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Obstructive sleep apnea as a risk factor for the onset and progression of aortic dissection

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Abstract:

Background: Aortic dissection is thought to develop and progress due to hypertension and atherosclerosis, but the detailed mechanisms of the onset and progression are still unknown. In this study, we investigated the relationship between type of aortic dissection and the atherosclerotic risk factors including obstructive sleep apnea (OSA) and discussed potential mechanisms. **Methods:** There were 52 consecutive patients with aortic dissection who were admitted to our hospital, and a sleep study was performed to look for OSA in 42 of them (27 men and 15 women, age: 67 ± 12 years, BMI: 24 ± 4, DeBakey type I: n=6, type IIIa: n=7, type IIIb: n=29). **Results:** In the 42 patients who had a sleep study, OSA was seen in 36 patients (86%). OSA was more frequent in type IIIb (n=27) than in type IIIa (n=4) aortic dissection (93% vs 57%, p= 0.01). Univariate logistic regression analysis indicated that the presence of OSA could distinguish type IIIb from IIIa (odds ratio: 10.125, 95% confidence interval: 1.272-80.623, P=0.029). **Conclusion:** OSA was frequently associated with aortic dissection and its prevalence was higher in type IIIb than type IIIa, suggesting that OSA may be associated with the development and progression of aortic dissection.

Key words:

Aortic dissection, Atherosclerosis, Obstructive sleep apnea, Risk factor

Introduction

Aortic dissection is a life-threatening disease caused by a tear in the intimal layer of the aorta or bleeding within the aortic wall, resulting in the dissection of the layers of the aortic wall. Aortic dissection is most common in patients 65-75 years old, with an incidence of 0.035% per year in this population[1)]. Except for genetic connective tissue disorders, such as Marfan syndrome, Ehlers-Danlos syndrome or Takayasu disease, aortic dissection is thought to develop and progress due to hypertension and atherosclerosis, but the detailed mechanisms of its onset and progression are still unknown.

Obstructive sleep apnea (OSA) is characterized by repetitive partial or complete obstruction of the pharynx during sleep. Despite increasing breathing efforts, upper airway collapse results in episodes of obstructive hypopnea or apnea affecting sleep architecture and the entire body via both immediate and long-term mechanisms. OSA has been confirmed to be a causal factor in the pathogenesis of hypertension and atherosclerosis[2,3)]. In addition, OSA is thought to be related to aortic disease including aortic dissection[4)]. However, the pathophysiological role of OSA in the onset and progression of aortic dissection is not well understood.

In the present study, we investigated the prevalence of OSA in patients with aortic dissection and tried to elucidate the clinical significance of OSA as a complication of aortic dissection.

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Methods

Study protocol

We recruited 52 consecutive patients with acute aortic dissection who were admitted to our hospital between April 2013 and March 2016. The diagnosis and DeBakey type classification of aortic dissection was based on contrast-enhanced computed tomography. Patients who had been diagnosed with clinical OSA before admission were excluded. Of these 52 patients, we performed a sleep study in 42 patients (27 men and 15 women, age: 67 ± 12 years, BMI: 24 ± 4, DeBakey type I: n=6, type IIIa: n=7, type IIIb: n=29) for screening of subclinical OSA as a complication. In the 6 patients with DeBakey type I dissection, 4 underwent emergent surgical treatment. In these patients, the sleep study was performed only after there was a stable post-operative status. The remaining 2 patients with type I dissection and 36 with type III dissection underwent conservative treatment with antihypertensive therapy, and a sleep study was performed after the acute phase had passed. We analyzed clinical features in these patients. The local institutional review board approved the study protocol, and written informed consent was obtained from each patient.

Sleep study

Overnight pulse oximetry was performed while the patients were breathing room air under stable conditions as a screening test for sleep-related breathing disorders. An oxygen saturation monitor (Pulsox-M24®, Konica Minolta Sensing Inc., Osaka, Japan) was attached to the left fourth finger to determine oxygen saturation (SpO2) and pulse rate from 10 pm to 6 am. The frequency of reductions in SpO2 by ≥ 3% per hour (3% oxygen desaturation index: 3% ODI) and the lowest SpO2 were used as parameters of sleep-related breathing disorders. For the patients who had ≥5 ODI events, portable polysomnography with electroencephalography (Sleep Watcher®, Compumedics Ltd, Abbotsford, Australia) was performed to assess OSA. The parameters were analyzed by 2 experienced technicians who were unaware of the study design. A respiratory amplitude reduction ≥50% was defined as hypopnea and ≥80% as apnea, and the number of apnea or hypopnea events/hour was determined as the apnea-hypopnea index (AHI). OSA was defined as an AHI ≥ 5, based on the recommendation of the American Academy of Sleep Medicine Task Force[5].

