Table 1 Clinical characteristics and polysomnographic data on 170 patients.

	non OSA ($n = 20$)	mild OSA ($n = 25$)	moderate OSA ($n = 52$)	severe OSA ($n = 73$)	p value
Sex (male/female)	12/8	16/9	37/15	62/11[a,c]	0.04
Age (years)	43.6 ± 17.7	56.7 ± 15.7[a]	57.5 ± 15.6[a]	57.3 ± 13.5[a]	0.003
BMI (kg/m^2)	24.8 ± 3.4	25.7 ± 4.1	25.6 ± 5.3	28.7 ± 6.1[a,b,c]	0.002
Smoking history (current/ex/never)	12/6/2	9/9/7	26/18/8	18/39/16[a,c]	0.02
Smoking (pack years)	5.4 ± 12.7	18.0 ± 23.3	21.1 ± 34.2[a]	28.3 ± 30.9[a]	0.02
Serum KL-6 (U/ml)	198.7 ± 56.0	227.2 ± 90.0	246.8 ± 117.1	285.7 ± 170.8[a]	0.04
Serum SP-D (ng/ml)	41.6 ± 26.4	48.4 ± 22.3	53.0 ± 43.7	51.9 ± 36.1	0.65
Serum CRP (mg/dl)	0.14 ± 0.27	0.20 ± 0.40	0.13 ± 0.22	0.21 ± 0.32	0.53
AHI (events/hour)	2.2 ± 1.5	9.8 ± 2.8	22.1 ± 4.3[a,b]	54.3 ± 21.6[a,b,c]	<0.0001
Lowest SpO_2 (%)	89.7 ± 6.4	84.4 ± 8.3	80.3 ± 11.3[a]	73.9 ± 9.3[a,b,c]	<0.0001
VC (% predicted)	107.3 ± 13.3	107.8 ± 19.0	113.0 ± 15.5	110.6 ± 17.4	0.46
ERV (% predicted)	82.8 ± 26.1	81.6 ± 36.9	83.1 ± 38.5	71.1 ± 35.8	0.23
FVC (% predicted)	107.7 ± 14.0	105.4 ± 19.7	111.8 ± 16.3	108.5 ± 17.9	0.46
FEV_1 (% predicted)	99.4 ± 13.6	98.9 ± 20.7	107.2 ± 15.5	106.3 ± 17.9	0.10
FRC (% predicted)	106.9 ± 24.4	103.2 ± 30.2	111.5 ± 47.9	125.4 ± 41.9	0.71
RV (% predicted)	108.4 ± 37.6	113.2 ± 38.9	104.9 ± 26.9	106.4 ± 41.2	0.81
TLC (% predicted)	95.3 ± 13.8	102.0 ± 25.9	99.3 ± 18.9	96.6 ± 15.4	0.50
DL_{CO} (% predicted)	89.4 ± 15.7	82.0 ± 17.3	81.1 ± 19.3	85.7 ± 15.1	0.21
$PaCO_2$ (kPa)	5.7 ± 0.5	5.6 ± 0.5	5.7 ± 0.5	5.6 ± 0.6	0.61
PaO_2 (kPa)	12.0 ± 1.7	11.6 ± 1.7	11.5 ± 1.4	10.9 ± 1.6[a,c]	0.01
A-aDO_2 (kPa)	0.9 ± 1.7	1.5 ± 1.6	1.3 ± 0.4	2.1 ± 1.5[a,c]	0.003

Data presented as number or mean ± SD.
[a] $p < 0.05$ versus non OSA.
[b] $p < 0.05$ versus mild OSA.
[c] $p < 0.05$ versus moderate OSA. OSA: obstructive sleep apnea; BMI: body mass index; SP-D: surfactant protein-D; CRP: C-reactive protein; AHI: apnea/hypopnea index; VC: vital capacity; ERV: expiratory reserve volume; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; FRC: functional residual capacity; RV: residual volume; TLC: total lung capacity; DL_{CO}: diffusing capacity for carbon monoxide; $PaCO_2$: arterial partial tension of carbon dioxide; PaO_2: arterial partial tension of oxygen; A-aDO_2: alveolar-arterial oxygen tension difference.

other potential biomarkers. Moreover, elevated KL-6 levels were also significantly associated with restrictive lung function disturbance and gas exchange derangement, which are characteristic features in lung injury. Lederer et al. speculated that the possible mechanisms whereby OSA leads to lung injury include chronic oxidative stress associated with repeated intermittent hypoxia and reoxygenation and mechanical stretch caused by dynamic changes in intrathoracic pressure.[7] In addition to these factors, snoring-induced vibratory force might be a candidate as another factor causing lung injury.[19] Although both comorbid obesity and smoking exposure could affect plasma cytokine levels[20] or the subjects' lung diffusion capacity,[21,22] we showed that even after adjustment for these confounders the association between KL-6, pulmonary function impairment and OSA remained significant, indicating the possible pathogenetic role of OSA itself in lung injury.

