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【 ORIGINAL ARTICLE 】

Severity Indices for Obstructive Sleep Apnea Syndrome Reflecting Glycemic Control or Insulin Resistance

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Abstract:

Objective We aimed to identify obstructive sleep apnea syndrome (OSAS) severity indices reflecting the anthropometric and metabolic characteristics of patients with OSAS.

Methods A total of 76 patients with OSAS underwent nasal continuous positive airway pressure (nCPAP). We also investigated the effects of nCPAP on OSAS-associated muscle sympathetic nerve activity (MSNA), risk for cardiovascular diseases, and insulin secretion and sensitivity.

Results Among the OSAS severity indices, HbA1c was significantly correlated with the apnea-hypopnea index, whereas HOMA-beta, HOMA-IR, and hepatic insulin resistance were significantly correlated with % SpO_2<90%, independent of age, gender, and body mass index (BMI). Burst incidence of MSNA was independently associated with only a 3% oxygen desaturation index. nCPAP therapy significantly lowered the OSAS severity indices and reduced the burst rate, burst incidence, and heart rate.

Conclusion The OSAS severity indices reflecting apnea/hypopnea are associated with glycemic control, whereas those reflecting hypoxia, particularly % SpO_2<90%, are associated with hepatic insulin resistance independent of obesity. Both types of OSAS severity indices, especially the 3% oxygen desaturation index (reflecting intermittent hypoxia), are independently associated with MSNA, which is dramatically lowered with the use of nCPAP therapy. These findings may aid in interpreting each OSAS severity index and understanding the pathophysiology of OSAS in clinical settings.

Key words: obstructive sleep apnea syndrome, nasal continuous positive airway pressure, muscle sympathetic nerve activity

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Introduction

Obstructive sleep apnea syndrome (OSAS) is defined as repetitive episodes of decreased or total loss of respiratory airflow during sleep due to collapse of the upper airway during inspiration and is accompanied by strenuous breathing. In addition, it is associated with changes in glucose and lipid metabolism, leading to cardiovascular risks. OSAS patients with high OSAS severity indices have a higher risk of developing diabetes (1, 2), nonalcoholic fatty liver disease (3-5), and cardiovascular diseases (6-9) than those with lower indices. Regarding OSAS and glucose metabolism, it was reported that increasing OSAS severity is associated with poor glycemic control (2) and development of type 2 diabetes (10). However, what pathophysiological aspects of OSAS affect glucose homeostasis, including the secretion and action of insulin, remain unclear.

In addition, sustained hypoxemia causes a continuous increase in sympathetic nerve activity and blood pressure, which largely persist following the return to normoxia (7, 9, 11). To assess sympathetic nerve activity, muscle sympathetic nerve activity (MSNA), a direct recording of efferent sympathetic nerve activity, is still recognized as the

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gold standard method (12, 13). Numerous studies on OSAS patients have used the apnea-hypopnea index as an OSAS severity index. Furthermore, various OSAS severity indices are clinically available and can be classified into two categories: those reflecting apnea/hypopnea [apnea index, hypopnea index, apnea-hypopnea index (AHI), and arousal index] and those directly reflecting hypoxia (3% oxygen desaturation index, and % SpO_2<90%). Previous studies have suggested an inconsistent association of each OSAS severity index with indices of glucose homeostasis. Makino et al. reported that both the AHI and % SpO_2<90% are associated with higher insulin resistance index HOMA-IR (14). Tanno et al. reported that a 3% oxygen desaturation index is associated with a higher HOMA-IR and lower insulin sensitivity Matsuda index (15). In contrast, Otake et al. reported that the AHI is not independently associated with HOMA-IR (16). However, the pathophysiological features of OSAS that are uniquely associated with each category of the severity indices have not yet been comprehensively investigated.

The conventional choice for treating OSAS is nasal continuous positive airway pressure (nCPAP) (17). Theoretically, nCPAP ameliorates OSAS-associated pathophysiology; however, whether or not nCPAP has beneficial effects on insulin secretion, insulin resistance, and glucose and lipid metabolism is debatable (18, 19). Specifically, the pathophysiology of OSAS has not been adequately investigated in Japanese subjects who are less obese but have more severe OSAS due to micrognathia than white male subjects (20, 21).

In the present study, we tested our hypothesis that apnea/hypopnea and hypoxia exert different pathological impacts on energy metabolism and the sympathetic nervous system. In addition, we investigated the effects of nCPAP on OSAS-associated increases in MSNA and energy metabolism.

