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ORIGINAL ARTICLE**Case Control Study**

- 1 Relationship between metabolic syndrome and hypercapnia among obese patients with sleep apnea
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Case Control Study

Relationship between metabolic syndrome and hypercapnia among obese patients with sleep apnea

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Abstract

BACKGROUND

In the obese patient population, some patients have severe obstructive sleep apnea (OSA) with daytime hypoventilation. Such patients are generally identified on the basis of the presence or absence of daytime hypercapnia, and the condition is called obesity hypoventilation syndrome. However, mechanisms for such daytime hypoventilation remain unclear.

AIM

To investigate metabolic syndrome and daytime hypercapnia association based on hypercapnia prevalence in obese OSA patients in a nested case-control study.

METHODS

Consecutive obese patients (body mass index ≥ 30 kg/m²) who underwent polysomnography due to suspected OSA were included. Among them, patients with severe OSA (apnea hypopnea index ≥ 30 /h) were divided into two groups

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according to the presence or absence of hypercapnia during wakefulness (arterial partial pressure of carbon dioxide $\geq$ or $<$ 45 Torr, respectively). The characteristics and clinical features of these two groups were compared.

RESULTS

Among 97 eligible patients, 25 patients (25.8%) had daytime hypercapnia. There were no significant differences in age, gender, body mass index, apnea-hypopnea index, and Epworth Sleepiness Scale scores between the two groups. However, patients with hypercapnia had a significantly lower arterial partial pressure of oxygen level (75.8 ± 8.2 torr *vs* 79.9 ± 8.7 torr, $P = 0.042$) and higher arterial partial pressure of carbon dioxide level (46.6 ± 2.5 torr *vs* 41.0 ± 2.9 torr, $P < 0.001$). Additionally, patients with hypercapnia were more likely to have metabolic syndrome (72.0% *vs* 48.6%, $P = 0.043$) and a higher metabolic score (the number of satisfied criteria of metabolic syndrome). In multivariate logistic regression analysis, the presence of metabolic syndrome was associated with the presence of hypercapnia (OR = 2.85, 95%CI: 1.04-7.84, $P = 0.042$).

CONCLUSION

Among obese patients with severe OSA, 26% of patients had hypercapnia during wakefulness. The presence of metabolic syndrome was independently correlated with the presence of daytime hypercapnia.

Key words: Arterial partial pressure of carbon dioxide; Hypercapnia; Metabolic syndrome; Obesity hypoventilation syndrome; Obstructive sleep apnea; Sleep disordered breathing

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Core tip: Daytime hypercapnia presents with severe obstructive sleep apnea in some obese patients, and the condition is called obesity hypoventilation syndrome. However, the prevalence, characteristics, and other clinical features of hypercapnic obese patients with severe obstructive sleep apnea remain unelucidated. Among 97 obese patients with severe obstructive sleep apnea, 25 had daytime hypercapnia, and they were more likely to have the metabolic syndrome. In multivariable analysis, metabolic syndrome was associated with daytime hypercapnia. Although the cause or consequence remains unclear, coexisting metabolic syndrome may play some roles; thus, clinicians should check for metabolic syndrome in obese patients with severe obstructive sleep apnea.

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INTRODUCTION

Obesity is a growing public health concern, not only in the Western countries but also in the Eastern countries, along with the related comorbid conditions, which lead to an impairment of the patients' quality of life and an increase in mortality^[1]. One such comorbid condition is obstructive sleep apnea (OSA); it is caused by repetitive collapse of the pharynx during sleep and owing to a narrow pharynx due to fat accumulation in the neck, which compromises the pharyngeal lumen^[2]. Approximately 10%-20% of obese patients with severe OSA have daytime hypoventilation manifested as daytime hypercapnia, which is generally defined as an arterial partial pressure of carbon dioxide (PaCO_2) $\geq$ 45 Torr^[3], and the combination of such daytime hypercapnia and obesity [*i.e.*, body mass index (BMI) $\geq$ 30 kg/m²] in patients with OSA is called obesity hypoventilation syndrome (OHS)^[4]. It has been reported that patients who are diagnosed with OHS consume more healthcare resources than do eucapnic obese patients with OSA^[5], and that patients with OHS are associated with increased morbidity and mortality compared with eucapnic controls because of the cardiometabolic consequences related to OHS^[6]. Thus, OHS is distinct from OSA or simple obesity^[7]. It is not known why only some obese patients with

OSA develop daytime hypoventilation. The presence of excess adipose tissue in the abdomen (*i.e.*, abdominal obesity) and surrounding chest wall may be one cause of hypoventilation; it possibly causes this condition through impeding diaphragm motion and reduced lung compliance^[8].

Abdominal obesity plays a central role in metabolic syndrome (MetS), which represents an accumulation of cardiovascular risk factors including high blood pressure, impaired glucose tolerance, and dyslipidemia, and abdominal obesity as an essential condition^[9-11]. MetS is also known to be associated with an increased incidence of diabetes and cardiovascular disease^[12-17]. Previous studies have suggested that an independent relationship exists between OSA and MetS^[18]. If abdominal obesity and/or visceral adiposity play a role in daytime hypoventilation, there may be numerous patients with coexisting MetS and severe OSA with daytime hypercapnia, and the presence of MetS may be associated with daytime hypoventilation. However, data pertaining to the relationship between MetS and daytime hypercapnia in obese patients with severe OSA is absent. The aims of the present study were to investigate the prevalence of daytime hypercapnia in obese patients with severe OSA, to compare obese patients with severe OSA with and without daytime hypercapnia, and to determine whether a relationship exists between MetS and daytime hypercapnia. We hypothesized that obese patients with severe OSA and hypercapnia are more likely to have MetS compared with those without daytime hypercapnia, and that a presence of MetS is associated with daytime hypercapnia.