KL-6 is a well-known biomarker for the diagnosis of IPF and determination of the severity of this condition.[23,24]

Table 2 Trends of serum biomarker levels across OSA groups.

	Model 1		Model 2	
	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
Serum KL-6 (U/ml)	$\beta = 0.22$	$\beta = 0.18$	$\beta = 0.22$	$\beta = 0.18$
	$p = 0.004$	$p = 0.02$	$p = 0.004$	$p = 0.02$
Serum SP-D (ng/ml)	$\beta = 0.08$	$\beta = 0.04$	$\beta = 0.07$	$\beta = 0.02$
	$p = 0.28$	$p = 0.67$	$p = 0.39$	$p = 0.80$
Serum CRP (mg/dl)	$\beta = 0.06$	$\beta = -0.02$	$\beta = 0.08$	$\beta = -0.01$
	$p = 0.41$	$p = 0.84$	$p = 0.32$	$p = 0.88$

Model 1: Linear model with three indicator variables for mild, moderate, and severe OSA as independent variables. Model 2: Linear model in which indicator variables were replaced with a single ordinal variable equal to the median AHI in the mild, moderate and severe OSA groups, respectively, and 0 in the non OSA group. OSA: obstructive sleep apnea; SP-D: surfactant protein-D; CRP: C-reactive protein.
[a] Adjusted for body mass index and smoking.

Table 3 Relationships between serum biomarker levels and pulmonary function and arterial blood gas data.

	Serum KL-6 (U/ml)		Serum CRP (mg/dl)	
	β coefficient	p value	β coefficient	p value
VC (% predicted)	−0.20	0.01	−0.08	0.24
ERV (% predicted)	−0.15	0.07	−0.03	0.75
FVC (% predicted)	−0.22	0.003	−0.11	0.14
FEV_1 (% predicted)	−0.11	0.17	−0.19	0.008
FRC (% predicted)	0.15	0.11	−0.02	0.79
RV (% predicted)	0.05	0.53	0.12	0.11
TLC (% predicted)	−0.14	0.049	0.18	0.01
DL_{CO} (% predicted)	−0.22	0.005	−0.14	0.06
$PaCO_2$ (kPa)	−0.12	0.12	0.10	0.16
PaO_2 (kPa)	−0.13	0.11	−0.11	0.16
A-aDO_2 (kPa)	0.18	0.02	0.06	0.45

These analyses were adjusted by body mass index and smoking. VC: vital capacity; ERV: expiratory reserve volume; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; FRC: functional residual capacity; RV: residual volume; TLC: total lung capacity; DL_{CO}: diffusing capacity for carbon monoxide; $PaCO_2$: arterial partial tension of carbon dioxide; PaO_2: arterial partial tension of oxygen; A-aDO_2: alveolar-arterial oxygen tension difference.

Although the pathophysiological link between IPF and OSA remains unclear, as a new topic in the field of IPF, recent studies have reported a high prevalence of OSA in IPF patients.[16,25] Our findings may partially explain potential mechanisms underlying this association and also provide a warning that their combination as a comorbid condition may additively worsen lung injury.

Serum levels of CRP did not correlate with the severity of OSA independently of BMI in our study, which is consistent with some reports.[26,27] Obesity was shown to be associated with chronic low-grade inflammation as indicated by raised serum CRP levels.[28] Considering that CRP reflects obesity-related inflammation, it could be anticipated that CRP might have an association with reduced lung volume due to obesity, particularly visceral adiposity. However, notably, we found that elevated CRP levels were significantly associated with worsened airflow limitation and increased lung volume independently of obesity and smoking, as contrasted with the significant relationship between KL-6 and restrictive defects. Increased levels of CRP also have been reported in obstructive and restrictive lung disease,[29] and were shown to be correlated with lower levels of FEV_1[30–32] and a decline in FEV_1.[33] Moreover, a recent large-scale population-based study showed that abdominal obesity was positively related to both obstructive and restrictive ventilatory patterns regardless of BMI.[34] Thus, the inter-relationships among OSA, pulmonary function, obesity and inflammatory markers are complicated, and further studies are needed.

Contrary to our hypothesis, unlike KL-6, SP-D was not significantly associated with the severity of OSA, although both are mainly produced by alveolar type II cells. Leakage of these markers into the bloodstream may be dependent on an alteration of production by alveolar type II cells and, in addition, on the intensity, extent, and type of injuries that precipitate the increase in alveolar wall permeability.[24] Thus, the magnitude of lung injury in patients with OSA might be too subtle to increase the production of SP-D by alveolar type II cells, although we did not assess the local concentrations of SP-D in lung compartments. SP-D was recently reported to be a promising lung-specific biomarker in COPD.[10] However, results of previous studies suggested that KL-6 was a more discriminative biomarker than SP-D in IPF and collagen vascular disease-associated interstitial pneumonitis,[24] idiopathic pulmonary alveolar proteinosis[35] or sarcoidosis.[36] Madsen et al. reported that SP-D was widely distributed in epithelial cells in a variety of tissues and was not restricted to the respiratory system.[37] Only a weak, though significant, relationship between serum levels of KL-6 and SP-D in the present study indicates that the blood level of these two cytokines may not necessarily reflect the same pathological state of the disease. Thus, although KL-6 appears to be superior to SP-D in evaluating subclinical lung injury associated with OSA, further study is needed to explain this discrepancy.