Materials and Methods

Participants and study design

Between 2005 and 2011, we enrolled a total of 76 patients with OSAS (63 men and 13 women) who were outpatients at Kanazawa Municipal Hospital (Ishikawa, Japan). OSAS was diagnosed using overnight polysomnography (PSG). Patients with >5 central sleep apnea events per hour who could not undergo nCPAP therapy were excluded from the study. nCPAP therapy was indicated for subjects with moderate to severe OSAS, defined as an AHI ≥20 (events/hour) with strong subjective symptoms, such as excessive daytime sleepiness and morning headache (International Classification of Sleep Disorders-Second Edition).

The study was approved by the ethics committee at Kanazawa Municipal Hospital and was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000017612). Because this was a retrospective study, potential participants had the opportunity to opt out of the research.

Biochemical and anthropometric parameters

Blood samples were collected from all subjects following an 8-hour fast. The samples were centrifuged, and plasma and serum samples were stored at -20℃ until future analyses. Glucose was measured using a standard glucose oxidase method. Low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured enzymatically with a chemical analyzer (AV680; Beckman Coulter, Tokyo, Japan). Subjects with triglyceride levels >400 mg/dL were excluded. The Friedewald formula was used to calculate total cholesterol levels. Fasting serum levels of insulin were determined using chemiluminescence, and glycosylated hemoglobin was measured using immunoturbidimetry.

Insulin resistance was estimated using the homeostatic model assessment of insulin resistance (HOMA-IR), which was calculated as:

[fasting insulin (pmol/L) × fasting glucose (mmol/L)] / 22.5 (22).

The quantitative insulin sensitivity check index (QUICKI), a measure of insulin sensitivity, was calculated by logarithmic transformation using the following formula:

1 / [log fasting insulin (U/mL) + log fasting glucose (mg/dL)] (23).

The Matsuda index, an index of whole-body (mainly skeletal muscle) insulin sensitivity, was calculated from oral glucose tolerance test (OGTT) data using the following formula (24, 25):

Matsuda index = 10,000 / $\sqrt{}$ (fasting plasma glucose × fasting insulin) × (mean glucose × mean insulin during OGTT).

The hepatic insulin resistance index was defined as the product of the total area under the curve (AUC) for glucose and insulin during the first 30 minutes of an OGTT and was calculated using the following formula:

hepatic insulin resistance = ($AUC_{[glucose]}$ 0-30) × ($AUC_{[insulin]}$ 0-30).

The BMI was calculated as the weight (kg) divided by the height (m) squared. The waist circumference was measured at the umbilical level. Body composition was assessed using a multifrequency bioelectrical impedance analysis with an X-SCAN PLUS Body Composition Analyzer (Owa Medical, Fukuoka, Japan), as described previously (26).

PSG measurements

Overnight PSG was performed using multichannel monitoring, including neurophysiological variables (electroencephalogram, electrooculogram, and chin electromyogram) and cardiorespiratory variables (thermistor, chest wall motion, abdominal wall motion, arterial oxygen saturation, and electrocardiogram). Continuous recordings were obtained using a computerized diagnostic system (Alice 3™ or Alice 4™; Respironics, Pittsburgh, USA). The data were recorded during the examination from 21:00 to 6:00. PSG measurements were taken before and after nCPAP therapy.

OSAS severity indices

Apnea was defined as a cessation of airflow for at least 10 seconds, and hypopnea was defined as having a significant decline (>50%) in airflow for at least 10 seconds accompanied by 3% oxygen desaturation or arousal. The AHI was determined as the number of apnea and hypopnea episodes per hour. The arousal index was the total number of arousals on electroencephalogram per hour of total sleep time. The 3% oxygen desaturation index was defined as the number of dips in oxygen saturation (SpO_2) ≥3% per hour of total sleep time. In addition, we recorded PSG parameters, and the lowest O_2 saturation (minimum SpO_2) and percentage of sleep time with SpO_2<90% (% SpO_2<90%) were also recorded.

MSNA measurements

MSNA recordings were taken of patients who had been diagnosed with OSAS after undergoing PSG. Patients with significant neuropathy were excluded from the MSNA measurements. All data were collected in the morning (9:00-12:00). All participants abstained from alcohol and caffeine for 24 hours and were tested after fasting for at least 12 hours. Postganglionic MSNA was measured at the right peroneal nerve at the fibular head using a high-impedance (10 MΩ) tungsten microelectrode. As previously described (27-30), the common peroneal nerve was detected by palpation and electrical stimulation of the skin surface. A tungsten microelectrode was inserted percutaneously into a motor fascicle of the peroneal nerve and adjusted until spontaneous pulse-synchronous, multi-unit bursts of sympathetic nervous activity could be validated. Multi-unit MSNAs were recorded simultaneously from the same microelectrode. Data were acquired over at least 1 minute after a 2-min stabilization period.