MATERIALS AND METHODS

Subjects

Consecutive obese (body mass index, BMI ≥ 30 kg/m²) Japanese patients who underwent overnight polysomnography between October 2005 and September 2006 at our sleep center (*i.e.*, Toranomon Hospital) due to suspected OSA were targeted. Among them, data of eligible patients with severe OSA (apnea-hypopnea index, AHI ≥ 30 events per hour of sleep) were analyzed. Exclusion criteria were as follows: (1) Age < 20 years; (2) Having chronic pulmonary disease (obstructive and/or restrictive); (3) History of heart failure; (4) History of hemodialysis; (5) History of stroke with neurological deficits; and (6) Undergoing current treatment for OSA.

This nested case-control study was carried out in accordance with the Declaration of Helsinki, and was approved by the Toranomon Hospital Ethics Board. Since in the present study, sleep study, anthropometric data collection, blood sampling including arterial blood gas analysis, which had already been obtained as routine clinical check-up were analyzed, the requirement to obtain informed consent was waived by Toranomon Hospital Ethics Board using opt-out methods.

Sleep study

All subjects underwent full-attended in-hospital overnight polysomnography, using a digital polygraph (SomnoStar[®] Sleep System; SensorMedics Corp., Yorba Linda, CA) equipped with electroencephalograms, electrooculograms, submental electromyogram, chest and abdominal movement recording, body position monitoring, oronasal airflow monitoring, and oxyhemoglobin saturation (SO₂) recording. Generally accepted definitions and scoring methods for respiratory events, sleep stages, and arousals were used^[19]. Apneas and hypopneas were classified into obstructive and central^[19,20]. The AHI was calculated as the number of apneas and hypopneas per hour of sleep. Subjects with AHI ≥ 5 events per hour of sleep and obstructive AHI $\geq 50\%$ of the total AHI were defined as having OSA. All sleep stages, arousals, and respiratory events were manually scored and interpreted by experienced sleep specialists blinded to information of the subjects.

Metabolic syndrome

MetS was diagnosed according to the Japanese definition^[10]. Briefly, central obesity was defined as waist circumference ≥ 85 cm for males and ≥ 90 cm for females, high triglycerides was defined as serum triglycerides ≥ 150 mg/dL, low high-density lipoprotein (HDL) cholesterol was defined as serum HDL cholesterol < 40 mg/dL, high blood pressure was defined as systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, and high fasting blood sugar was defined as serum blood sugar ≥ 110 mg/dL. In subjects who were on specific medications for the abovementioned components, each component was counted as positive for the diagnosis. Subjects with at least two components in addition to central obesity were defined as having MetS. Metabolic score was defined as the number of each component of the MetS criteria.

Blood tests and other data

Fasting venous blood samples were obtained after an overnight fast, in the early morning and at the time of the sleep study. The glycated hemoglobin (HbA1c) value was estimated according to the National Glycohemoglobin Standardization Program equivalent value^[21]. Arterial blood for blood gas analysis was obtained under room air conditions just before starting the sleep study with the subjects in the supine position, maintained for 20 min before sampling. Arterial partial pressure of carbon dioxide (PaCO_2) ≥ 45 Torr was regarded as daytime hypercapnia, and all eligible patients were divided into two groups according to the presence or absence of hypercapnia during wakefulness (*i.e.*, $\text{PaCO}_2 \geq 45$ Torr as cases or $\text{PaCO}_2 < 45$ Torr as controls). Blood pressure (BP) was measured by trained nurses with the patient in a sitting position, in the early morning following the sleep study. The Epworth Sleepiness Scale (ESS) score was computed to assess subjective sleepiness^[22]. All medications used by the subjects at the time of sleep study were recorded.

Statistical analysis

The null hypothesis for this study was that the proportions of MetS in patients with and without daytime hypercapnia were equal among obese patients with severe OSA. Because there are no previous data regarding proportions of MetS in patients with and without daytime hypercapnia, a medium effects size (*i.e.*, 0.3) was applied. Assuming a 2-tailed Type I error of 0.05, we required a total sample size of 88 with a power of 0.8.

Continuous variables are expressed as mean $\pm$ SD or median (interquartile range), and were compared between patients with and without daytime hypercapnia using a Student's *t*-test or Mann-Whitney *U*-test. Categorical variables are shown as numbers and percentages and were compared using χ^2 or Fisher's exact test. Associations between the presence of hypercapnia and subjects' characteristics, features, and sleep study results were analyzed using univariable logistic regression analyses including the presence of hypercapnia as a dependent variable and age, gender, BMI, total cholesterol, HbA1c, uric acid, C-reactive protein, ESS score, awake PaO_2 , sleep study results (total sleep time, total, obstructive, and central AHI, the percent of time spent $\text{SO}_2 < 90\%$, lowest SO_2 , arousal index, sleep stages), metabolic score, and MetS as independent variables. Then, variables with $P < 0.10$ in univariable analysis were entered into two separate multivariate logistic regression models ($P < 0.10$ for inclusion and $P > 0.05$ for exclusion). One included MetS as one of the independent variables and the other included metabolic score as one of the independent variables with the presence of hypercapnia as a dependent variable. A P value of < 0.05 was considered statistically significant. All statistical analyses were performed using the IBM SPSS version 23.0 (IBM Corp., Tokyo, Japan).

