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 % SpO₂<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 % SpO₂<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...
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 % SpO2<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 % SpO2<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.

Biochemical and anthropometric parameters

Blood samples were collected from all subjects following an 8-h fast. The samples were centrifuged, and plasma and serum samples were stored at −20°C 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:

\[
\frac{[\text{fasting insulin (pmol/L)} \times \text{fasting glucose (mmol/L)}]}{22.5}
\]

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

\[
1 / \left( \log \text{fasting insulin [U/mL]} + \log \text{fasting glucose [mg/dL]} \right)
\]

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):

\[
\text{Matsuda index} = \frac{10,000}{\sqrt{\text{fasting plasma glucose × fasting insulin}}} \times \left( \frac{\text{mean glucose}}{\text{mean insulin during OGTT}} \right)
\]

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:

\[
\text{hepatic insulin resistance} = (\text{AUC}_{[\text{glucose}]} 0−30) \times (\text{AUC}_{[\text{insulin}]} 0−30)
\]

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).

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.
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 (SpO₂) ≥3% per hour of total sleep time. In addition, we recorded PSG parameters, and the lowest O₂ saturation (minimum SpO₂) and percentage of sleep time with % SpO₂<90% (% SpO₂<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 MSNA was 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 second 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 second 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, NY, 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/m², 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 % SpO₂<90%, independent of age and gender. Of these, HOMA-beta, HOMA-IR, and hepatic insulin resistance remained significantly correlated with % SpO₂<90% even after adjusting for the BMI (Model 2 in Table 3).
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 3% oxygen desaturation index, and % SpO2<90%, independent of age and gender, and 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).

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 % SpO2<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).
| Table 2. Univariate Correlation between Clinical Parameters, OSAS Severity Indices, and MSNA. |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| *p* | age (year) | body weight (kg) | BMI (kg/m²) | waist circumference (cm) | fat mass (kg) | fat-free mass (kg) | hypopnea index (events/hour) | arousal index (events/hour) | apnea index (events/hour) | % time spent with oxygen saturation <90% (% of total sleep time) | % time spent with oxygen saturation <90% (events/hour) | systolic blood pressure (mmHg) | diastolic blood pressure (mmHg) | heart rate (beats/min) | fasting plasma glucose (mg/dL) | HOMA-β | QUICKI | Matsuda index | hepatic insulin resistance index | HOMA-IR |
|-----|-----------|------------------|------------|--------------------------|-------------|-------------------|-------------------------------|-------------------------------|--------------------------|--------------------------------|-------------------------------|----------------|--------------------------|-------------------------|----------------|----------|----------------|----------------|----------|
| H    | 0.397     | 0.011            | 0.012      | 0.021                    | 0.019       | 0.022             | 0.083                         | 0.005                         | -0.024                   | 0.010                         | 0.128                       | 0.010           | 0.027                    | 0.027                   | 0.006           | 0.004    | 0.001          | 0.004          | 0.001    |
| P    | 0.150     | 0.001            | 0.001      | 0.001                    | 0.001       | 0.001             | 0.001                         | 0.001                         | 0.001                    | 0.001                         | 0.001                       | 0.001           | 0.001                    | 0.001                   | 0.001           | 0.001    | 0.001          | 0.001          | 0.001    |
| rho  | -0.193    | 0.008            | 0.011      | 0.025                    | 0.023       | 0.032             | 0.066                         | -0.066                        | -0.086                   | -0.086                         | -0.066                       | -0.086          | -0.086                    | -0.086                   | -0.086          | -0.086   | -0.086         | -0.086         | -0.086   |
| N    | 40        | 41               | 44         | 48                       | 49           | 50                | 51                            | 52                            | 53                       | 54                            | 55                            | 56               | 57                        | 57                       | 57              | 57       | 57             | 57             | 57       |
| %    |             |                  |            |                          |              |                   |                               |                               |                         |                               |                               |                 |                           |                           |                 |          |                |                |          |