The electrodes were connected to a preamplifier at a gain of 1,000 and to an amplifier at a gain of 70. The signal was fed through a band-pass filter (500-3,000 Hz) and a resistance-capacitance integrated circuit with a time constant of 0.1 seconds in order to produce a mean voltage neurogram on a Power Lab recoding system (Model 8/30; ADI Instruments, Bella Vista, Australia). The raw nerve signal was acquired at 12 kHz; other signals were obtained at 1,000 Hz. Experienced investigators identified multi-unit MSNA peaks in the integrated nerve recording based on their relationship with cardiac activity in a blinded fashion. Multi-unit MSNA was expressed as the number of bursts per minute (burst rate) and the number of bursts per 100 heartbeats (burst incidence). The amplified and filtered nerve activity was full-wave rectified and passed through a resistance-capacitance integrated circuit with a time constant of 0.1 seconds and connected to an audio speaker in order to produce a mean voltage neurogram for analyzing multi-unit MSNA. Multi-unit integrated nerve activity was digitized at a sampling rate of 1,000 Hz. Both the raw nerve signals and the mean voltage neurogram were displayed on a personal computer (CF-F10: Panasonic, Osaka, Japan).

Statistical analyses

Normally, distributed data are presented as means±standard deviations, and the differences between the two groups were analyzed using Student's *t*-test; the paired *t*-test was used for paired samples. Irregularly distributed data were presented as medians and ranges, and the differences between groups were assessed using the Mann-Whitney *U* test. Relationships were determined using regression analyses, and a P value <0.05 was considered statistically significant. Multivariate logistic regression analyses (forced entry method) were performed using MSNA and metabolic parameters as explanatory factors and OSAS severity indices as dependent variables. All of the explanatory variables were tested for collinearity, and only those that could be confirmed to have no collinearity by the values of variance inflation factor (VIF) and tolerance were used as independent explanatory variables in the multivariate logistic regression analyses. All statistical analyses were performed using SPSS software, version 16.0 (IBM, Armonk, USA).

Results

OSAS severity indices correlated with clinical parameters

Table 1 shows the baseline anthropometric and biochemical characteristics of the study subjects. The median BMI was 25.6 kg/m^2, fasting plasma glucose (FPG) was 94 mg/dL, and hemoglobin A1c (HbA1c) was 5.9%. Medications for hypertension, diabetes, and dyslipidemia were prescribed to 40.8%, 10.5%, and 18.4% of the patients, respectively. The AHI ranged from 6.8 to 141.4.

Many of the pre-nCPAP OSAS severity indices except for the arousal index were correlated with age, BMI, waist circumference, fat mass, fat-free mass, burst rate, burst incidence, and heart rate but not with systolic/diastolic blood pressure (Table 2), and some were correlated with liver enzymes, HDL cholesterol (data not shown), FPG, insulin secretion indices (HOMA-beta, insulinogenic index), or insulin sensitivity/resistance indices (HOMA-IR, Matsuda index, and hepatic insulin resistance index).

OSAS severity indices correlated with glucose metabolism indices

After adjusting for age and gender, multiple linear regression analyses revealed that HbA1c was significantly correlated with the AHI, which remained significant even after adjusting for the BMI (Model 2 in Table 3). Insulin secretion indices (HOMA-beta, insulinogenic index) and insulin sensitivity/resistance indices (HOMA-IR, QUICKI, and hepatic insulin resistance index) were significantly correlated with % SpO_2<90%, independent of age and gender. Of these, HOMA-beta, HOMA-IR, and hepatic insulin resistance remained significantly correlated with % SpO_2<90%

Table 1. Anthropometry and Biochemical Characteristics of the Study Subjects before and after Nasal Continuous Positive Airway Pressure Therapy.

