. An EDTA tube was used for CBC and plain tubes were used for serologic and biochemical analyses.

All the SSc patients were subjected to modified Rodnan score in order to determine the severity of skin involvement[12]. The disease activity was evaluated by Valentini Disease Activity Criteria[13].

Furthermore, for each patient, the 'UK Functional Scoring' questionnaire was completed to assess the ability to carry out daily activities. This questionnaire comprises 11 items and each item is scored between 0 (normal ability) and 3 (complete inability). The total score is obtained from summation of the scores for each item[14].

ADMA MEASUREMENT

The blood sample obtained for ADMA measurement was stored at -80°C until laboratory testing was carried out with an ADMA ELISA (Enzyme Immunoassay) kit (Immune Diagnostic). A micro Elisa method using a Dynex device was preferred. The dilution tubes were filled with 200μL standard, 200 μL control, and 50 μL sample. The derivitization reactive was prepared for the standard and control. The sample was pipetted and mixed before being left for incubation for 45 minutes at 45°C. Thereafter, 250 μL of dilution buffer was added to each tube and left for incubation at room temperature. We pipetted standard, control, and sample dilutions, respectively, into each well. Then we pipetted 100 μL of ADMA antibody into each well and let the samples incubate for 15-20 hours. Thereafter, they were left in the device. Pod antibody of 250 μL was pipetted into the plates five times. The plate was left for incubation in a shaker at room temperature. It was washed 5 times with 250 μL wash buffer and left for incubation for 6-10 minutes. Stop solution at a volume of 100 μl was pipetted into each well and read at 450--620 nm. The results were obtained in μMol/L.

ECHOCARDIOGRAPHIC EXAMINATION

Each patient received transthoracic echocardiographic and tissue Doppler echocardiographic examinations using a transducer of 3.5 MHz frequency under ECG monitoring at the Echocardiography Unit, Department of Cardiology, Dicle University School of Medicine. The examination was performed with the patient lying down in supine or left recumbent position and by using the appropriate echocardiographic windows.

Each patient received a transthoracic echocardiographic examination along with ECG monitoring, according to the criteria of the *American College of Rheumatology* by a VIVID S6 device capable of standard 2S

and M-mode recording with 2.5-3.25 MHz transducer at the Echocardiography Laboratory, Department of Cardiology, Dicle University School of Medicine[12]. The examination was performed by making the patient take supine or left-recumbent position and using apical 4-chamber, apical 2-chamber, parasternal long and short axis, Doppler, color Doppler, tissue Doppler, and M-mode sections via proper windows. The following parameters were evaluated by the echocardiographic examination:

- Left ventricular ejection fraction (EF-left)
- Right ventricular ejection fraction (EF-right)
- Mitral valve early diastolic wave (MIT-E)
- Mitral valve late diastolic wave (MIT-A)
- Mitral valve early diastolic wave / Mitral valve late diastolic wave (MIT-E / MIT A) ratio
- Left ventricular lateral wall tissue Doppler early diastolic wave (T-left-Em)
- Left ventricular lateral wall tissue Doppler late diastolic wave (T-left-Am)
- Left ventricular diastolic dysfunction (T-left-Em/T--left-Am)
- Right ventricular lateral wall tissue Doppler early diastolic wave (T-right-E)
- Right ventricular lateral wall tissue Doppler late diastolic wave (T-right-A)
- Right ventricular diastolic dysfunction (T-right-E//T-right-A)
- Pulmonary arterial systolic pressure (PASP)
- Pulmonary arterial mean pressure (PAMP)

A pulmonary arterial pressure above 40 mmHg was recognized as high.

STATISTICAL ANALYSES

The statistical analyses were performed by SPSS 15.0 for Windows. The continuous variables were expressed by mean ± SD, whereas the categorical variables were expressed as percentage values. Intergroup comparison of the normally distributed data was carried out with Student's t-test, categorical variables were compared by Chi-square and Fisher exact tests, and the relations between the parameters were evaluated by Pearson's correlation test. $P < 0.05$ was recognized as statistically significant.

RESULTS

The results of our study were obtained from 30 patients with a definitive diagnosis of SSc based on ACR criteria and 30 controls. The characteristic and socio-demographic attributes of the study groups are shown in Table I. In both the SSc and control groups, 28 patients were female and 2 were male. The mean age of the SSc and control groups was 42.5±12.8 and 40.5±9.3, respectively. There were no differences between the groups with regard to age and gender. The mean duration of disease for SSc was 8.1±6.1 years (Table I). Clinical characteristics and medications of patients with SSc are shown in Table II.