**Note:** HOMA-β: homeostatic model assessment of insulin resistance, QUICKI: quantitative insulin sensitivity check index.
### Table 3. Independent Explanatory Variables for OSAS Severity Indices.

| Variable                                | Model 1 | Model 2 | Model 3 |
|-----------------------------------------|---------|---------|---------|
|                                          | burst rate (bursts/minute) | burst incidence (bursts/100 heartbeats) | burst rate (bursts/minute) |
| anaemia index (events/hour)             | 0.311 (2.484, 0.016)       | 0.180 (0.813, 0.005)       | 0.19 (0.83, 0.019)       |
| hypoapnea index (events/hour)           | 0.170 (1.200, 0.020)       | 0.170 (1.200, 0.020)       | 0.180 (1.30, 0.018)      |
| anaemia-hypoapnea index (events/hour)   | 0.431 (3.629, 0.001)       | 0.431 (3.629, 0.001)       | 0.431 (3.629, 0.001)     |
| arousals index (events/hour)            | 0.431 (3.629, 0.001)       | 0.431 (3.629, 0.001)       | 0.431 (3.629, 0.001)     |
| 3% oxygen desaturation index (events/hour) | 0.472 (3.923, 0.001)       | 0.472 (3.923, 0.001)       | 0.472 (3.923, 0.001)     |
| % SpO2<90% (% of total sleep time)      | 0.401 (3.386, 0.001)       | 0.401 (3.386, 0.001)       | 0.401 (3.386, 0.001)     |
| HbA1c (%)                               | 0.001 (0.216, 0.001)       | 0.001 (0.216, 0.001)       | 0.001 (0.216, 0.001)     |
| insulinogenic index                     | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)      |
| HOMA-IR                                 | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)      |
| QUICKI                                  | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)      |
| Matsuda index                           | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)      |
| hepatic insulin resistance index        | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)      |
| HbA1c (%)                               | 0.001 (0.216, 0.001)       | 0.001 (0.216, 0.001)       | 0.001 (0.216, 0.001)     |
| insulinogenic index                     | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)      |
| HOMA-IR                                 | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)      |
| QUICKI                                  | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)      |
| Matsuda index                           | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)      |
| hepatic insulin resistance index        | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)      |
| HbA1c (%)                               | 0.001 (0.216, 0.001)       | 0.001 (0.216, 0.001)       | 0.001 (0.216, 0.001)     |
| insulinogenic index                     | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)      |
| HOMA-IR                                 | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)      |
| QUICKI                                  | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)      |
| Matsuda index                           | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)      |
| hepatic insulin resistance index        | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)      |
| HbA1c (%)                               | 0.001 (0.216, 0.001)       | 0.001 (0.216, 0.001)       | 0.001 (0.216, 0.001)     |
| insulinogenic index                     | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)      |
| HOMA-IR                                 | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)      |
| QUICKI                                  | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)      |
| Matsuda index                           | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)      |
| hepatic insulin resistance index        | 0.096 (0.85, 0.012)        | 0.096 (0.85, 0.012)        | 0.096 (0.85, 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

HOMA-beta: homeostatic model assessment beta cell function, HOMA-IR: homeostasis model assessment of insulin resistance, QUICKI: quantitative insulin sensitivity check index
<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 % SpO2<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 % SpO2<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 % SpO2<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 SpO2 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 SpO2 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 SpO2, 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 % SpO2<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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Author contributions

TT is the guarantor of this study and has full access to all of the data. He takes full responsibility for the integrity and accuracy of the data and data analysis. YI analyzed the data and wrote the manuscript. YN recruited the patients, evaluated the OSAS severity, and collected clinical information. YS measured MSNA. HM, TH, MT, and SK contributed to the discussion. TT designed the study, interpreted the data, and edited the manuscript. All authors have read and approved the final version of the manuscript. No potential conflicts of interest relevant to this article are reported.
References

