

Reverse dipper pattern of blood pressure as an indicator of sympathetic over activity in patients with systemic sclerosis and its relation with serum asymmetric dimethylarginine (ADMA) level

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Systemic sclerosis (SSc) is a multisystem disorder characterized by extensive vascular damage, with early generalized microangiopathy and fibrosis of the skin and internal organs. SSc is characterized by parasympathetic impairment and marked sympathetic over activity. The aim of this study was to investigate the potential relationship between serum asymmetric dimethylarginine (ADMA) levels and blood pressure pattern with sympathetic over activity in patients with SSc. Thirty patients with systemic sclerosis and thirty controls who had no cardiovascular risk factors were included in this study. All patients and the controls underwent a 24-hour holter recording and their plasma ADMA levels were measured. A total of 10 patients had dipper status (33.3%), 16 patients had non-dipper status (53.3%), 2 patients had reverse dipper status (6.7%) and 2 patients had extreme dipper status (6.7%). ADMA levels were higher in SSc patients when compared with control group and especially significantly higher in SSc patients with reverse dipper status. The relationship between elevated ADMA serum levels and reverse dipper blood pressure patterns in patients with SSc may be the result of sympathetic over activity.

Keywords: 24-hour blood pressure monitoring, Systemic sclerosis, ADMA, reverse dipping status.

INTRODUCTION

Systemic sclerosis (SSc) is a multisystem disorder characterized by extensive vascular damage with early generalized microangiopathy and fibrosis of the skin and internal organs. Endothelial dysfunction and damage are primary events throughout the course of the disease, which result in vascular obliteration and diminished blood flow to the viscera. Endothelium injury is considered as one of the earliest key steps throughout the disease course. In SSc, microvascular involvement results in a transient vasospastic phenomenon and culminates in

myointimal proliferation causing microvascular obliterations (Dimitroulas et al., 2008).

Nitric oxide (NO) is a potent vasodilator synthesized by NO synthetase (Nos) isoforms and negatively regulated by Asymmetrical dimethylarginine (ADMA). ADMA levels are considered as the reflection of the endothelial dysfunction observed in several cardiovascular disorders. ADMA represents a novel risk factor for endothelial dysfunction. High ADMA levels predispose to acute coronary events, correlate with the severity of atherosclerotic disease and predict mortality of cardiovascular events in patients with end-stage renal disease (Valkonen et al 2001; Zoccali et al., 2001). It is also known that primary cardiac problems include pericarditis, heart failure; serious arrhythmias emerge in

patients with SSc. It is not known if these patients present hypertension or hypotension and which parameter of the ambulatory blood pressure (BP) may influence such a disease course.

The aim of this study was to investigate the relationship between serum ADMA levels and systemic hypertension in patients with SSc. This is the first article investigating the relationship between blood pressure pattern and serum ADMA levels with sympathetic over activity in SSc patients.

MATERIALS AND METHODS

Study population

The current study was carried out in the Department of Cardiology, Faculty of Medicine, Dicle University between January 2010 and May 2011. The local ethics committee approved the study and all the subjects gave written informed consent. We prospectively studied 30 SSc patients as defined according to the criteria of the American College of Rheumatology (SCL-group) (Subcommittee for Systemic sclerosis Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee, 1980) and 30 controls who complain of musculoskeletal pain. Patients with evidence of cardiomyopathy, congenital, or rheumatic heart disease and atrial fibrillation, ischemic heart disease or any other cardiac or systemic disease were excluded. All patients and controls underwent ambulatory 24-hour BP monitoring and transthoracic echocardiography. All the patients received nifedipin 60 mg/day drug therapy for SSc-related digital vasculopathy. Blood samples of all participants were drawn and analyzed for routine laboratory parameters (lipid parameters, glucose, whole blood) at the same day of echocardiography examination.