	before		after		p
	N	Mean±SD/Median (minimum-maximum)	N	Mean±SD/Median (minimum-maximum)	
age (year)	76	62.0 (25-88)			
gender (M/F)	76	63/13			
body weight (kg)	62	74.5±16.1			
BMI (kg/m^2)	62	25.8 (16.9-44.7)			
waist circumference (cm)	62	94.9±12.2			
fat mass (kg)	62	19.0 (7.5-47.6)			
fat-free mass (kg)	62	52.6 (5.5-73.1)			
nCPAP therapy period (day)	62	123 (10-1,662)			
nCPAP mounting time (hours/day)	75	4.8±1.9			
Epworth sleepiness scale test (point)	76	7 (0-24)			
apnea index (events/hour)	75	18.9 (0.0-138.7)	67	0.3 (0.0-8.7)	<0.001
hypopnea index (events/hour)	75	17.6 (0.0-76.7)	67	2.3 (0.2-23.1)	<0.001
apnea-hypopnea index (events/hour)	75	45.0 (6.8-141.4)	76	2.6 (0.3-23.1)	<0.001
3% oxygen desaturation index (events/hour)	73	30.9 (4.3-97.6)	66	1.0 (0.0-17.2)	<0.001
% SpO_2<90% (% of total sleep time)	74	7.29 (0.00-76.91)	67	0.00 (0.00-14.0)	<0.001
SpO_2 minimum (%)	75	76 (38-90)	67	90 (73-97)	<0.001
arousal index (events/hour)	74	39.7 (12.5-120.2)	64	16.8 (0.0-52.3)	<0.001
burst rate (bursts/minute)	58	62 (24-101)	38	44 (23-74)	<0.001
burst incidence (bursts/100 heartbeats)	58	88 (42-100)	38	58 (42-100)	<0.001
systolic blood pressure (mmHg)	73	131 (98-165)	63	130 (107-174)	0.645
diastolic blood pressure (mmHg)	73	80 (39-117)	63	76 (56-109)	0.071
heart rate (beats/minute)	58	71±11	38	69±11	0.017
fasting plasma glucose (mg/dL)	63	94 (79-159)	20	94 (86-150)	0.663
HbA1c (%)	76	5.9 (4.6-9.4)	19	6.0 (5.2-8.8)	0.360
HOMA-beta	57	55 (6-241)	20	67 (7-285)	0.296
insulinogenic index	58	0.4 (0.0-1.9)	20	0.3 (-0.6-1.8)	0.224
HOMA-IR	57	1.2 (0.1-3.9)	20	1.5 (0.6-5.9)	0.931
QUICKI	57	0.37 (0.31-0.61)	20	0.36 (0.30-0.42)	0.849
Matsuda index	56	7.1 (1.3-89.0)	20	8.8 (1.2-21.7)	0.058
hepatic insulin resistance index	56	2.2×10^6 (2.5×10^4-1.3×10^7)	20	1.6×10^6 (1.0×10^5-1.2×10^7)	0.157

nCPAP: nasal continuous positive airway pressure, HOMA-beta: homeostatic model assessment beta cell function, HOMA-IR: homeostasis model assessment of insulin resistance, QUICKI: quantitative insulin sensitivity check index

even after adjusting for the BMI (Model 2 in Table 3). The % SpO_2<90% was significantly correlated with all of the insulin secretion and insulin sensitivity/resistance indices, independent of MSNA (Model 4 in Table 3).

OSAS severity indices correlated with MSNA

Multiple linear regression analyses showed that both the burst rate and burst incidence were significantly correlated with the apnea index, AHI, 3% oxygen desaturation index, and % SpO_2<90%, independent of age and gender. However, after adjusting for the BMI, only the burst incidence showed a significant correlation-with the 3% oxygen desaturation index (Models 1 and 2 in Table 3). These findings suggest that the OSAS severity indices are associated with muscle sympathetic activity, independent of age and gender, but are largely dependent on obesity.

It was previously reported that glycemic control decreases MSNA in patients with type 2 diabetes (31). However, in the present study, there was no significant association between MSNA and HbA1c (Table 2).

Next, we conducted experiments to determine whether or not the associations between glucose metabolism indices and MSNA and OSAS severity indices were affected by HbA1c (Model 3 in Table 3). A multiple linear regression analysis revealed that MSNA was significantly correlated with the AHI, 3% oxygen desaturation index, and % SpO_2<90%, after adjusting for age, gender, and HbA1c in Model 3. After further adjusting for the BMI, the burst incidence remained significantly correlated with the 3% oxygen desaturation index (data not shown).

Changes in clinical anthropometrics and biochemical characteristics before and after nCPAP therapy

Table 1 summarizes the observed changes in clinical anthropometric and biochemical characteristics before and after nCPAP therapy. The median period of nCPAP therapy was 123 days. As expected, nCPAP therapy significantly reduced the OSAS severity indices, including the apnea index, hy-