Assessment of clinical features

Prevalence of atherosclerotic risk factors such as smoking habits, hypertension, diabetes mellitus and dyslipidemia, and underlining medications at the onset of aortic dissection were assessed as categorical variables via the patients' history and medical examinations. Body mass index was calculated as weight (kg)/[height (m)]^2. Blood pressure, fasting blood glucose and lipid profiles including low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol and triglyceride at admission were assessed. Hypertension was defined as pointing out at previous health check or by medical institutions somewhere, receiving antihypertensive medications, or systolic blood pressure (SBP) > 140 mmHg and/or diastolic blood pressure (DBP) >90 mmHg measured in the supine position at admission. Diabetes was defined as a fasting blood glucose level ≥126 mg/dl and/or a hemoglobin A1c level ≥6.5% and/or a random blood sugar level ≥200 mg/dl and/or receiving anti-diabetic agents. The LDL-cholesterol level ≥140 mg/dl, HDL-cholesterol level ≤40 mg/dl, or triglyceride level ≥150 mg/dl and/or receiving lipid lowering drugs were included in dyslipidemia. History of coronary artery disease and stroke was also assessed.

Statistical analysis

Data were expressed as the mean ± standard deviation (SD) for continuous variables or as the number (percent) of patients for categorical variables. Normality for the distribution of continuous variables was assessed using the Shapiro-Wilk test. Comparisons between two groups were performed using an unpaired t test for continuous variables and a Chi-square test for categorical variables. The comparisons among 3 groups were performed using one-way analysis of variance followed by a post-hoc Bonferroni test for continuous variables and Chi-square test for categorical variables. Univariate logistic regression analysis was performed to determine the variables that could distinguish type IIIb from type IIIa. All statistical analyses were performed using the statistical package for Social Science (Dr. SPSS II for Windows, SPSS Inc., Tokyo, Japan). $P<0.05$ was considered significant.

Results

In a total of 42 patients with aortic dissection who had a sleep study, OSA was seen in 36 patients (86%), in whom AHI was 34 ± 24. In these patients, mild OSA (5≤ AHA< 15) was seen in 8 patients, moderate OSA (15≤ AHA<30) in 10, and severe OSA (30≤AHA) in 18. There were no differences in age, gender, prevalence of current smoking, diabetes and dyslipidemia between the 36 patients with OSA and the 6 without OSA. Blood pressure and lipid profiles at admission were also comparable between the 2 groups with and without OSA. BMI and the prevalence of hypertension were higher in patients with than without OSA. Although a history of coronary artery disease was comparable between the two groups, a history of stroke was more frequent in patients without OSA. Regarding DeBakey type, 75% of patients with OSA showed type IIIb, whereas 50% of patients without OSA showed type IIIa (**Table 1**).

Among the patient groups with type I, IIIa and IIIb, there were no differences in age, gender, prevalence of current smoking, hypertension and dyslipidemia. Blood pressure and lipid profiles at admission were also comparable among the 3 groups. The BMI was higher in the group with type I than the type IIIa and type IIIb groups. When the BMI was com-

Table 1. Baseline characteristics in patients with and without obstructive sleep apnea