RESULTS

Characteristics of patients

Figure 1 shows a flow chart of the patient recruitment process. During the study period, 876 patients were diagnosed with OSA (*i.e.*, AHI ≥ 5 events per hour of sleep) with overnight polysomnography. Among them, 97 patients were eligible for the present study and their data were analyzed.

Out of 97 patients, 25 patients (25.8%) had daytime hypercapnia. Table 1 lists the characteristics of the patients. Overall, middle aged men with an abdominal obesity were enrolled in this study. We found that apart from PaO_2 and PaCO_2 , the characteristics were similar between the two groups. In patients with daytime hypercapnia, PaO_2 was significantly lower compared with those without daytime hypercapnia, in addition to the significantly higher PaCO_2 by definition.

The sleep study results are summarized in Table 2. Interestingly, there were no significant differences in the frequency and type of apnea and hypopnea, hypoxia parameters during sleep, and the sleep stages between the two groups. However, the prevalence of MetS and the metabolic scores were greater in patients with daytime hypercapnia than in patients without it (Figure 2).

Relationship between daytime hypercapnia and other parameters

In univariable analysis, only the lower awake PaO_2 levels, presence of MetS, and the metabolic scores were significantly associated with presence of daytime hypercapnia (Table 3). Thus, two separate multivariable logistic regression models, one which included awake PaO_2 and MetS and another which included awake PaO_2 and metabolic scores, were created (Table 3). In the multivariable models, the presence of MetS and the increased metabolic scores were associated with the presence of daytime

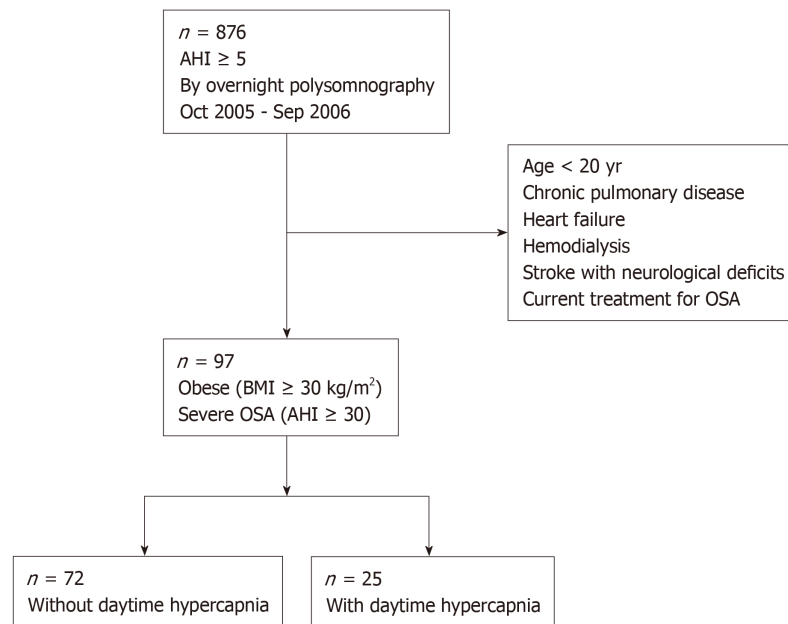


Figure 1 Flowchart depicting the patient recruitment process. AHI: Apnea-hypopnea index; BMI: Body mass index; OSA: Obstructive sleep apnea.

hypercapnia (OR = 2.85; $P = 0.042$, and OR = 1.66; $P = 0.048$, respectively) in obese patients with severe OSA.

DISCUSSION

The present study provides several insights into the relationship between MetS and daytime hypercapnia in obese patients with severe OSA. Firstly, among obese patients with severe OSA, 25.8% had daytime hypercapnia. Secondly, in patients with daytime hypercapnia, prevalence of MetS and the metabolic scores were greater than in patients without daytime hypercapnia. Furthermore, awake PaO_2 was significantly lower in patients with daytime hypercapnia than in those without. In addition, despite no differences in the study results including AHI, PaCO_2 was significantly higher. Thirdly, in the multivariable analysis, a significant relationship between MetS and daytime hypercapnia was observed in obese patients with severe OSA. Finally, a significant dose-response relationship was observed between metabolic scores and daytime hypercapnia in obese patients with severe OSA. Therefore, this study is the first to show that the presence of MetS and increased metabolic scores were associated with a greater risk of daytime hypercapnia in these patients. The importance of the present study is that physicians will be able to identify patients at risk for OHS, on noting MetS or high metabolic scores in obese patients with severe OSA, without determining arterial blood gas. Because patients with OHS consume greater levels of healthcare resources^[5], and are associated with increased morbidity and mortality compared with eucapnic controls^[6], distinguishing patients with and without OHS is highly valuable.