Table 2. **Univariate Correlation between Clinical Parameters, OSAS Severity Indices, and MSNA.**

	apnea/hypopnea								hypoxia				MSNA			
	apnea index (events/hour)		hypopnea index (events/hour)		apnea-hypopnea index (events/hour)		arousal index (events/hour)		3% oxygen desaturation index (events/hour)		% SpO_2<90% (% of total sleep time)		burst rate (bursts/minute)		burst incidence (bursts/100 heartbeats)	
	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p
age (year)	-0.193	0.098	0.011	0.925	-0.246	0.032	-0.066	0.572	-0.128	0.279	-0.305	0.008	0.037	0.785	0.244	0.065
body weight (kg)	0.397	0.001	-0.122	0.345	0.402	0.001	0.105	0.422	0.345	0.007	0.560	<0.001	0.121	0.403	-0.077	0.596
BMI (kg/m^2)	0.436	<0.001	0.007	0.955	0.510	<0.001	-0.001	0.993	0.439	<0.001	0.653	<0.001	0.150	0.297	-0.028	0.849
waist circumference (cm)	0.450	<0.001	-0.018	0.890	0.514	<0.001	0.051	0.699	0.465	<0.001	0.610	<0.001	0.208	0.146	0.019	0.895
fat mass (kg)	0.445	<0.001	-0.001	0.995	0.516	<0.001	0.054	0.677	0.458	<0.001	0.600	<0.001	0.212	0.139	0.023	0.873
fat-free mass (kg)	0.320	0.011	-0.227	0.076	0.262	0.039	0.101	0.439	0.194	0.138	0.334	0.009	0.027	0.855	-0.154	0.286
apnea index (events/hour)			-0.468	<0.001	0.881	<0.001	0.050	0.672	0.852	<0.001	0.712	<0.001	0.294	0.025	0.239	0.071
hypopnea index (events/hour)	-0.468	<0.001			0.004	0.970	-0.007	0.954	-0.053	0.657	-0.142	0.227	0.182	0.170	0.089	0.504
apnea-hypopnea index (events/hour)	0.881	<0.001	0.004	0.970			0.053	0.653	0.919	<0.001	0.713	<0.001	0.419	0.001	0.310	0.018
arousal index (events/hour)	0.676	<0.001	-0.011	0.928	0.758	<0.001			0.708	<0.001	0.608	<0.001	0.333	0.011	0.172	0.201
3% oxygen desaturation index (events/hour)	0.852	<0.001	-0.053	0.657	0.919	<0.001	0.044	0.711			0.731	<0.001	0.460	<0.001	0.392	0.003
% SpO_2<90% (% of total sleep time)	0.712	<0.001	-0.142	0.227	0.713	<0.001	-0.068	0.566	0.731	<0.001			0.380	0.004	0.261	0.050
burst rate (burstsr/minute)	0.294	0.025	0.182	0.170	0.419	0.001	-0.177	0.187	0.460	<0.001	0.380	0.004			0.789	<0.001
burst incidence (bursts/100 heartbeats)	0.239	0.071	0.089	0.504	0.310	0.018	-0.169	0.210	0.392	0.003	0.261	0.050	0.789	<0.001		
systolic blood pressure (mmHg)	0.072	0.544	-0.014	0.909	0.074	0.533	-0.213	0.072	0.081	0.500	0.083	0.490	0.077	0.571	0.103	0.445
diastolic blood pressure (mmHg)	-0.071	0.552	0.095	0.425	-0.030	0.801	-0.264	0.025	-0.013	0.916	0.108	0.366	0.211	0.114	0.040	0.766
heart rate (beats/minute)	0.218	0.100	0.116	0.386	0.301	0.022	-0.045	0.741	0.251	0.062	0.292	0.027	0.633	<0.001	0.052	0.701
fasting plasma glucose (mg/dL)	-0.024	0.850	0.413	0.001	0.224	0.078	-0.178	0.166	0.122	0.348	0.146	0.256	0.246	0.100	0.188	0.211
HbA1c (%)	0.028	0.814	0.010	0.933	0.139	0.233	-0.014	0.910	-0.022	0.855	-0.103	0.384	0.020	0.886	0.005	0.970
HOMA-beta	0.016	0.892	-0.067	0.566	-0.015	0.898	0.002	0.990	0.041	0.728	0.375	0.001	0.253	0.105	0.117	0.461
insulinogenic index	0.088	0.517	0.195	0.150	0.197	0.146	0.023	0.866	0.163	0.234	0.340	0.010	0.168	0.292	0.063	0.697
HOMA-IR	0.048	0.725	0.143	0.289	0.125	0.356	-0.141	0.300	0.129	0.344	0.404	0.002	0.271	0.083	0.159	0.313
QUICKI	0.018	0.893	-0.050	0.712	-0.004	0.978	0.053	0.700	-0.008	0.952	-0.255	0.056	-0.095	0.551	-0.031	0.846
Matsuda index	0.304	0.023	-0.230	0.088	0.234	0.083	0.209	0.122	0.277	0.041	0.017	0.898	-0.177	0.268	-0.016	0.922
hepatic insulin resistance index	0.110	0.421	0.121	0.375	0.185	0.173	0.021	0.878	0.152	0.267	0.392	0.003	0.339	0.030	0.172	0.282

