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[Original Article]

FLOW-MEDIATED DILATATION IDENTIFIES IMPAIRED ENDOTHELIAL FUNCTION IN PATIENTS WITH SLEEP APNEA SYNDROME

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Abstract: [Background] Non-invasive detection of vascular dysfunction in the early stage is clinically important in patients with sleep apnea syndrome (SAS). Flow-mediated dilatation (FMD) is a novel clinical marker of endothelial function. However, it is not clear whether this is useful in the SAS patient. [Methods] Echocardiographic parameters and FMD were measured in 129 patients with SAS. Apnea-hypopnea index (AHI) was defined by polygraphy, and patients were divided into the two Groups: Group A (moderate-severe SAS: AHI≥15 times/hr, $n=93$) and Group B (mild SAS: AHI 5-15 times/hr, $n=36$). [Results] There were no significant differences in echocardiographic parameters between the two groups. However, FMD was significantly lower in Group A than in Group B (3.5±1.6 vs. 7.8±3.1, $P<0.01$). [Conclusions] Although cardiac function was not different, vascular dysfunction was evident in patients with moderate-severe SAS. FMD is a useful tool to identify impaired endothelial function non-invasively in patients with SAS.

Key words: sleep apnea syndrome, vascular function, endothelial function, flow-mediated dilatation

INTRODUCTION

Sleep apnea syndrome (SAS) has a critical association with cardiovascular mortality and morbidity. It has been recently recognized that SAS plays a role in the pathogenesis of systemic hypertension, ischemic heart disease, heart failure, and arrhythmia[1]. Since an arteriosclerotic initial change to cause cardiovascular events is vascular endothelial dysfunction, the evaluation of endothelial function is clinically important. The assessment of flow-mediated dilatation (FMD) of the brachial artery has been recently used as a non-invasive method for evaluating endothelial function[2].

Therefore, the aim of this study was to examine whether endothelial function assessed by FMD is impaired in patients with SAS. We compared the FMD data between patients with mild SAS and those with moderate-severe SAS.

METHODS

Subjects and study protocol

In the present study, 129 patients with SAS were enrolled. SAS was diagnosed by polygraphic data. Apnea was defined as an absence of airflow for >10 s. Hypopnea was defined as a >30% reduc-

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tion in monitored airflow accompanied by a decrease in SaO_2 of ≧4%. The apnea-hypopnea index (AHI) was defined as the number of apnea and hypopnea episodes per hour of sleep. Patients with AHI greater than 5 were considered as having SAS. Generally, it is classified as normal (AHI<5), mild SAS (5≦AHI<15), moderate SAS (15≦AHI<30) and severe SAS (30≦AHI). Echocardiography and FMD were performed in all patients. Patients were divided into the two groups according to the AHI value : Group A (moderate-severe SAS : AHI ≥15 times/hr, mean 34.8±14.8, range 15.1-77.9, n =93) and Group B (mild SAS : AHI 5-15 times/hr, mean 8.4±4.0, range 5.6-14.9, n=36)[3-6]. We compared clinical characteristics, laboratory data, echocardiographic parameters, and FMD between the two groups. The study protocol was approved by the Ethics Committee of the Fukushima Medical University, and written informed consent was obtained from all subjects.

Polygraphy

All subjects underwent overnight polygraphy with the use of standard techniques[7,8]. Overnight polygraphy was performed using a type 3 polygraph system (LS-300, Fukuda Denshi, Tokyo, Japan) that consisted of the monitoring of electrocardiogram, thoracoabdominal motion, nasal airflow by an airflow pressure transducer, and arterial oxyhemoglobin saturation (SpO_2) by pulse oximetry. Obstructive apnea was defined as the absence of airflow for ≧10 s associated with ribcage and abdominal motion. Central apnea was defined as the absence of airflow for >10 s associated without ribcage and abdominal motion. The major polygraphic parameters investigated were AHI, central apnea index (CAI), obstructive apnea index (OAI), lowest pulse oxygen saturation (Lowest SpO_2), and mean pulse oxygen saturation (Mean SpO_2)[7,8].

Echocardiography

Echocadiography was performed using the standard techniques. Two dimensional echocardiographic images were acquired from the parasternal long and short axis, apical long axis, and apical four chamber views by an experienced echocardiographer. The major echocardiographic parameters investigated were interventricular septal thickness (IVS), posterior wall thickness (PW), left ventricular mass index (LVMI), left atrial volume index (LAVI), left ventricular ejection fraction (LVEF), LV inflow E wave deceleration time (DcT), the ratio of LV inflow E wave to A wave peak velocity (E/A), and the ratio of transmitral early left ventricular filling velocity to early diastolic Doppler tissue imaging of the mitral annulus (E/e'). All recordings were performed on ultrasound systems (Acuson Sequoia, Siemens, Erlangen, Germany).