The prevalence of daytime hypercapnia in obese patients with OSA was reported to be 10%–20%^[3,23,24]. In Japan, there are two reports outlining the prevalence of OHS; one of these reports showed that daytime hypercapnia was present in 9% of patients with OSA (AHI ≥ 20 events per hour of sleep), and in 32% of patients with obesity and OSA (AHI ≥ 20 events per hour of sleep and BMI $\geq 30 \text{ kg/m}^2$)^[25]. In another report, Harada and colleagues showed that daytime hypercapnia ($\text{PaCO}_2 \geq 45 \text{ Torr}$) was present in 2.3% of patients with OSA (AHI ≥ 5 events per hour of sleep) and 12.3% of obese patients with OSA (AHI ≥ 5 events per hour of sleep and BMI $\geq 30 \text{ kg/m}^2$)^[26]. In the present study, approximately one fourth (25.8%) of the participants had daytime hypercapnia. This prevalence is greater than those found in the previous studies in the Japanese population and may be due to the inclusion of only obese (BMI $\geq 30 \text{ kg/m}^2$) and severe OSA (AHI ≥ 30 events per hour of sleep) patients in this study (Table 4). Because our center is one of the biggest sleep centers in Japan, the possibility of a referral bias may exist. Therefore, this should be taken into account while interpreting the prevalence of daytime hypercapnia among obese patients with

Table 1 Characteristics of the study patients

	OSA without hypercapnia (n = 72)	OSA with hypercapnia (n = 25)	P value
Age, yr	44.6 ± 11.2	45.6 ± 12.3	0.731
Men, n (%)	67 (93)	24 (96)	0.960
BMI, kg/m ²	33.8 ± 4.1	33.6 ± 3.4	0.790
Waist circumference, cm	109.3 ± 10.4	110.7 ± 11.6	0.567
Systolic blood pressure, mmHg	118.6 ± 35.5	129.3 ± 30.6	0.183
Diastolic blood pressure, mmHg	71.5 ± 22.1	76.6 ± 18.9	0.313
Total cholesterol, mg/dL	195.6 ± 39.9	202.2 ± 25.3	0.439
Triglycerides, mg/dL	150.0 (94.0)	164.0 (93.0)	0.351
HDL cholesterol, mg/dL	43.7 ± 7.8	41.9 ± 9.1	0.360
Fasting blood glucose, mg/dL	110.3 ± 29.8	114.6 ± 38.5	0.567
HbA1c %	6.4 ± 1.4	6.3 ± 1.2	0.923
Uric acid, mg/dL	5.7 ± 3.0	6.7 ± 3.4	0.173
CRP, mg/dL	0.1 (0.2)	0.2 (0.3)	0.275
Epworth Sleepiness Scale	11.0 (8.0)	10.5 (9)	0.862
Awake PaO ₂ , Torr	79.9 ± 8.7	75.8 ± 8.2	0.042
Awake PaCO ₂ , Torr	41.0 ± 2.9	46.6 ± 2.5	<0.001
Medications, n (%)			
Antihypertensive	18 (25)	8 (32)	0.675
Antidyslipidemic	1 (1)	2 (8)	0.162
Antidiabetic	4 (6)	1 (4)	0.999
Antihyperuricemic	5 (7)	1 (4)	0.999

BMI: Body mass index; CRP: C-reactive protein; HbA1c: Glycosylated hemoglobin A1c; HDL: High density lipoprotein; OSA: Obstructive sleep apnea; PaCO₂: Arterial partial pressure of carbon dioxide; PaO₂: Arterial partial pressure of oxygen.

OSA in the present study.

In the present study, however, compared to patients without daytime hypercapnia, PaO₂ was significantly lower, probably in association with daytime hypoventilation, and prevalence of MetS and metabolic scores were significantly greater in those with daytime hypercapnia. MetS is strongly associated with abdominal obesity and/or visceral adiposity^[9,10,27]. As previously reported, abdominal obesity has an independent effect on hypoventilation^[28]. Abdominal obesity with excess adiposity surrounding the chest wall can restrict respiration by impairing diaphragm motion and reducing lung compliance^[8], and is associated with a reduction in PaO₂^[29], thereby inducing daytime hypoxia^[30] in addition to daytime hypercapnia. Such mechanisms may play a central role in the daytime hypercapnia prevalent in our patient population. However, considering the fact that there was no significant difference in waist circumference between patients with and without hypercapnia, MetS by itself or along with other factors, rather than abdominal obesity alone may contribute to the development of daytime hypercapnia. For instance, one of the MetS components, accumulation of each MetS component, quality of abdominal/visceral fat, or mediators/products from the adipose tissue are potential contributors. Nevertheless, whether daytime hypercapnia can be reversed by the reduction of waist circumference may be of interest.

Leptin, a circulating protein known to inhibit appetite centrally and stimulate ventilation, is produced mainly by the adipose tissue^[7]. However, plasma leptin levels are high in obese individuals; it is hypothesized that these individuals may have leptin resistance, and consequently have central leptin deficiency^[7,31]. Patients with OSA and OHS had higher plasma levels of leptin than did weight-matched controls without either OSA or OHS^[32,33]. Furthermore, leptin levels may be a better predictor of hypercapnia than degree of adiposity^[33], as higher leptin levels are associated with a reduced response to hypercapnia in severely obese individuals^[34]. In contrast, hyperleptinemia and leptin resistance were observed in patients with MetS independent of obesity^[35-37]. In addition, increased levels of leptin and leptin resistance are associated with the development and worsening of each component of MetS independent of obesity^[38]. Thus, hyperleptinemia and leptin resistance may play a key role in the relationship between MetS and daytime hypercapnia in obese patients with severe OSA independent of abdominal obesity. Furthermore, coexistence of MetS and