OSAS: obstructive sleep apnea syndrome, MSNA: muscle sympathetic nerve activity, HOMA-beta: homeostatic model assessment beta cell function, HOMA-IR: homeostasis model assessment of insulin resistance, QUICKI: quantitative insulin sensitivity check index

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Table 3. Independent Explanatory Variables for OSAS Severity Indices.

		apnea/hypopnea												hypoxia					
		apnea index (events/hour)			hypopnea index (events/hour)			apnea-hypopnea index (events/hour)			arousal index (events/hour)			3% oxygen desaturation index (events/hour)			% SpO_2<90% (% of total sleep time)		
		β	t	p	β	t	p	β	t	p	β	t	p	β	t	p	β	t	p
Model 1	burst rate (bursts/minute)	0.311	2.484	0.016	0.170	1.290	0.202	0.431	3.629	0.001	-0.184	-1.376	0.175	0.472	3.923	<0.001	0.401	3.386	0.001
	burst incidence (bursts/100 heartbeats)	0.338	2.607	0.012	0.059	0.425	0.673	0.403	3.188	0.002	-0.197	-1.416	0.163	0.470	3.718	<0.001	0.372	2.960	0.005
	fasting plasma glucose (mg/dL)	0.055	0.415	0.680	0.479	3.925	<0.001	0.337	2.734	0.008	-0.132	-0.998	0.322	0.223	1.697	0.095	0.207	1.607	0.113
	HbA1c (%)	0.205	1.748	0.085	0.024	0.196	0.845	0.239	2.101	0.039	-0.037	-0.302	0.763	0.063	0.518	0.606	0.112	0.947	0.347
	HOMA-beta	0.103	0.736	0.465	0.000	0.001	0.999	0.117	0.875	0.385	-0.011	-0.080	0.936	0.201	1.477	0.146	0.441	3.584	0.001
	insulinogenic index	0.061	0.446	0.657	0.187	1.373	0.176	0.161	1.250	0.217	-0.003	-0.023	0.982	0.136	1.015	0.315	0.302	2.380	0.021
	HOMA-IR	0.098	0.715	0.478	0.190	1.374	0.175	0.205	1.585	0.119	-0.116	-0.829	0.411	0.199	1.486	0.143	0.393	3.170	0.003
	QUICKI	-0.041	-0.301	0.765	-0.095	-0.682	0.498	-0.094	-0.715	0.478	0.009	0.061	0.951	-0.084	-0.615	0.541	-0.263	-2.024	0.048
	Matsuda index	0.255	1.865	0.068	-0.310	-2.245	0.029	0.139	1.032	0.307	0.166	1.175	0.245	0.209	1.516	0.136	0.019	0.138	0.890
	hepatic insulin resistance index	0.118	0.881	0.382	0.131	0.957	0.343	0.199	1.568	0.123	0.025	0.184	0.854	0.166	1.254	0.216	0.368	2.996	0.004
Model 2	burst rate (bursts/minute)	0.157	1.146	0.258	0.001	0.008	0.994	0.185	1.435	0.158	-0.059	-0.371	0.712	0.261	1.922	0.061	0.138	1.343	0.186
	burst incidence (bursts/100 heartbeats)	0.210	1.492	0.143	-0.075	-0.487	0.629	0.213	1.603	0.116	-0.021	-0.126	0.900	0.315	2.283	0.027	0.167	1.578	0.122
	fasting plasma glucose (mg/dL)	0.103	0.711	0.480	0.069	0.451	0.654	0.149	1.175	0.246	-0.160	-1.024	0.311	0.050	0.366	0.716	0.106	0.840	0.405
	HbA1c (%)	0.231	1.835	0.072	-0.067	-0.493	0.624	0.232	2.007	<0.050	-0.022	-0.151	0.881	0.050	0.400	0.691	0.024	0.228	0.821
	HOMA-beta	-0.010	-0.053	0.958	-0.128	-0.688	0.495	-0.073	-0.454	0.652	0.193	0.999	0.323	0.065	0.378	0.707	0.373	2.568	0.014
	insulinogenic index	-0.005	-0.035	0.972	0.185	1.180	0.245	0.084	0.617	0.541	0.179	1.101	0.277	0.067	0.459	0.648	0.226	1.759	0.086