TABLE I. COMPARISION OF DEMOGRAPHIC ATTRIBUTES AND LABORATORY PARAMETERS BETWEEN PATIENTS AND CONTROLS

(mean ± SD)	Patient group (n=30)	Control group (n=30)	*p
Age (year)	42.53 ± 12.85	40.56 ± 9.31	0.500
Sex (female, n)	28	28	1
Duration of disease (year)	8.1 ± 6.1		
Hb (g/dl)	12.73 ± 1.2	12.85 ± 1.3	0.344
Hct (%)	37.66 ± 3.94	38.47 ± 3.6	0.408
WBC (K/UL)	8.53 ± 3.43	7.54 ± 1.33	0.149
Plt (K/UL)	291.6 ± 75.17	266.9 ± 59.5	0.164
Cholesterol (mg/dl)	171.2 ± 35.4	174.03 ± 21.3	0.243
Triglycerides (mg/dl)	129.8 ± 42.1	116.86 ± 42.77	0.710
ESR (mm/h)	21.46 ± 13.51	11.33 ± 7.07	0.001*
CRP (mg/dl)	0.53 ± 0.44	0.39 ± 0.18	0.122

*p <0.05, SD – Standard deviation, ESR – Erythrocyte sedimentation rate, CRP – C-reactive protein, WBC – White blood cell count, Hb – Haemoglobin, Hct – Hematocrit, Plt – Platelets

TABLE II. CLINICAL CHARACTERISTICS AND MEDICATIONS OF PATIENTS

	N %
Raynaud's phenomenon	28 (93.3)
Digital pitting	22 (73.3)
Telangiectasia	10 (33.3)
Arthritis	8 (26.7)
Dyspnea	23 (76.7)
Dysphagia	17 (56.7)
Dyspepsia	11 (36.7)
Lung involvement	22 (78.5)
Calcinosis	1 (3.3)
Calcium channel blockers	22 (73.3)
Corticosteroids	18 (60)
Colchicine	11 (36.6)
Pentoxifylline	1 (3.3)
Azathioprine	2 (6.7)
Methotrexate	2 (6.7)
Cyclophosphamide	3 (10)
Not use	5 (16.7)

Seventy percent of the patients were positive for ANA. However, positivity for anti-Scl 70 and ACA was low. Erythrocyte sedimentation rate (ESR) was significantly higher in the patient group than in the control group (p= 0.001); however, there was no significant difference in terms of CRP (p= 0.122). We found significant differences between inactive and active patients in terms of Modified Rodnan (p=0.041) and functional scores (p=0.003). Modified Rodnan and functional scores were significantly higher in active patients (20.50±7.75, 19.71±8.24 respectively) than inactive patients (14.86±6.19, 10.33±7.42 respectively). The comparison of Doppler echocardiographic parameters between the patient and control groups is shown in Table III. The patient group was found to have statistically significantly higher T-right-Am, PASP, and T-right-E//T-right-A values than the control group. MPAP was nearly significantly higher in the patient group than in the control group (p= 0.054). There was a significant difference between the patient and control groups with regard to RVEF (p<0.05). No significant difference was determined in other parameters.

Doppler echocardiography results of the active and inactive SSc patients are shown in Table IV. There were no significant differences between the active and inactive patients regarding Doppler echocardiographic pa-

rameters. Of the 30 scleroderma patients, 5 had elevated pulmonary arterial pressure, whereas there were 3 people with high pulmonary arterial pressure in the control group.

Serum ADMA levels were significantly higher in the patient group (0.545± 0.130) than in the control group (0.130± 0.155) (p = 0.034)) (Figure 1). Furthermore, in the patient group, ADMA levels were significantly higher in active patients (0.608± 0.128) than in inactive patients (0.494 ± 0.109) (p=0.016)) (Figure 2). There was no correlation found between ADMA and the echocardiographic parameters. PASP and T-left-Em demonstrated a significant positive correlation. There was also a significant correlation between PASP and MPAP. PASP and MIT-E displayed a significant negative correlation. There was a significant relationship of PASP with T-left-Em and MPAP. A significant correlation between T-left-Am and T-right-Em was also found. In addition, there was a significant correlation between duration of disease and RVEF.

ADMA levels and MPAP exhibited a nearly significant relationship, with a negative correlation between the two parameters (p=0.067).

We determined a significant negative correlation between CRP and RVEF. The relationship of CRP with MIT-A and T-right-A was significant.

We did not find significant differences between patient and control groups except for ESR (Table I). There was also no association between ADMA levels and inflammatory markers (CRP and ESR) in both the active and inactive patient groups.

DISCUSSION

Since previous studies have shown contradictory findings concerning the echocardiographic data of SSc patients, we aimed to evaluate the cardiac functions based on echocardiographic data enriched by measurement of pulmonary arterial pressure with various methods such as color and tissue Doppler imaging, while also trying to determine cardiac involvement at a preclinical stage and reveal its relationship with serum ADMA levels[15-18].