Table 2 Sleep study data

	OSA without hypercapnia (n = 72)	OSA with hypercapnia (n = 25)	P value
TST, min	333.5 ± 82.7	330.6 ± 69.7	0.876
Total AHI, events/h	60.8 ± 20.5	65.6 ± 26.1	0.353
Obstructive	58.0 ± 21.9	64.8 ± 26.6	0.206
Central	0.3 (0.9)	0.3 (0.6)	0.815
Time spent SO ₂ < 90%/TST, %	46.1 (54.7)	56.9 (60.0)	0.128
Lowest SO ₂ , %	69.5 ± 9.2	68.8 ± 7.8	0.764
Arousal index, events/h	55.2 ± 24.1	59.1 ± 25.1	0.491
Sleep stages, %TST			
N1	40.5 ± 16.7	45.2 ± 18.7	0.245
N2	44.8 ± 13.2	39.4 ± 15.1	0.094
N3	2.3 (9.0)	6.1 (9.7)	0.817
REM	9.1 (6.2)	10.8 (5.7)	0.494

AHI: Apnea-hypopnea index; OSA: Obstructive sleep apnea; REM: Rapid eye movement; SO₂: Oxyhemoglobin saturation; TST: Total sleep time.

high metabolic scores with daytime hypercapnia might explain the increased morbidity and mortality in patients with OHS^[6].

The present study has several limitations. Firstly, the number of enrolled participants was relatively small, from a single center, and included only a Japanese patient population. Secondly, this study was a cross-sectional study; thus, a causal relationship between MetS and daytime hypercapnia could not be determined. Thirdly, although we assumed that leptin resistance may play a key role in the relationship between MetS and daytime hypercapnia in our patients, circulating levels of leptin were not measured. This was a pilot study; however, it may contribute to generating further hypotheses that hyperleptinemia contributes to the daytime hypoventilation in obese patients with severe OSA. Finally, although patients with chronic pulmonary disease were excluded, there may be some patients with subclinical impairment of pulmonary function. Thus, a lack of pulmonary function test data is one of the major limitations and the present results should be interpreted with caution.

In conclusion, we have shown that approximately one fourth of obese patients with severe OSA had daytime hypercapnia and that the presence of MetS and increased number of MetS components were independently correlated to daytime hypercapnia. However, whether this relationship is causal or consequential remains unclear. Coexistence of MetS may play a role, and its determination may be important in obese patients with severe OSA. Physicians should consider the possibility of daytime hypercapnia in cases of obese patients with severe OSA presenting with coexisting MetS.

Table 3 Results of logistic regression analyses

	OR (95%CI)	P value	OR (95%CI)	P value
Awake PaO ₂ (1 Torr increase)	0.94 (0.89-0.99)	0.047	0.94 (0.89-0.99)	0.043
Metabolic syndrome	2.72 (1.01-7.30)	0.047	2.85 (1.04-7.84)	0.042
Awake PaO ₂ (1 Torr increase)	0.94 (0.89-0.99)	0.047	0.94 (0.89-1.00)	0.052
Metabolic score (1-point increase)	1.65 (1.01-2.68)	0.044	1.66 (1.01-2.74)	0.048

PaO₂: Arterial partial pressure of oxygen.

Table 4 Summary of studies investigating the prevalence of daytime hypercapnia in Japanese obese patients with obstructive sleep apnea

Ref.	n	Population	Prevalence of daytime hypercapnia (PaCO ₂ ≥ 45 Torr)
Akashiba <i>et al</i> ^[25]	172	OSA (AHI ≥ 20 events/h) with Obesity (BMI ≥ 30 kg/m ²)	32.0%
Harada <i>et al</i> ^[26]	162	OSA (AHI ≥ 5 events/h) with Obesity (BMI ≥ 30 kg/m ²)	12.3%
Current research	97	OSA (AHI ≥ 30 events/h) with Obesity (BMI ≥ 30 kg/m ²)	25.8%

AHI: Apnea-hypopnea index; BMI: Body mass index; OSA: Obstructive sleep apnea; PaCO₂: Arterial partial pressure of carbon dioxide.

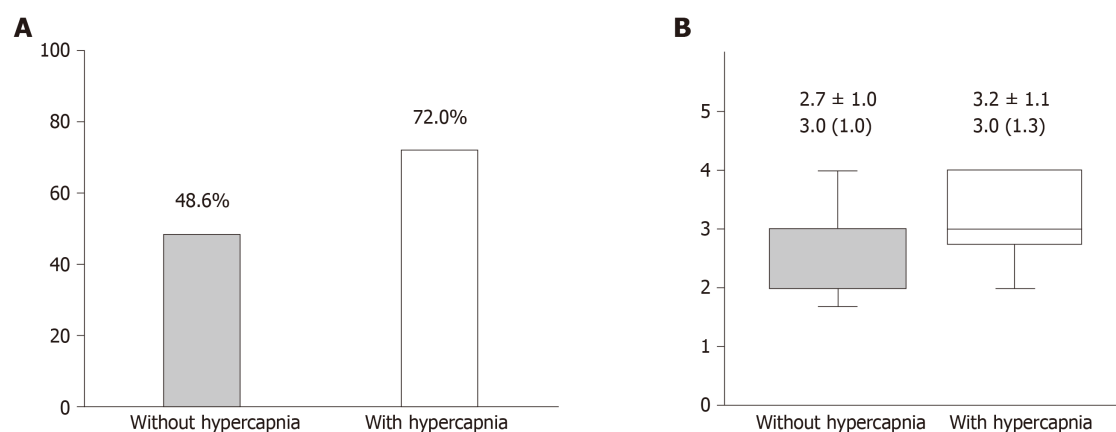


Figure 2 Prevalence of metabolic syndrome prevalence in and metabolic scores of patients with and without daytime hypercapnia. A: Prevalence of metabolic syndrome was significantly greater in patients with daytime hypercapnia ($P = 0.043$); B: Metabolic score was significantly greater in patients with daytime hypercapnia ($P = 0.035$).