	HOMA-IR	0.059	0.333	0.741	0.063	0.342	0.734	0.095	0.602	0.550	-0.047	-0.245	0.807	0.144	0.856	0.397	0.405	2.876	0.006
	QUICKI	-0.053	-0.352	0.727	-0.012	-0.076	0.939	-0.064	-0.473	0.639	-0.104	-0.636	0.528	-0.073	-0.507	0.615	-0.226	-1.791	0.081
	Matsuda index	-0.045	-0.294	0.771	0.010	0.065	0.948	-0.044	-0.321	0.750	-0.085	-0.517	0.608	-0.055	-0.377	0.708	-0.201	-1.556	0.127
	hepatic insulin resistance index	0.076	0.490	0.627	0.010	0.065	0.948	0.097	0.696	0.490	0.173	1.039	0.305	0.095	0.639	0.527	0.304	2.386	0.022
Model 3	burst rate (bursts/minute)	0.302	2.431	0.019	0.189	1.409	0.165	0.425	3.679	<0.001	-0.181	-1.314	0.195	0.475	3.855	<0.001	0.402	3.333	0.002
	burst incidence (bursts/100 heartbeats)	0.320	2.470	0.017	0.086	0.599	0.552	0.391	3.139	0.003	-0.196	-1.365	0.178	0.461	3.512	<0.001	0.354	2.716	0.009
	HOMA-beta	0.089	0.646	0.521	-0.004	-0.026	0.980	0.100	0.765	0.448	-0.006	-0.039	0.969	0.190	1.400	0.168	0.437	3.514	<0.001
	insulinogenic index	0.092	0.675	0.502	0.201	1.451	0.153	0.204	1.616	0.112	-0.014	-0.099	0.922	0.168	1.252	0.216	0.326	2.549	0.014
	HOMA-IR	0.044	0.305	0.761	0.192	1.306	0.197	0.144	1.072	0.289	-0.105	-0.705	0.484	0.167	1.178	0.244	0.401	3.054	0.004
	QUICKI	-0.001	-0.006	0.995	-0.088	-0.610	0.545	-0.044	-0.335	0.739	-0.006	-0.043	0.966	-0.053	-0.380	0.706	-0.254	-1.896	0.064
	Matsuda index	0.254	1.874	0.067	-0.310	-2.231	0.030	0.137	1.046	0.301	0.166	1.170	0.248	0.207	1.518	0.135	0.019	0.133	0.895
	hepatic insulin resistance index	0.124	0.936	0.354	0.133	0.964	0.340	0.207	1.677	0.100	0.023	0.167	0.868	0.172	1.307	0.197	0.371	3.022	0.004
Model 4	fasting plasma glucose (mg/dL)	0.037	0.257	0.799	0.597	4.386	<0.001	0.388	3.015	0.004	-0.165	-1.017	0.315	0.256	1.833	0.074	0.149	1.115	0.271
	HbA1c (%)	0.280	2.194	0.033	0.051	0.363	0.718	0.330	2.688	0.010	-0.078	-0.547	0.587	0.129	0.994	0.325	0.171	1.332	0.189
	HOMA-beta	0.128	0.805	0.426	-0.008	-0.045	0.965	0.141	0.877	0.386	-0.065	-0.361	0.720	0.226	1.410	0.167	0.492	3.753	<0.001
	insulinogenic index	0.026	0.175	0.862	0.169	1.054	0.299	0.114	0.774	0.444	0.081	0.495	0.623	0.129	0.867	0.392	0.295	2.223	0.033
	HOMA-IR	0.191	1.229	0.227	0.140	0.807	0.425	0.286	1.871	0.069	-0.201	-1.143	0.261	0.246	1.561	0.127	0.474	3.630	0.001
	QUICKI	-0.217	-1.527	0.135	-0.025	-0.152	0.880	-0.257	-1.816	0.077	0.038	0.230	0.820	-0.211	-1.437	0.159	-0.286	-2.161	0.037
	Matsuda index	-0.211	-1.474	0.149	-0.058	-0.358	0.723	-0.267	-1.886	0.067	0.013	0.081	0.936	-0.247	-1.714	0.095	-0.305	-2.312	0.027
	hepatic insulin resistance index	0.052	0.343	0.733	0.140	0.844	0.404	0.129	0.853	0.399	0.047	0.278	0.782	0.109	0.707	0.484	0.351	2.633	0.012

Model 1, adjusted for age and gender; Model 2, adjusted for age, gender, and BMI; Model 3, adjusted for age, gender, and HbA1c; Model 4, adjusted for age, gender, and burst incidence.