In a study comprised of 54 SSc patients, 69% of the patients demonstrated abnormal findings in echocardiography. The most common pathologic findings shown by echocardiography are elevated right ventricular systolic pressure, pericardial effusion, increased right ventricular diameter, and left atrial enlargement[19].

TABLE III. COMPARISON OF DOPPLER ECHOCARDIOGRAPHIC PARAMETERS BETWEEN PATIENTS AND CONTROL GROUPS

Parameter	Patient group n=30	Control group n=30	*p
T-right-E (m/s)	0.171 ± 0.178	0.144 ± 0.032	0.411
T-right-A (m/s)	0.199 ± 0.087	0.156 ± 0.068	0.039*
PASP (mmHg)	29.90 ± 8.82	22.93 ± 9.80	0.005*
PAMP (mmHg)	17.80 ± 6.31	14.43 ± 6.93	0.054
LVEF (%)	60.06 ± 8.50	61.73 ± 6.66	0.402
T-left-Em (m/s)	0.12 ± 0.04	0.13 ± 0.04	0.456
T-left-Am (m/s)	0.14 ± 0.14	0.13 ± 0.12	0.744
RVEF (%)	56.73 ± 7.67	50.46 ± 8.45	0.004*
MIT-E (m/s)	3.31 ± 13.35	0.79 ± 0.18	0.310
MIT-A (m/s)	0.72 ± 0.22	0.66 ± 0.19	0.268
MIT E/MIT A	1.28 ± 0.52	1.39 ± 1.29	0.906
T-left-Em/T-left-Am	1.24 ± 0.77	1.62 ± 1.73	0.355
T-right-E/T-right-A	1.01 ± 1.31	1.19 ± 0.89	0.026*

EF-left – Left ventricular ejection fraction, EF-right – Right ventricular ejection fraction, MIT-E – Mitral valve early diastolic wave, MIT-A – Mitral valve late diastolic wave, MIT-E / MIT A – Mitral valve early diastolic wave / Mitral valve late diastolic wave ratio, T-left-Em – Left ventricular lateral wall tissue Doppler early diastolic wave, T-left-Am – Left ventricular lateral wall tissue Doppler late diastolic wave, T-left-Em/T-left-Am – Left ventricular diastolic dysfunction, T-right-E Right – ventricular lateral wall tissue Doppler early diastolic wave, T-right-A – Right ventricular lateral wall tissue Doppler late diastolic wave, T-right-E/T-right-A – Right ventricular diastolic dysfunction, PASP – Pulmonary arterial systolic pressure, PAMP – Pulmonary arterial mean pressure
* $p < 0.05$

TABLE IV. COMPARISON OF DOPPLER ECHOCARDIOGRAPHIC PARAMETERS BETWEEN ACTIVE AND INACTIVE PATIENTS

[a]Parameters (mean±SD)	Active patients (n=14)	Inactive patients (n=16)	p*
T-right-E (m/s)	0.16 ± 0.15	0.18 ± 0.20	0.743
T-right-A (m/s)	0.18 ± 0.05	0.19 ± 0.08	0.868
PASP (mm/Hg)	27.78 ± 7.48	31.86 ± 10.03	0.224
PAMP (mm/Hg)	16.71 ± 5.36	18.66 ± 7.31	0.418
LVEF (%)	56.92 ± 7.26	62.26 ± 8.77	0.085
T-left-Em (m/s)	0.12 ± 0.04	0.13 ± 0.05	0.583
T-left-Am (m/s)	0.14 ± 0.18	0.14 ± 0.10	0.957
RVEF (%)	55.85 ± 8.75	57.33 ± 7.00	0.622
MIT-E (m/s)	5.96 ± 19.58	0.98 ± 0.29	0.359
MIT-A (m/s)	0.67 ± 0.22	0.78 ± 0.22	0.174

a. See Table 2 for acronym definitions
* $p < 0.05$, SD Standard deviation

The patient may not exhibit clinicals symptoms of cardiac involvement if present during the early period, however progression may lead to significant cardiac involvement at later stages. Currently, clinical examination and transthoracic echocardiography are recommended for routine cardiac evaluation in SSc cases. However, it is inadequate for diagnosis at the preclinical stage[20]. Cardiac involvement can be detected at the preclinical stage by evaluating right and left ventricular functions with tissue Doppler echocardiography, which enables early treatment.