ARTICLE HIGHLIGHTS

Research background

In the obese patient population, some patients have severe obstructive sleep apnea (OSA) with daytime hypoventilation. Such patients are generally identified on the basis of the presence or absence of daytime hypercapnia, and the condition is called obesity hypoventilation syndrome (OHS). However, mechanisms for such daytime hypoventilation remain unclear.

Research motivation

Because patients with OHS consume greater levels of healthcare resources, and are associated with increased morbidity and mortality compared with eucapnic controls, identifying patients with OHS is highly valuable.

Research objectives

To investigate metabolic syndrome and daytime hypercapnia association based on hypercapnia prevalence in obese OSA patients in a nested case-control study.

Research methods

Consecutive obese patients (body mass index ≥ 30 kg/m²) who underwent polysomnography due to suspected OSA were included. Among them, patients with severe OSA (apnea hypopnea index ≥ 30/h) were divided into two groups according to the presence or absence of hypercapnia

during wakefulness (arterial partial pressure of carbon dioxide $\geq$ or $<$ 45 Torr, respectively).

Research results

Among 97 eligible patients, 25 patients (25.8%) had daytime hypercapnia. There were no significant differences in age, gender, body mass index, apnea-hypopnea index, and Epworth Sleepiness Scale scores between the two groups. However, patients with hypercapnia had a significantly lower arterial partial pressure of oxygen level (75.8 ± 8.2 torr *vs* 79.9 ± 8.7 torr, $P = 0.042$) and higher arterial partial pressure of carbon dioxide level (46.6 ± 2.5 torr *vs* 41.0 ± 2.9 torr, $P < 0.001$). Additionally, patients with hypercapnia were more likely to have metabolic syndrome (MetS) (72.0% *vs* 48.6%, $P = 0.043$) and a higher metabolic score (the number of satisfied criteria of metabolic syndrome). In multivariate logistic regression analysis, the presence of MetS was associated with the presence of hypercapnia (OR = 2.85, 95%CI: 1.04-7.84, $P = 0.042$).

Research conclusions

This study is the first to show that the presence of MetS and increased metabolic scores were associated with a greater risk of daytime hypercapnia in these patients. The importance of the present study is that physicians will be able to identify patients at risk for OHS, on noting MetS or high metabolic scores in obese patients with severe OSA, without determining arterial blood gas. Physicians should consider the possibility of daytime hypercapnia in cases of obese patients with severe OSA presenting with coexisting MetS. In addition, we have suggested that hyperleptinemia and leptin resistance may play a key role in the relationship between MetS and daytime hypercapnia in obese patients with severe OSA independent of abdominal obesity.

Research perspectives

Although a causal relationship between MetS and daytime hypercapnia remains to be elucidated, and although circulating levels of leptin were not measured in the present study, this study may contribute to generating hypotheses that hyperleptinemia in association with MetS contributes to the daytime hypoventilation in obese patients with severe OSA. Thus, further large-scale prospective studies including measurement of circulating levels of leptin are needed.

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EDITORIAL

- 11 Personalising exacerbation prediction strategies in chronic obstructive pulmonary disease

Ellis PR, Turner AM

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Editor-in-Chief of *World Journal of Respiriology*, Dr. Kazuhiro Yamaguchi obtained his MD, specializing in Internal Medicine, and his PhD degree from Keio University (Tokyo, Japan). He then continued his training through a research fellowship at the Max-Planck Institute for Experimental Medicine (Göttingen, Germany). His professional career began as Associate Professor in the Department of Internal Medicine and Head of the Pulmonary Division at Keio University Hospital, after which he was promoted to Professor at Tokyo Women's Medical University. He currently serves as Councilor of the Japanese Organization of Clinical Research Evaluation and Review and of the Japanese Society of Microcirculation. His research on patho-physiological aspects of abnormal gas exchange in the lung and sleep-related abnormal breathing has led to over 200 peer-reviewed articles. He developed a confocal laser microscopic technique allowing real-time visualization of blood cells in pulmonary microcirculation and a method for analyzing the autonomic-nerve abnormality during sleep. (L-Editor: Filipodia)

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Personalising exacerbation prediction strategies in chronic obstructive pulmonary disease

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Abstract

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of mortality and morbidity worldwide. One of the most important features of this disease is exacerbations where a patient's respiratory symptoms episodically worsen. Exacerbations accounted for over 140000 hospital admissions in 2012 in the United Kingdom with considerably more exacerbations being treated in primary care. Despite significant research in this area in recent years, treatment of acute exacerbations in the community remains limited to oral glucocorticoids, antibiotics and bronchodilators. One of the issues with unpicking the complexity of exacerbations is trying to find out the exact underlying cause and mechanism that leads to symptoms and lung destruction. Currently symptoms are initially guided by symptoms alone though multiple causes of exacerbations have common presentations. This includes viral and bacterial infections and episodes relating to environmental triggers such as pollen and pollution. There is also evidence that cardiovascular factors can contribute to symptoms of breathlessness that can mimic COPD exacerbations. In this editorial we discuss recent advances in the use of precision medicine to more accurately treat exacerbations of COPD. This includes identification of phenotypes that could help rationalise treatment and more importantly identify novel drug targets. We also consider the future role of precision medicine in preventing exacerbations and identifying COPD patients that are at increased risk of developing them.