Ambulatory Blood Pressure Monitoring

BP was measured for 24 consecutive hours, at 15-min intervals during the day (from 08:00 to 20:00) and at 30-min intervals at night (from 20:00 to 08:00), using an ambulatory device. (BPM-AM 2000, NihonKoden Co. Ltd, Tokyo, Japan). The average BP during diurnal or nocturnal time was calculated: Daytime systolic blood pressure (SBP) (≤ 135 and > 135 mm Hg), daytime diastolic blood pressure (DBP) (≤ 80 and > 80 mm Hg), nighttime SBP (≤ 120 and > 120 mm Hg) and nighttime DBP (≤ 70 and > 70 mm Hg) (Guidelines Subcommittee, 1999).

Patients were also divided into four categories for nocturnal BP: Dippers, nondippers, extreme dippers and reverse dippers.

Dippers; systolic BP during nocturnal time fall by 10% of

the diurnal BP or more,

Non dippers; nocturnal reduction in average daytime systolic blood pressure of less than 10% extremedippers; whose nighttime BP is more than 20% lower than the daytime BP,

Reverse dippers; an increase in nocturnal BP was defined reverse dipper (O'Brien et al., 198).

Biochemical analyses

A venous blood sample was taken under fasting conditions for the measurement of routine blood parameters (lipid parameters, glucose, whole blood) and plasma ADMA levels. ADMA levels were measured in plasma samples by using a commercial ELISA (Enzyme-linked immunosorbent assay) kit (DLD Diagnostica, Germany).

Echocardiography

All echocardiographic examinations were performed by an experienced echocardiographer blinded to clinical data with the use of a commercially available ultrasound system (Vivid

S 5, GE). Standard echocardiography was performed with the participants in the partial left decubitus position and measurements were done according to the guidelines of the American Society of Echocardiography (American Society of Echocardiography Committee on Standards 1989). Left ventricular ejection fraction was estimated by Simpson's method. The estimated pulmonary arterial systolic pressure was calculated as the sum of the transtricuspid gradient and the estimated right atrial pressure. From the apical four-chamber view, right ventricular inflow, parasternal short axis or subcostal view, continuous wave Doppler echocardiography was used to assess the peak tricuspid regurgitant velocity (Currie et al., 1985). Using the simplified Bernoulli equation, the right atrial pressure was estimated using the diameter of the inferior vena cava and the response to changes in respiration (Ommen et al., 2000). Pulmonary hypertension was defined as a systolic pulmonary artery pressure value ≥ 40 mmHg (Mukerjee et al., 2004).

Statistical analysis

All data were expressed as mean and standard deviation. Differences between groups were evaluated by Kruskal-Wallis variance analysis followed by Mann-Whitney U-test with Bonferroni correction for binary comparisons for nonparametric data. Groups were compared by using One-way analysis of variance (ANOVA) test followed by post hoc Scheffe test for parametric data. A value of $p \leq$

Table 1. Clinical and laboratory characteristics of the subjects.

	Scleroderma (n=30)	Control (n=30)
Age (mean±S.D), (years)	40.7 ± 11.6	40.6±13.7
Female (%)	93.3	91.3
Hemoglobin(mg/dL)	11.6 ± 1.3	12.4 ± 1.3
Hematocrit (%)	37.6 ± 3.1	38.8 ± 6.1
Platelet assay(10/micL)	288.8 ± 123.5	225.7 ± 65.3
Total-Cholesterol (mg/dl)	176.0 ± 53.8	166.0 ± 45.6
Triglyceride (mg/dl)	117.9 ± 84.1	119.2± 97.5
HDL-Cholesterol (mg/dl)	45.7 ± 15.2	46.8 ± 11.3
LDL-Cholesterol mg/dl)	111.1 ± 33.3	115.7 ± 25.8
Plasma glucose (mg/dl)	89.48 ± 25.55	88.06± 58.54

Table 2. Correlation Between Diurnal Blood Pressure Pattern and ADMA Levels.

Diurnal BP pattern	Dipper	Nondipper	Extreme Dipper	Reverse Dipper
n (%)	10 (33.3%)	16 (53.3%)	2 (6.7%)	2 (6.7%)
ADMA (mmol/L)	0.508±0.127	0.526±0.110	0.575±0.019	0.796±0.756

Data were given as Mean±SD for ADMA values. ADMA; *Asymmetric Dimethylarginine*

0.05 was considered to be statistically significant.