OSAS: obstructive sleep apnea syndrome, HOMA-beta: homeostatic model assessment beta cell function, HOMA-IR: homeostasis model assessment of insulin resistance, QUICKI: quantitative insulin sensitivity check index

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popnea index, AHI, 3% oxygen desaturation index, % SpO_2 <90%, and arousal index, to normal values.

nCPAP therapy dramatically reduced the burst rate, burst incidence, and heart rate (Table 1); however, it did not change the blood pressure, triglycerides, HDL cholesterol, or parameters for insulin secretion (HOMA-beta and insulinogenic index) or insulin resistance (HOMA-IR, QUICKI, Matsuda index, and hepatic insulin resistance index).

Discussion

How each category of the severity index is uniquely associated with the pathological features of OSAS remains unclear. In the present study of Japanese patients with OSAS, we found that different OSAS severity indices were associated with unique metabolic parameters. The OSAS severity indices reflecting apnea/hypopnea (apnea index, hypopnea index, AHI, and arousal index) were associated with glycemic control, independent of obesity. It is possible that the electroencephalogram bursts caused by apnea/hypopnea led to deteriorated glycemic control, possibly via perturbation of the neural networks modulating glucose metabolism. In contrast, the OSAS severity indices reflecting hypoxia (3% oxygen desaturation index and % SpO_2<90%) were associated with glucose-induced insulin secretion and insulin resistance. These findings are consistent with those of a previous report stating that insulin resistance is associated with BMI, but not the AHI, in Japanese OSAS patients (16). Because the association of % SpO_2<90% with insulin sensitivity/resistance indices was significant after adjusting for MSNA, hypoxia may cause insulin resistance independent of activating the sympathetic nervous system. In addition, it is interesting that % SpO_2<90% was associated with insulin resistance indices in the liver (HOMA-IR and hepatic insulin resistance index) rather than insulin sensitivity indices in skeletal muscle (QUICKI and Matsuda index) (32). Although hypoxia itself may lead to insulin resistance due to deterioration of the microcirculation in the skeletal muscle, future studies should investigate the causal link between hypoxia and insulin resistance in the liver.

The present study also revealed that the OSAS severity indices reflecting apnea/hypopnea and decreased SpO_2 are associated with MSNA, independent of age and gender. In particular, the 3% oxygen desaturation index was associated with the burst incidence, even after adjusting for age, gender, BMI, and HbA1c. Although there is a significant association between a decreased SpO_2 and obesity, whether the BMI is associated with MSNA (33, 34) or not (35, 36) remains controversial. The current findings suggest that a decrease in SpO_2, especially intermittent hypoxia reflected by the 3% oxygen desaturation index, is associated with sympathetic hyperactivity, independent of obesity.

We previously reported that switching from alpha-glucosidase inhibitors to pioglitazone treatment for 3 months significantly decreased MSNA in patients with type 2 diabetes (31). In addition, a decreased insulin resistance index (HOMA-IR), but not BMI or HbA1c, was significantly correlated with a decreased burst incidence (31). Indeed, hyperinsulinemia can lead to increased sympathetic activity (37). However, the current investigation into the effects of nCPAP on metabolic dysregulation and MSNA associated with OSAS found that nCPAP therapy dramatically lowered MSNA without affecting glycemic parameters or insulin resistance indices, suggesting a dissociation of OSAS-associated sympathetic hyperactivity and insulin resistance.

The present study has some limitations. First, because it was a retrospective observational study, nCPAP therapy was not randomized, and therapy durations varied. Therefore, future randomized controlled studies are needed in order to confirm the present findings. Second, there was insufficient information regarding the changes in medication uses to treat hypertension and/or diabetes due to a lack of clinical information for some patients who were followed by local general physicians, which might have affected the results regarding the effects of nCPAP on blood pressure and glycemic control.

Conclusion

In summary, we identified specific OSAS severity indices that are distinctively associated with the pathophysiological features of OSAS patients. The OSAS severity indices reflecting apnea/hypopnea are associated with glycemic control, whereas those reflecting hypoxia, particularly % SpO_2 <90%, are associated with the hepatic insulin resistance independent of obesity. MSNA is independently associated with both types of OSAS severity indices, particularly the 3% oxygen desaturation index (reflecting intermittent hypoxia). nCPAP therapy lowered all OSAS severity indices and MSNA without ameliorating insulin resistance. These findings suggest that hypopnea and hypoxia make distinct contributions to the pathophysiology of OSAS and can help us interpret each OSAS severity index in a clinical setting.

The authors state that they have no Conflict of Interest (COI).

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