Key Words: Chronic obstructive pulmonary disease; Exacerbations; Phenotypes; Endotypes; Precision medicine; Clinical

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exacerbations they suffer are complex and heterogenous in nature. They should all be treated on an individual basis with detailed clinical history and initial work up to better understand the impact it is having on their life. Careful consideration of the benefits of treatment should be weighed up against the risks of their side effects to ensure the maximum benefit of treatment. Precision medicine is starting to appear in management of COPD, both for acute exacerbations and their prevention.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable chronic lung condition that is projected to be the third leading cause of death globally by 2030. It is a diverse disease with a wide variation in symptoms and severity and associated comorbidities including osteoporosis^[1] and sarcopenia^[2]. One of the most important features of COPD are episodes of acute worsening of respiratory symptoms, more commonly known as exacerbations. Such episodes often require additional therapy in an attempt to reduce their impact, duration and limit damage to the lungs. COPD exacerbations are associated with increased mortality^[3], worse quality of life^[4] and more rapid lung function decline.

There has been little change to the repertoire of therapies available to acute exacerbation of COPD (AECOPD) in the last 30 years^[5]. The main stay of treatment remains oral glucocorticoids and inhaled bronchodilators plus antibiotics if a bacterial infection is suspected^[6]. Treatment of COPD exacerbations in the community is mainly based on symptoms alone. Since the symptoms of COPD exacerbations are the result of numerous possible aetiologies (infection, environmental, psychological, cardiovascular) with little in the way of features that can predict the exact cause, most are treated with a “one size fits all” approach.

COPD patients also suffer with marked variation in day to day symptoms including breathlessness, sputum production, sputum colour, fatigue and levels of stress and anxiety. This presents a challenge for physicians to accurately treat exacerbations. How can a distinction be made between the usual daily variation in symptoms and an emerging exacerbation?

It is clear that more sophisticated and personalised approaches are required to improve accuracy of treating COPD exacerbations and crucially early identification of moderate or severe exacerbations to enable prompt treatment. Precision medicine has been defined as “treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations^[7]”. The ultimate aim of personalised medicine is to improve clinical outcomes for patients whilst avoiding side effects for those who are unlikely to benefit from therapy^[7]. In the context of treating COPD exacerbations this means diagnosing and treating patients based on factors that separate exacerbations into unique phenotypes. This is likely to include measurement of biological samples (blood, urine or sputum) during the early phase of an exacerbation and potentially by monitoring them at regular intervals to detect when an exacerbation is developing. Such advanced near patient testing is on the horizon with the development of more reliable and cost-effective methods of measuring patient biomarkers in a primary care setting^[8].

Precision medicine for COPD exacerbations could also mean identifying those at an increased risk of future exacerbations and tailoring treatment to individuals to reduce the rate and impact of them on the patient. This again is likely to involve cross sectional biomarker measurement or even genetic analysis.

PERSONALISED APPROACHES TO TREATMENT OF ACUTE EXACERBATIONS

Exacerbations have numerous causes, often with similar presentations, namely breathlessness and sputum production. Similar symptoms do not infer similar underlying pathophysiology. For example, a bacterial exacerbation may respond well to antibiotics but may be worsened by the use of steroids due to immunosuppression. Equally, exacerbations with an allergic or environmental trigger may have little or no response to antibiotics and expose the patient to side effects and potential antibiotic resistance needlessly. It is also difficult to be sure which types of exacerbations lead to lung destruction (if at all). Causes of exacerbations that mimic symptoms of “true” AECOPD, such as those triggered by cardiogenic factors by stress or anxiety, may not be associated with underlying damage to lung tissue or disease progression. Discovery of exacerbation phenotypes; traits that are observed clinically or functionally, or even endotypes; cellular and molecular pathways involved in the pathogenesis of the disease, would enable more personalised treatment of acute episodes^[9]. This is likely to include use of symptoms, physiological measurements or biomarkers to stratify exacerbations.

The acute phase protein C reactive protein (CRP) is a widely used clinical biomarker of inflammation and infection^[10] and several studies have looked at its usefulness as a biomarker to select patients who would benefit from antibiotics during COPD exacerbations^[8,11]. Most studied hospitalised patients and though use of CRP to guide treatment was non-inferior and led to a reduction in antibiotic use it did not lead to any improvement in other outcomes. Only the PACE study^[8] has carried out a randomized controlled trials (RCT) of COPD patients in a primary care setting and results of other studies may not be generalisable to the majority of COPD exacerbations that are treated in the community.

Procalcitonin has also been touted as a potential biomarker though currently its expense and lack of availability in routine clinical care make it less attractive^[12].

As with predicting future risk using eosinophils, acute treatment of exacerbations with oral glucocorticoids in those patients with higher eosinophil counts was found to be non-inferior to standard treatment in hospitalised patients^[13] and further adds merit to the theory of the eosinophilic exacerbation phenotype.

Despite their promise, use of CRP and procalcitonin to guide antibiotic treatment and eosinophils to guide use of oral glucocorticoids may be seen as a backward step. Instead of pioneering new treatments for exacerbations it is merely rationalising old ones. To truly move forward into the age of precision medicine we must identify specific exacerbation endotypes with the hope of identifying novel drug targets. In order to achieve this, we must deepen our understanding of the pathophysiological process's involved in the early and established stages of the exacerbation period.