	Patients with OSA (n=36)	Patients without OSA (n=6)	P value
Age: yrs	67±12	72±13	0.319
Male gender: n (%)	24 (67)	3 (50)	0.440
BMI: kg/m^2	24±4	20±3	0.040
Current smoking: n (%)	23 (64)	4 (67)	0.965
Hypertension: n (%)	27 (75)	2 (33)	0.029
Diabetes: n (%)	3 (5)	0 (0)	0.469
Dyslipidemia: n (%)	9 (25)	3 (50)	0.237
SBP at admission: mmHg	170±32	156±12	0.295
DBP at admission: mmHg	90±15	85±19	0.406
LDL-cholesterol: mg/dl	111±33	117±50	0.693
HDL-cholesterol: mg/dl	49±14	53±12	0.536
Triglyceride: mg/dl	135±115	127±97	0.877
Underling medications: n (%)			
ACE inhibitors/ARBs	13 (36)	1 (17)	0.350
Calcium channel blockers	12 (33)	4 (67)	0.120
Statins	12 (33)	2 (33)	1.000
Anti-diabetic drugs	3 (8)	1 (17)	0.520
History of CAD: n (%)	1 (3)	1 (17)	0.154
History of stroke: n (%)	7 (17)	4 (67)	0.016
DeBakey type: n (%)			0.050
I	5 (14)	1 (17)	
IIIa	4 (11)	3 (50)	
IIIb	27 (75)	2 (33)	

OSA, obstructive sleep apnea; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low density lipoprotein; HDL, high density lipoprotein; ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease

pared between type IIIa and type IIIb groups, it was higher in the type IIIb group. The prevalence of diabetes was higher in the type I than the type IIIb group. Regarding underling medications, the use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers and that of statins were comparable among the 3 groups. However, the use of calcium channel blockers was more frequent in the type I and type IIIa groups, compared with type IIIb group. The use of anti-diabetic drugs was more frequent in the type I group, compared with type IIIb group. Although a history of coronary artery disease was comparable among the 3 groups, a history of stroke was more frequent in the type IIIa than the type IIIb group (**Table 2**). The prevalence of OSA was higher in the type IIIb (27 patients) than the type IIIa group (4 patients) (93% vs 57%, p=0.01) (**Figure 1**).

Univariate logistic regression analysis indicated that BMI (odds ratio: 1.426, 95% confidence interval: 1.035-1.963, P= 0.025), underling use of calcium channel blockers (odds ratio: 0.043, 95% confidence interval: 0.004-0.434, P=0.0075), history of stroke (odds ratio: 0.064, 95% confidence interval: 0.009-0.450, P=0.0057) and prevalence of OSA (odds ratio: 10.125, 95% confidence interval: 1.272-80.623, P= 0.029) could distinguish type IIIb from type IIIa aortic dissection (**Table 3**).

Discussion

In this small cohort study, we demonstrated that OSA was highly prevalent (86%) in patients with acute aortic dissection. The prevalence of OSA was higher in DeBakey type IIIb than type IIIa. In addition, the presence of OSA could distinguish between type IIIa and IIIb in univariate analysis. These results suggest the presence of OSA might be related to the development and progression of aortic dissection.

The relationship between aortic dissection and OSA has not been assessed widely in large scale epidemiological studies. In several small cohort studies, however, a higher prevalence of OSA was observed in patients with aortic dissection than in control subjects. Naito et al.[6] demonstrated that the 3% ODI, a major component of OSA, was closely associated with aortic dissection. Hata et al.[7] observed a higher prevalence of sleep disorders including OSA in younger active patients with aortic dissection. Zhang et al.[8] demonstrated that OSA was highly prevalent and independently associated with Stanford type B (i.e., DeBakey type III aortic dissection). In addition, Wan et al.[9] demonstrated that the severity of OSA was significantly associated with an increased risk of partial false lumen thrombosis in type III aortic dissection. The results of our study support the results of these previous studies. However, our finding of a higher prevalence of OSA in type IIIb than type IIIa is a novel finding. Recently, Zhou et al.[10] performed a meta-analysis of observational studies using a systematic search of PubMed, Embase and Cochrane Library. In their meta-analysis, information on 424 cases of aortic dissection among 56,291 patients was obtained from one cohort, four case-control and

Table 2. Baseline characteristics in DeBakay type I, IIIa and IIIb aortic dissection patients