Flow-mediated dilatation (FMD) measurements

Endothelial function was evaluated by means of FMD within one week before or after polygraphy as previously reported[2]. After fasting for at least 5 hr, patients were required to lie at rest for at least 15 min, and FMD was assessed in the right arm in a supine position in a quiet temperature-controlled room by using high-resolution ultrasound (UNEXEF18G, UNEX Corporation, Nagoya, Japan). The brachial artery was scanned laterally and its diameter at end-diastole (from the inner border line of adventitia to adventitia) was measured. The cut off was obtained 5 cm proximal to the antecubital fossa, fitted at 8 cm distal to the brachial artery, near the wrist. The transmit focus zone was set at the depth of the anterior wall. Anatomical landmarks and snapshot images were used to assess FMD in the exact same vessel selection on each study day and at each time point. A view of a 5 cm transversal section of the brachial artery was recorded for periods of 30 s at the baseline and during the peak (up to 2 min after cuff release) reactive hyperemia (after deflation of the blood pressure cuff previously inflated to 50 mmHg above the patients' systolic blood pressure around the forearm for 5 min). The vessel diameter was automatically measured by built-in software. FMD was calculated as the percentage of change in diameter from the baseline value before cuff release to the peak value after cuff release : %FMD=[(vessel diameter reactive hyperemia−vessel diameter at rest)×100]/ vessel diameter at rest.

Statistical analysis

Data are presented as mean±SD. We used the chi-square test for categorical variables and the independent t-test for continuous variables. If the data were not distributed normally, the Mann-Whitney U test was used. A p value of <0.05 was considered significant for all comparisons. All analyses were performed using a statistical software package (StatView version 5.0, SAS Institute Inc., Abacus Concepts, Berkeley, CA, USA).

RESULTS

Clinical characteristics of study subjects

The clinical characteristics of Group A and Group B are shown in Table 1. C-reactive protein was significantly higher in Group A than in Group B. However, there were no other differences in the laboratory data between the two groups.

Polygraphic data are shown in Table 2. AHI, CAI and OAI were significantly higher in Group A than in Group B. The mean SpO_2 was significantly lower in Group A than in Group B.

Echocardiographic data are shown in Table 3. There were no significant differences in all parameters between the two groups.

Results of FMD are shown in Figure 1. The percentage of FMD was significantly lower in Group A than in Group B (3.5±1.6 vs. 7.8±3.1, $P<0.01$).

DISCUSSION

The influence of sleep apnea syndrome on cardiac function

Since obstruction of upper respiratory airway causes negative intra-thoracic pressure and hypoxia results in sympathetic nervous overactivity, SAS may contribute to cardiac systolic and diastolic dysfunction[4,9,10]. However in the present study, significant differences in cardiac function were not observed between mild and moderate-severe SAS in our study population. In a previous study by Romero-Corral *et al*[4], severe SAS was associated with diastolic dysfunction (LAVI), but not systolic dysfunction (LVEF). Their study population included more severe SAS and OSA dominant compared to our study. In our study population, BMI and OAI were much lower than those in their study. These differences might relate to no significant changes in cardiac systolic and diastolic function even in moder-

Table 1. Comparisons of clinical characteristics between patients in groups A and B

		Group A AHI≥15 (n=93)	Group B AHI<15 (n=36)	P value
Physical	Age (years)	59.1±13.9	57.8±14.8	0.32
	Male (n, %)	72 (77.4)	21 (58.3)	0.06
	BMI (kg/m^2)	23.9±5.2	23.7±5.7	0.73
	SBP (mmHg)	124.2±14.0	122.5±15.5	0.54
	DBP (mmHg)	77.8±8.6	76.2±9.6	0.33
Labo data	Hb (g/dl)	12.6±2.2	13.1±2.2	0.37
	BUN (mg/dl)	18.9±8.3	17.1±9.4	0.31
	Creatinine (mg/dl)	1.0±0.4	0.9±0.7	0.70
	TP (g/dl)	6.7±0.8	6.7±0.8	0.80
	ALB (g/dl)	3.6±0.6	3.7±0.6	0.74
	AST (IU/l)	27.9±16.0	25.1±8.2	0.26
	ALT (IU/l)	28.8±21.2	24.7±15.9	0.20
	TB (mg/dl)	0.9±0.5	0.8±0.6	0.42
	DB (mg/dl)	0.2±0.1	0.1±0.1	0.80
	ALP (IU/l)	257.3±165.8	246.1±102.7	0.55
	γGTP (IU/l)	77.1±108.2	64.3±47.8	0.54
	CRP (mg/dl)	1.2±1.9	0.7±1.0	$P<0.01$
	TG (mg/dl)	114.6±56.8	116.5±51.3	0.89
	TC (mg/dl)	163.6±33.9	163.0±40.6	0.72
	LDL (mg/dl)	104.8±33.1	100.6±28.7	0.55
	HDL (mg/dl)	47.5±13.0	50.4±20.4	0.34
	FPG (mg/dl)	117.3±38.3	105.8±18.5	0.19
	HbA1c (%)	5.7±1.9	5.5±0.5	0.35