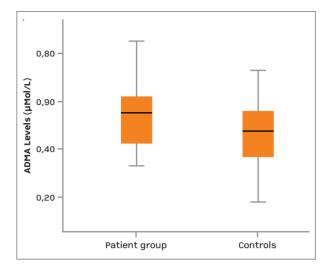In our study, we enrolled SSc patients with no

FIGURE 1. Comparison of ADMA levels of study groups (p<0.05)

FIGURE 2. Comparison of ADMA levels in disease group according to the disease activity (p<0.05)

known cardiac complaint. Our patients demonstrated significant increases in parameters indicating right ventricular diastolic dysfunction: T-right-E/T-right-A, T-right-A, and PASP. There was a nearly significant increase of MPAP as well. Compared with the control group, significant or nearly significant increases in pulmonary arterial pressure may be beneficial in taking timely precautions before the expected clinical development of PH.

Dimitroulas et al. studied 52 SSc patients with no clinical cardiac involvement. They examined left and right ventricular functions by tissue Doppler echocardiography and determined reduced right and left ventricular function in these asymptomatic patients[20]. Similarly, in our study, right ventricular function was observed to be decreased.

Plazak et al. studied 46 SSc patients and found significantly higher pulmonary arterial pressure in SSc patients than in controls[21]. In the present study, systolic pulmonary artery pressure was significantly higher in the SSc patient group than in the control group. Furthermore, although not statistically significant, the SSc patients had higher MPAP values.

Hural et al. evaluated left ventricular systolic and diastolic functions by echocardiography in 31 SSc patients and found depressed left ventricular function along with impaired systolic and diastolic functions[22]. In another study, left ventricular dysfunction was assessed by conventional echocardiography in 7073 patients and left ventricular dysfunction was observed in 5.4% of the patients. In the present study, we evalua-
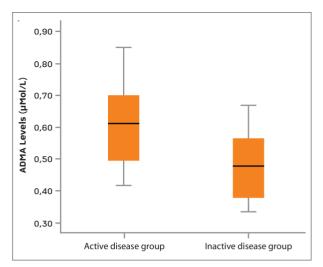
ted the left ventricular function as well; however, no dysfunction was detected. We failed to determine left ventricular dysfunction, which was expected to be statistically significant. This may have been due to the small number of patients. This may also be associated with the short duration of disease in our patients. Hural et al. did not study right ventricular function[22]. However, in our study, as expected, right ventricular diastolic dysfunction was detected. Furthermore, right ventricular systolic function was reduced in patients with active disease compared to patients with inactive disease. However, this decrease was not significant.

ADMA is an endogenous inhibitor of NO. It is produced by the methylation of arginine. It is known to cause endothelial dysfunction by reducing the NO level. ADMA levels have been observed to be high in systemic diseases with cardiac involvement accompanied by endothelial dysfunction. Many studies have found a correlation between ADMA levels and cardiac involvement[23,24]. In the present study, we found significantly higher serum ADMA levels in the patient group than in the control group. We also determined a nearly significant relationship between ADMA levels and MPAP values.

Perna et al. studied 125 SLE patients and found a relationship between elevated ADMA levels and cardiovascular involvement. ADMA levels were particularly high in SLE patients with arterial wall thickening. The authors concluded that ADMA could be a biochemical marker with regard to risk of cardiovascular involvement[23].

Sahin et al. conducted a study on patients with Behçet's disease and detected higher ADMA levels, particularly in patients with vascular involvement[24].

ADMA levels are increased in diffuse, cutaneous subtypes of SSc disease and in patients with pulmonary hypertension[25]. Furthermore, a study by Dimitroulas et al. consisted of 66 patients and 30 controls. Patients with and without PH, and controls were compared. They found significantly higher ADMA levels in SSc patients with PH[25]. In the present study, we determined a close relationship between MPAP and serum ADMA levels in SSc patients, a relationship that was nearly statistically significant. Dimitroulas et al. investigated the links between ADMA and echocardiographic parameters of SSc patients with cardiac involvement in 56 patients and determined a considerably close relationship between ADMA levels and echocardiographic measures of LV diastolic dysfunction[25]. In our study, ADMA levels were observed to be high in SSc patients. In addition, ADMA levels were found to be higher in active patients than in inactive patients. However, no link was detected between ADMA levels and echocardiographic parameters. The small number of our study population and short duration of disease may explain this result.

There is no clear association between ADMA and systemic inflammation. ADMA has been associated with inflammatory indicators only in some studies in patients with arthritis[26-27]. We did not find a relationship between ADMA and inflammatory markers in the present study. Our results may be related to this unclear association with inflammatory indices and also may be attributed to mild inflammatory markers of SSc.

In conclusion, SSc patients demonstrate elevated ADMA levels which are correlated with the disease activity. This increase may be a precursor of possible cardiac and vascular complications in the future. In the present study, we detected impaired cardiac diastolic functions by applying advanced echocardiographic methods on SSc patients exhibiting no symptom of known cardiac involvement. At the subclinical stage, determination of the cardiac involvement may allow taking precautionary steps and thus contribute positively to the long-term prognosis of the disease.

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2º CONGRESSO DE OSTEOGÉNESE IMPERFEITA

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