	Type I (n=6)	Type IIIa (n=7)	Type IIIb (n=29)	P value
Age: yrs	62±16	74±5	67±12	0.197
Male gender: n (%)	3 (50)	5 (71)	19 (66)	0.702
BMI: kg/m^2	27±4	20±3**	23±3*†	0.025
Current smoking: n (%)	4 (67)	5 (71)	19 (66)	0.957
Hypertension: n (%)	4 (67)	6 (86)	20 (69)	0.721
Diabetes: n (%)	2 (33)	0 (0)	1 (0.3)†	0.026
Dyslipidemia: n (%)	3 (50)	3 (43)	7 (24)	0.270
SBP at admission: mmHg	161±29	167±23	170±32	0.851
DBP at admission: mmHg	88±16	94±15	89±16	0.776
LDL-cholesterol: mg/dl	124±30	128±38	105±34	0.338
HDL-cholesterol: mg/dl	47±13	52±13	50±15	0.816
Triglyceride: mg/dl	177±80	117±75	130±127	0.586
Underling medications: n (%)				
ACE inhibitors/ARBs	4 (67)	2 (29)	8 (28)	0.174
Calcium channel blockers	4 (67)	6 (86)	6 (21)*†	0.002
Statins	3 (50)	4 (57)	7 (24)	0.162
Anti-diabetic drugs	2 (33)	1 (17)	1 (3)*	0.068
History of CAD: n (%)	1 (17)	0 (0)	1 (0.3)	0.311
History of stroke: n (%)	2 (33)	5 (71)	4 (14)††	0.007

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low density lipoprotein; HDL, high density lipoprotein; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker, CAD, coronary artery disease
*P<0.05, **P<0.001 vs I, †P<0.05, ††P<0.01 vs IIIa

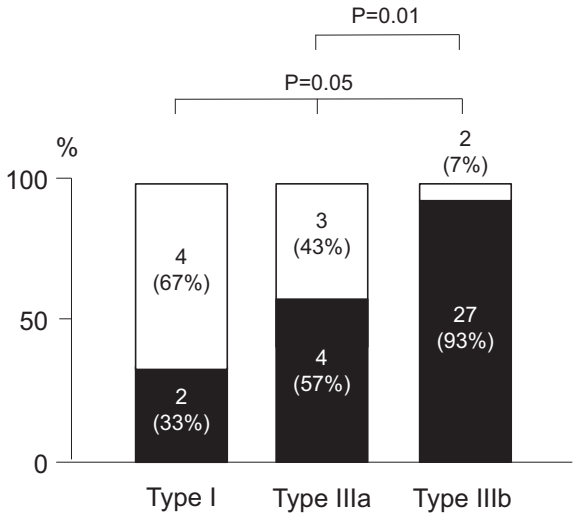

Figure 1. Prevalence of obstructive sleep apnea in the groups with DeBakey type I, type IIIa and type IIIb aortic dissection. It was higher in type IIIb than in type IIIa.

two cross-sectional studies. As a result, OSA was associated with an overall significant 60% increase in the risk of aortic dissection, compared with the absence of OSA (odds ratios 1.60; 95% confidence interval: 1.01-2.53), and there was a significantly higher AHI (mean difference: 10.71; 95% confidence interval: 7.46-13.96) in those with OSA. Therefore, the presence of OSA appears to be a major risk factor for the development and progression of aortic dissection and may also be related to its pathogenesis.

The underlying mechanisms by which OSA may promote the development and progression of aortic dissection are not fully understood. Studies investigating the impact of OSA on aortic disease have discussed several pathogenetic mechanisms, including intrathoracic pressure changes leading to shear stress on the aortic wall, intermittent hypoxia leading to oxidative stress and sympathetic stimulation, and arousal-induced sympathetic activation with subsequent repetitive blood pressure surges[11]. OSA results in an inspiratory effort against an occluded airway, producing negative intrathoracic pressure swings. These forces support an elevated blood pressure that stretches the aortic wall where blood pressure surges are highest and lead to pathological shear stress. It is known that systolic blood pressure promotes the fragmentation of fibrin and collagen deposition, leading to stiffening of the aortic wall[12]. Additional physical dilation or shear stress itself might cause development of aortic dissection[13]. These mechanisms could explain the close association of OSA with DeBakey type III, because the descending aorta might be susceptible to the influence of intrathoracic pressure. A higher prevalence of OSA, especially in type IIIb aortic dissection in our results, suggests that OSA might accelerate the progression of aortic dissection.