An alternative to measuring direct markers of inflammation is to identify biomarkers that represent organ or tissue damage. One well established example is troponin which has revolutionised triage of patients with myocardial infarction^[14]. It has been proposed that COPD exacerbations should be considered “lung attacks” with each episode furthering damage to the lungs with consequences for future morbidity and mortality^[15]. Markers of elastin degradation have been proposed as the lung equivalent biomarker of lung tissue destruction since loss of alveolar elastic tissue within the lungs is the main contributor to pulmonary emphysema, a process driven by an imbalance of proteases and anti-proteases^[16]. This has led to particular interest into elastin degradation products as biomarkers of emphysema progression^[17] and pulmonary exacerbations of COPD^[18] though it has proved difficult to validate clinically^[19,20]. Elastin is also found in blood vessels^[21] and therefore “non-lung” elastin may introduce additional noise to the data. Furthermore, in advanced pulmonary emphysema the baseline desmosine level may be lower since there is less lung tissue left to be broken down, independent of disease activity^[22], making direct comparisons difficult.

An emerging area of study is the role of the lung microbiome and its influence on exacerbations^[23]. Advances in DNA sequencing in recent years has allowed for sophisticated profiling of the lung microbiome, something that traditional cell culture could not achieve consistently. The interplay between the host immune system and lung microbiota are complex but studies have shown the relative abundance and variety of bacteria within the respiratory tract is dynamic between stable state and exacerbations^[24]. This may provide new opportunity for identifying biomarkers of exacerbations and crucially new therapies^[25].

PREDICTING FUTURE EXACERBATIONS OF COPD

Assessing individual risk of having pulmonary exacerbations forms a key part in choosing initial and subsequent therapy. Stratifying COPD exacerbation risk continues to be a challenge, particularly when a COPD patient is first diagnosed. Analysis of data from the SPIROMICS cohort in 2017 found marked variation in annual frequency of moderate to severe exacerbations requiring hospitalization^[26].

Spirometry is a useful tool to assess COPD severity, and those with a forced expiratory volume in 1 s (FEV₁) < 50% predicted are at higher risk of suffering with exacerbations. Although GOLD severity level correlates with risk of COPD exacerbations, FEV₁ alone varies too widely to be a reliable predictor. It is, however, useful in conjunction with other patient factors^[3]. Deteriorating airflow obstruction is associated with increasing prevalence of exacerbations and hospitalisations^[27]. An important predictor of future exacerbations is a previous history of pulmonary exacerbations^[28] and should be asked about in all patients with COPD.

In recent years there has been research interest in the role of eosinophils in precision prevention of exacerbations of COPD. A recent systematic review^[29] examined the results of 11 post-hoc analyses of RCTs ($n = 25881$) and 5 retrospective observational studies ($n = 109704$) of the effect of inhaled corticosteroids (ICS) on COPD exacerbation rates. They found a treatment effect at both a cut off of $\geq 2\%$ (RR, 0.80, 95%CI, 0.74-0.85) and ≥ 150 cells/ μ L blood eosinophil count (RR, 0.65, 0.52-0.79), though there was no observed effect in 4 of the 5 observational studies. The most recent GOLD guidelines have since incorporated eosinophil count to be considered as a factor for starting an ICS in those with a higher eosinophil count in combination with clinical assessment of exacerbation risk^[6]. Blood eosinophils are a good example of precision medicine in action today and its use as a biomarker for future exacerbations may mean that patients with a low eosinophil count will avoid unnecessary side effects such as osteoporosis^[30] who would have ordinarily received an ICS as part of routine care.

There are other factors that may influence a decision to use ICS in patients with COPD. In those with a previous history of asthma or significant bronchodilator reversibility it may be beneficial to add in ICS therapy. Risk of pneumonia should always be thought about too, especially in the elderly, those with a low body mass index and patients with bronchiectasis^[31]. These may be considered “treatable traits” and may be a flexible alternative to splitting COPD patients into rigid phenotypes^[9].

High eosinophils are also an example of a COPD phenotype in which a patient characteristic is associated with a clinically meaningful outcome, namely exacerbations. The underlying mechanism for eosinophilic exacerbations remains poorly understood but clinical trials that target inflammatory pathways that involve eosinophils have show promise^[32,33].

Other biomarkers of exacerbation risk have been explored *via* large cohort studies but have been unsuccessful so far. Comparison of SPIROMICS and COPD gene data ($n = 2146$ patients in total) showed no biomarker candidates that can predict retrospective self-reported exacerbations or prospective exacerbations as defined by health care use^[34].

FUTURE DIRECTIONS

Early changes in the inflammatory profile of an exacerbation may be key to understanding the downstream effects. It is well known that several inflammatory cells have similar end points in activating the immune system^[5]. If these early changes could be found then it may shed more light on the cause of an exacerbation. This is not easily done in a hospital setting but could be achieved in clinical trials with the use of home biomarker monitoring paired with symptom diaries. This would capture subclinical episodes and daily fluctuations that would otherwise be missed when using the healthcare utilisation criteria for exacerbations. It must be noted that even if a suitable biomarker is found, acceptable and applicable methods would need to be available and cost effective in order to make it clinically useful.

CONCLUSION

Currently limited therapies are available for the treatment and prevention of COPD exacerbations beyond antibiotics, oral and inhaled steroids and bronchodilators^[35]. This is in part due to challenges in identifying clinically meaningful endotypes for

COPD and stunted development of targeted therapies. Studies have also often excluded certain subgroups of COPD, such as those with other comorbidities, and subsequent poor identification of COPD endo/phenotypes. There have, however, been promising results from studies in eosinophilic COPD with further phenotypes emerging from more recent studies. In combination with advancements in near patient testing technologies there is hope for more precise treatment of COPD exacerbations in the near future.

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