1. Steiropoulos P, Papanas N. Continuous positive airway pressure to improve insulin resistance and glucose homeostasis in sleep apnea. World J Diabetes 2: 16-18, 2011.
2. Kent BD, Grote L, Ryan S, et al. Diabetes Mellitus Prevalence and Control in Sleep-Disordered Breathing: The European Sleep Apnea Cohort (ESADA) Study. Chest 146: 982-990, 2014.
3. Trzeziszur W, Martinez MC, Priou P, Andriantsitohaina R, Gagnadoux F. Microparticles and vascular dysfunction in obstructive sleep apnoea. Eur Respir J 44: 207-216, 2014.
4. Minville C, Hilleret M-N, Tamisier R, et al. Nonalcoholic Fatty Liver Disease, Nocturnal Hypoxia, and Endothelial Function in Patients With Sleep Apnea. Chest 145: 525-533, 2014.
5. Nobili V, Cutreria R, Liccodo D, et al. OSAS affects liver histology and inflammatory cell activation in paediatric NAFLD, regardless of obesity/insulin resistance. Am J Respir Crit Care Med 189: 66-76, 2013.
6. Can M, Acig oz S, Mungan G, et al. Serum cardiovascular risk factors in obstructive sleep apnea. Chest 129: 233-237, 2006.
7. Hansen J, Sander M. Sympathetic neural overactivity in healthy humans after prolonged exposure to hypobaric hypoxia. J Physiol 546: 921-929, 2003.
8. Lévy P, Bonsignore MR, Eckel J. Sleep, sleep-disordered breathing and metabolic consequences. Eur Respir J 13: 243-260, 2009.
9. Morgan BJ, Crabtree DC, Palta M, Skatrud JB. Combined hypoxia and hypercapnia evokes long-lasting sympathetic activation in humans. J Appl Physiol 79: 205-213, 1995.
10. Muraki I, Tanigawa T, Yamagishi K, et al. Nocturnal intermittent hypoxia and the development of type 2 diabetes: The Circulatory Risk in Communities Study (CIRCS). Diabetologia 53: 481-488, 2010.
11. Tamisier R, Anand A, Nieto LM, Cunnington D, Weiss JW. Arterial pressure and muscle sympathetic nerve activity are increased after two hours of sustained but not cyclic hypoxia in healthy humans. J Appl Physiol 98: 343-349, 2005.
12. Valbo AB, Hagbarth KE, Torebjork HE, Wallin BG. Somatosensory, proprioceptive, and sympathetic activity in human peripheral nerves. Physiol Rev 59: 919-957, 1979.
13. Hamaoka T, Murai H, Kaneko S, et al. Single-unit muscle sympathetic nerve activity reflects sleep apnea severity, especially in severe obstructive sleep apnea patients. Front Physiol 7: 1-9, 2016.
14. Makino S, Handa H, Suzukawa K, et al. Obstructive sleep apnoea syndrome, plasma adiponectin levels, and insulin resistance. Clin Endocrinol 64: 12-19, 2006.
15. Tanno S, Tanigawa T, Saito I, et al. Sleep-related intermittent hypoxemia and glucose intolerance: A community-based study. Sleep Med 15: 1212-1218, 2014.
16. Otake K, Sasanabe R, Hasegawa R, et al. Glucose intolerance in Japanese patients with obstructive sleep apnea. Intern Med 48: 1863-1868, 2009.
17. Phillips CL, Grunstein RR, Darendeliler MA, et al. Health Outcomes of Continuous Positive Airway Pressure versus Oral Appliance Treatment for Obstructive Sleep Apnea. Am J Respir Crit Care Med 187: 879-887, 2013.
18. Spiegel K, Tasali E, Leproult R, Van Cauter E. Effects of poor and short sleep on glucose metabolism and obesity risk. Nat Rev Endocrinol 5: 253-261, 2009.
19. Xu H, Yi H, Guan J, Yin S. Effect of continuous positive airway pressure on lipid profile in patients with obstructive sleep apnea syndrome: A meta-analysis of randomized controlled trials. Atherosclerosis 234: 446-453, 2014.