RESULTS

A total of 56 women and 4 men mean aged 40.7±11.6 years (range 17–70 years) were enrolled. Thirtypatients with SSc (28 females, mean age 40.7 ± 11.6 yrs) and 30 controls (28 females mean age 40.6±13.7). The two groups of patients were similar with regard to age, sex, blood and biochemical parameters (Table 1). SSc patients had significantly higher systolic pulmonary arterial pressure compared to controls ($p=0.036$) (Table-3). Twenty four hour mean heart rate values were not significantly different between two groups (Table-3). The demographic and biochemical parameters of patients and controls are summarized in Table-1. ADMA levels for SSc patients was higher when compared to control ($p=0.032$) group (Table-3).

A total of 10 patients showed dipper BP patterns (33.3%), 16 patients showed non-dipper status (53.3%), 2 patients showed extreme dipper status (6.7%) and 2 patients showed extremedipper status (6.7%). Plasma ADMA levels were higher in patients with SSc who showed reverse dipper status (Table 2).

According to the 24-hour noninvasive ambulatory BP monitoring results, average systolic blood pressure ($p=0.005$) and diastolic blood pressure ($p=0.003$), daytime systolic ($p=0.004$) and diastolic ($p=0.005$) and nighttime systolic ($p=0.043$) and diastolic ($p=0.017$) blood pressure were found significantly lower in patients with SSc when compared with control group (Table 3).

DISCUSSION

Systemic sclerosis is a multisystem autoimmune disease characterized by an excessive deposition of extracellular matrix both in the skin and the internal organs. Endothelial dysfunction is a primary event in systemic sclerosis. The endothelium plays a crucial role in the maintenance of vascular tone and structure by releasing the endothelium-derived vasoactive mediator, NO. NO has a protective role for the cardiovascular system because it inhibits vascular muscle cell proliferation, platelet aggregation tendency and the adhesion of monocytes to the endothelium. NOs can be inhibited by endogenous methylarginines, and ADMA seems to be the most important one of these endogenous NOs inhibitors. Elevated plasma levels of ADMA are associated with an increased risk of major adverse cardiovascular events. In this study, there were two important findings. First, plasma levels of ADMA were higher in SSc patients than controls. A couple of studies have previously reported that plasma ADMA levels were significantly higher in SSc. Dimitroulas T. and et al. showed that plasma ADMA levels were significantly higher in patients with systemic sclerosis-related pulmonary arterial hypertension (PAH) than the patients without PAH and healthy controls. Dimitroulas and et al. has been reported Plasma ADMA levels were measured in 66 patients with SSc. Mean value of ADMA for SScPAH patients was $0.44\pm0.22\mu\text{mol/l}$ compared with $0.26\pm0.18\mu\text{mol/l}$ for patients without PAH and $0.25\pm0.20\mu\text{mol/l}$ for controls ($P<0.001$). In the present study, similar to Dimitroulas's study, mean value of ADMA for SSc patients was higher (0.541 ± 0.13) than controls

Table 3. ADMA levels 24-hour blood pressure values and echocardiography parameters.

	Scleroderma (n=30)	Control (n=30)	p
Ambulatory average SBP	111.1±10.6 (95/147)	118.5±9.2 (100/140)	*0.005
Ambulatory average DBP	73.5±6.8 (62/90)	79.1±7.5 (64/99)	*0.003
Daytime SBP	113.0±10.9 (95/148)	120.3±8.8 (102/139)	*0.004
Daytime DBP	75.3±7.2 (64/93)	80.8±7.1 (65/99)	*0.005
Nighttime SBP	104.3±12.9 (80/143)	110.9±12.1 (89/143)	*0.043
Nighttime DBP	66.5±8.2 (50/82)	72.7±11.2 (53/109)	*0.017
LVEF %	64.65± 35.36	66.32 ± 33.81	0.074
24-Hour HR. Bpm	79± 3.2	75±2.1	0.068
PABsys (mmHg)	35±10.2	25±10	*0.036
ADMA (mmol/L)	0.541±0.13	0.464±0.15	*0.032

Data were given as Mean (min/max) mmHg for blood pressure and Mean±SD for ADMA values. SBP; Systolic blood pressure, DBP; diastolic blood pressure, ADMA; Asymmetric Dimethylarginine, LVEF; Left ventricular ejection fraction, PABsys; Systolic pulmonary arterial hypertension

(0.464±0.15) (p=0.045) (1).