In a mouse model, intermittent hypoxia increased chemoreflex and depressed baroreflex sensitivity, resulting in sympathoadrenal hyperactivity[14]. In humans, intermittent hypoxia due to OSA has been proposed to induce hypertension via increased release of vasoactive substances[15] and peripheral chemoreceptor activation[16]. In OSA patients, the sever-

Table 3. Univariate logistic regression analysis to distinguish DeBakey type IIIb from type IIIa aortic dissection

	Wald λ^2	Odds ratio	95% confidentiial interval	P value
Age	1.840	0.938	0.855-1.029	0.175
Male gender	0.088	0.760	0.124-4.644	0.766
BMI	4.719	1.426	1.035-1.963	0.025
Current smoking	0.088	0.760	0.124-4.644	0.766
Hypertension	0.743	0.370	0.039-3.545	0.389
Dyslipidemia	0.953	0.424	0.076-2.374	0.329
SBP at admission	0.029	1.003	0.973-1.033	0.864
DBP at admission	0.481	0.978	0.917-1.042	0.488
LDL-cholesterol	1.251	0.987	0.966-1.010	0.263
HDL-cholesterol	0.168	0.988	0.933-1.046	0.682
Triglyceride	0.063	1.001	0.993-1.009	0.802
ACE inhibitors/ARBs	0.003	0.952	0.153-5.943	0.958
Calcium channel blockers	7.141	0.043	0.004-0.434	0.0075
Statins	2.660	0.239	0.043-1.335	0.103
History of stroke	7.633	0.064	0.009-0.450	0.0057
OSA	4.783	10.125	1.272-80.623	0.029

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low density lipoprotein; HDL, high density lipoprotein; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; OSA, obstructive sleep apnea

ity of OSA is independently associated with oxidative stress caused by apneic events[17]. In several studies, the decrease in arterial oxygen saturation measured by pulse oximetry was correlated with the degree of aortic stiffness[18,19], which might be associated with development of aortic dissection. In OSA, each apneic event is accompanied by an arousal, which leads to transient increases in blood pressure despite a fall in cardiac output[20]. These events are caused by sympathetic vasoconstriction and their consequences include catecholamine release[21], endothelial dysfunction[22] and probably aortic dissection[12]. However, these mechanisms are somewhat speculative, so further investigation is needed to establish the causal relation between OSA and aortic dissection.

Continuous positive airway pressure (CPAP), a standard treatment for OSA, can reduce acute hemodynamic changes during sleep and inhibit atherosclerosis progression[23]. To fully understand the effect of CPAP treatment, it is important to know whether aortic dissection is caused by the acute effects of apneic episodes or the chronic structural and autonomic changes in OSA patients[24]. CPAP treatment can abolish the acute blood pressure surges and/or intrathoracic pressure swings and lower diurnal blood pressure in OSA patients. However, there is no evidence whether CPAP treatment prevents the onset of acute aortic dissection. Even if CPAP treatment is effective for disease prevention, patient adherence to this therapy is only about 30-60%, and this is a significant limitation[25]. Further investigation is needed to determine the value of CPAP treatment in the primary and secondary prevention of aortic dissection in OSA patients.

Study limitations

The present study has several potential limitations. The biggest limitation is that sample size was too small to draw a conclusion regarding the association between aortic dissection and OSA. Also, in the 42 study patients, 29 patients (69%) had DeBakey type IIIb, but there were only a few type I and IIIa patients (6 patients: 14% and 7 patients: 17%, respectively). Therefore, it possible that the difference in the prevalence of OSA between type IIIa and IIIb patients might be due to a type I error because of the small sample size. Although in the present study we performed univariate logistic regression analysis, multivariate analysis data are absent. It is important to note that this study was merely an observational study, in which we showed a high prevalence of OSA in patients with aortic dissection. A prospective event-driven study, such as registration research of OSA patients, would be useful to assess whether OSA is an independent risk factor for aortic dissection. In addition, more precise information regarding aortic dissection (onset time, blood pressure and/or hemodynamics during sleep) should be analyzed, although we could not collect such data in the present study.

Conclusion

OSA was frequently associated with aortic dissection, and its prevalence was higher in type IIIb than type IIIa, suggesting that OSA may be associated with the development and progression of aortic dissection.

Conflicts of Interest

Teruo Inoue has received honorariums from Mochida and Bayer; research grants from Astellas, Abbott Vascular, Boehringer Ingelheim, Bayer, Boston Scientific, Sanwa Kagaku Kenkyusho, Teijin Pharma, Takeda, Mitsubishi Tanabe and Medtronic. For the remaining authors none were declared.

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