20. Esaki K. Morphological Analysis by Lateral Cephalography of Sleep Apnea Syndrome in 53 Patients. Kurume Med J 42: 231-240, 1995.
21. Li KK, Kushida C, Powell NB, Riley RW, Guilleminault C. Obstructive sleep apnea syndrome: a comparison between Far-East Asian and white men. Laryngoscope 110: 1689-1693, 2000.
22. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28: 412-419, 1985.
23. Katz A, Nambi SS, Mather K, et al. Quantitative Insulin Sensitivity Check Index: A Simple, Accurate Method for Assessing Insulin Sensitivity In Humans. J Clin Endocrinol Metab 85: 2402-2410, 2000.
24. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 22: 1462-1470, 1999.
25. Abdul-Ghani MA, Matsuda M, Balas B, DeFronzo RA. Muscle and Liver Insulin Resistance Indexes Derived From The Oral Glucose Tolerance Test. Diabetes care 30: 89-94, 2007.
26. Isebo Y, Sakurai M, Kita Y, et al. Fat-free mass and calf circumference as body composition indices to determine non-exercise activity thermogenesis in patients with diabetes. J Diabetes Invest 7: 352-358, 2015.
27. Murai H, Takata S, Maruyama M, et al. The activity of a single muscle sympathetic vasoconstrictor nerve unit is affected by physiological stress in humans. Am J Physiol Heart Circ Physiol 290: H853-H860, 2006.
28. Murai H, Takamura M, Maruyama M, et al. Altered firing pattern of single-unit muscle sympathetic nerve activity during handgrip exercise in chronic heart failure. J Physiol 587: 2613-2622, 2009.
29. Ikeda T, Murai H, Kaneko S, et al. Augmented single-unit muscle sympathetic nerve activity in heart failure with chronic atrial fibrillation. J Physiol 590: 509-518, 2012.
30. Millar PJ, Murai H, Floras JS. Paradoxical muscle sympathetic reflex activation in human heart failure. Circulation 131: 459-468, 2015.
31. Kobayashi D, Takamura M, Murai H, et al. Effect of pioglitazone on muscle sympathetic nerve activity in type 2 diabetes mellitus with α-glucosidase inhibitor. Auton Neurosci 158: 86-91, 2010.
32. Kato K, Takeshita Y, Misu H, Zen Y, Kaneko S, Takamura T. Liver steatosis is associated with insulin resistance in skeletal muscle rather than in the liver in Japanese patients with non-alcoholic fatty liver disease. J Diabetes Invest 26: 158-163, 2015.
33. Ribeiro MM, Trombetta IC, Batalha LT, et al. Muscle sympathetic nerve activity and hemodynamic alterations in middle-aged obese women. Braz J Med Biol Res 34: 475-478, 2001.
34. Curry TB, Somaraju M, Hines CN, et al. Sympathetic support of energy expenditure and sympathetic nervous system activity after gastric bypass surgery. Obesity (Silver Spring) 21: 480-485, 2013.
35. Tank J, Heusser K, Diedrich A, et al. Influences of gender on the interaction between sympathetic nerve traffic and central adiposity. J Clin Endocrinol Metab 93: 4974-4978, 2008.
36. Park J, Middelkauff HR, Campese VM. Abnormal sympathetic reactivity to the cold pressor test in overweight humans. Am J Hypertens 25: 1236-1241, 2012.
37. Vollenweider P, Tappy L, Randin D, et al. Differential effects of hyperinsulinaemia and carbohydrate metabolism on sympathetic nerve activity to the cold pressor test in overweight humans. Am J Physiol Regul Integr Comp Physiol 297: R786-R792, 2009.

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