BMI, body mass index ; SBP, systolic blood pressure ; DBP, diastolic blood pressure

Table 2. Comparison of polygraphic data between patients in groups A and B

	Group A AHI≥15 (n=93)	Group B AHI<15 (n=36)	P value
AHI (times/h)	34.8±14.8	8.4±4.0	P<0.01
CAI (times/h)	12.6±11.7	3.1±2.8	P<0.01
CAI/AHI (%)	36.2	36.9	
OAI (times/h)	9.9±9.6	3.0±2.8	P<0.01
Lowest SpO_2 (%)	80.5±8.0	82.3±8.2	0.20
Mean SpO_2 (%)	94.9±2.7	96.0±3.4	0.07

AHI, apnea hypopnea index ; CAI, central apnea index ; OAI, obstructive apnea index ; Lowest SpO_2, lowest oxyhemoglobin saturation ; Mean SpO_2, mean oxyhemoglobin saturation

Table 3. Comparisons of echocardiographic data between patients in groups A and B

	Group A AHI≥15 (n=93)	Group B AHI<15 (n=36)	P value
IVS (mm)	10.9±2.9	11.3±4.0	0.53
PW (mm)	11.1±2.5	10.8±2.4	0.47
LVMI (g/m^2)	141.6±44.0	132.5±58.2	0.31
LAVI (ml/m^2)	42.7±29.2	39.5±20.6	0.59
LVEF (%)	48.7±14.6	50.0±16.3	0.55
Dct (msec)	210.7±72.9	203.9±69.8	0.87
E/A	1.1±0.7	1.4±0.9	0.41
E/e'	13.6±7.7	15.2±7.8	0.53
IVC (mm)	13.3±4.0	13.5±4.2	0.78

IVS, Inter ventricular septal thickness ; PW, posterior wall thickness ; LVMI, left ventricular mass index ; LAVI, left atrial volume index ; LVEF, left ventricular ejection fraction ; Dct, LV inflow E wave deceleration time ; E/A, LV inflow E wave /A wave peak velocity ; IVC, inferior vena cava

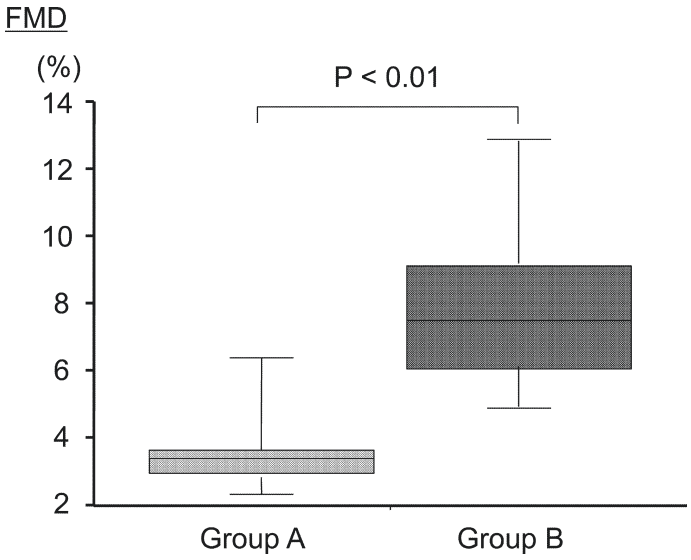

Fig. 1. Comparisons of flow-mediated dilatation (FMD) between patients in Groups A and B.

ate-severe SAS patients (Group A) in the present study.

The influence of sleep apnea syndrome on endothelial function

Endothelial dysfunction is one of important cardiovascular risk factors and precede or accelerate the development of atherosclerosis[11-14]. It has been shown to have a clear predictive value for future cardiovascular event. A number of circulating markers of endothelial function including nitric oxide, soluble cell adhesion molecules, fibrinogen and plasminogen activator inhibitor have been reported to be altered in SAS[15]. However, there are a few reports regarding direct evaluation of endothelial function in a clinical setting in patients with SAS. Tanriverdi *et al*. have recently reported that carotid intima-media thickness was greater and FMD was lower in the SAS group than in controls[16]. We demonstrated directly using FMD that endothelial function was impaired in patients with moderate-severe SAS compared to mild SAS. Among several available methods to evaluate endothelial function, FMD provides accurate data with high reproducibility and allows us repeated measurements because of its non-invasive characteristics. To identify vascular dysfunction in patients with SAS, non-invasive assessment of endothelial function with FMD has important clinical implications. In this study, CRP level was higher in patients with moderate-severe SAS than in mild SAS. Thus, an inflammatory change may participate in endothelial dysfunction observed in this study.

CONCLUSIONS

Moderate-severe SAS was associated with vascular endothelial dysfunction, and FMD is a useful tool to identify impaired endothelial function non-invasively in patients with SAS.

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