Dooley and et al. reported that increased levels of ADMA in patients with diffuse systemic sclerosis, but no correlation with PAH were reported (Dooley et al., 2006).

Our study population was younger than those of the two studies. In addition, in Dooley's study, the number of patients was quietly less than our study. Also, an increase of plasma ADMA levels were reported in patients with idiopathic PAH (Kielstein et al., 2005).

Inhibition of NO synthesis by ADMA, may account for the increased peripheral vascular tone associated with hypertension, as well as contribute to the clinical consequences of this condition, essential hypertension and cardiovascular diseases which include vascular hypertrophy, atherosclerosis, and myocardial infarction. Endothelial dysfunction is a primary event in systemic sclerosis. It is also known that primary cardiac problems include pericarditis, heart failure and malign arrhythmias in patients with SSc. In this study, ambulatory average systolic and diastolic blood pressure, daytime systolic, daytime diastolic nighttime systolic and nighttime diastolic BP were found significantly higher than controls (p=0.005, p=0.003, p= 0.004, p=0.005, p=0.043, p=0.0017, respectively) (Table-3).

Markopoulos NA and et al. reported 85 subjects underwent clinical BP readings, 24-hour ambulatory BP monitoring, left ventricular assessment by echocardiography and measurement of intima media thickness of the right-left internal carotid arteries and right-left common carotid arteries. The population consisted of 40 subjects with SSc who were not receiving any antihypertensive treatment and 45 healthy volunteers (control group). Clinical systolic and diastolic blood pressure, clinical heart rate, mean 24 h SBP, mean 24 h DBP, mean 24 h heart rate, pulse pressure 24 h, did not statistically significantly differ between the two groups. Zakopoulos NA and et al., concluded that systemic sclerosis is not associated with clinical BP or the

parameters of 24 h BP monitoring.

In this study, all BP parameters in SSc patients were lower than the control group. The most likely reason for these findings, patients with SSc received nifedipin 60 mg/day drug therapy for SSc-related digital vasculopathy.

In present study a total of 10 patients exhibited dipper BP patterns in 10 patients (33.3%), non-dipper status in 16 patients (53.3%), extreme dipper status in 2 patients (6.7%) and reverse dipper status in 2 patients (6.7%) were found. The reverse dipping BP pattern is associated with a sympathetic activity that is greater than that characterizing individual in whom BP shows a greater or smaller nighttime fall. In these patients with autonomic failure who frequently display a reverse dipping pattern, a reduction rather than an increase in sympathetic tone has been reported to take place (Grassi et al 2008). It has been previously reported that autonomic dysfunction is extremely common in SSc. It is characterized by parasympathetic impairment and marked sympathetic over activity (Dessein et al., 1992).

Nifedipine, causes vascular smooth-muscle relaxation and relief of arterial vasospasm. Therefore it is widely used in SSc. René R and et al. reported that nifedipine activates cardiac and peripheral sympathetic nerves differently depending on pharmacokinetics. These effects of nifedipine may be disadvantageous in cardiac patients with increased sympathetic activity (Wenzel et al., 2003). This effect of nifedipine on sympathetic activity in SSc may also contribute to the pathophysiology of reverse dipping BP pattern. Grassi et al. (2011) showed that sympathetic neural influences attenuate the NO-dependent vasoregulation and that conversely NO inhibition by ADMA triggers sympathoexcitatory effects (Grassi et al., 2011). Therefore, plasma ADMA levels are expected to be higher in patients with SSc who showed reverse dipper status.

CONCLUSIONS

Plasma ADMA levels were significantly higher in patients with SSc who showed reverse dipper status. These data suggest that sympathetic over activity in patients with SSc. The findings of this study emphasize the need for caution in prescribing Nifedipine for SSc patients with sympathetic over activity.

ACKNOWLEDGEMENT

This work was funded by authors.

There was no conflict of interest among all authors.

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