OSA is associated with significant morbidity and mortality. Analyses of biomarkers in OSA have been extensively performed in relation to its cardiovascular effects through systemic inflammation.[12] However, as well as systemic inflammation, local inflammation or injury is also implicated in the pathophysiology of OSA.[38,39] Local inflammation or injury has been assessed by surgical specimens, exhaled breath condensate (EBC), induced sputum, exhaled breath and oral air,[38,39] but more studies with a lung-specific biomarker in OSA are necessary for future use of such biomarkers in clinical practice. A recent study has also reported that the combination of two biomarkers, SP-D (lung epithelial barrier injury) and interleukin-8 (inflammation and neutrophil chemotaxis), had significant prognostic value, reflecting the two important pathogenetic pathways of acute lung injury.[40] Thus, KL-6 in association with a systemic biomarker such as CRP might provide complementarily useful information in assessing OSA.

In our study, there was a significant positive relationship between AHI and smoking. Airway inflammation and damage due to cigarette smoke could alter the mechanical and neural properties of the upper airway and increase its collapsibility during sleep, which may be related to sleep apnea.[41]

The prevalence of OSA in our population was high (88.2%). Since all participants in our study were referred to

our sleep unit with suspicious symptoms, there was a high clinical probability of OSA among these patients. Actually, the diagnostic rates in some other sleep laboratories were comparable to ours.[42–44]

The present study has some limitations. First, as we did not directly assess local expressions of KL-6 in the lung and alveolar wall permeability in OSA patients, our results cannot clearly establish the presence of lung injury in OSA. Measurements of KL-6, albumin concentration or cell count in bronchoalveolar lavage fluid, EBC or induced sputum would provide additional information and supporting evidence for our suggestions regarding the implications of these results. Second, as we did not assess serum biomarker levels after treatment of OSA, we could not confirm the specific association between OSA and serum biomarkers. Third, as the values of AHI and biomarkers tended to be skewed, we tried to transform them logarithmically. However, in 57 patients the CRP values could not be transformed logarithmically (CRP value was '0'). We then made calculations using absolute values. However, significance of the result between KL-6 and AHI remained even after logarithmic transformation ($r = 0.20$, $p = 0.01$).

In summary, serum levels of KL-6 but not SP-D were correlated with subclinical lung injury associated with OSA independently of obesity or smoking, and KL-6 could be a potential candidate as a lung-specific biomarker in OSA. KL-6 values may pathologically reflect epithelial and endothelial injury in the alveolus and pulmonary function impairment in OSA. This is in contrast to CRP, which is a well-studied systemic biomarker and may preferably cause an obstructive defect. A combination of two different types of biomarkers might be complementary and be superior to each biomarker alone from a pathogenesis perspective.

Conflict of interest disclosure

Kazuo Chin received Grants from the Japanese Ministry of Education, Culture, Sports, Science and Technology (nos. 20590921 and 22590860), Respiratory Failure Research Group and Health Science Research Grants (Comprehensive Research on Life-Style Related Diseases including Cardiovascular Diseases and Diabetes Mellitus: nos. 22110201 and 22111201) from the Ministry of Health, Labor and Welfare of Japan, and the Japan Vascular Disease Research Foundation.

References

1. Arnardottir ES, Mackiewicz M, Gislason T, Teff KL, Pack AI. Molecular signatures of obstructive sleep apnea in adults: a review and perspective. *Sleep* 2009;**32**:447–70.
2. Cochrane CG, Spragg R, Revak SD. Pathogenesis of the adult respiratory distress syndrome. Evidence of oxidant activity in bronchoalveolar lavage fluid. *J Clin Invest* 1983;**71**:754–61.
3. Kiefmann R, Rifkind JM, Nagababu E, Bhattacharya J. Red blood cells induce hypoxic lung inflammation. *Blood* 2008;**111**: 5205–14.
4. Kohno N, Inoue Y, Hamada H, et al. Difference in sero-diagnostic values among KL-6-associated mucins classified as cluster 9. *Int J Cancer Suppl* 1994;**8**:81–3.
5. Ishizaka A, Matsuda T, Albertine KH, et al. Elevation of KL-6, a lung epithelial cell marker, in plasma and epithelial lining fluid in acute respiratory distress syndrome. *Am J Physiol Lung Cell Mol Physiol* 2004;**286**:L1088–94.
6. Sato H, Callister ME, Mumby S, et al. KL-6 levels are elevated in plasma from patients with acute respiratory distress syndrome. *Eur Respir J* 2004;**23**:142–5.
7. Lederer DJ, Jelic S, Basner RC, Ishizaka A, Bhattacharya J. Circulating KL-6, a biomarker of lung injury, in obstructive sleep apnoea. *Eur Respir J* 2009;**33**:793–6.
8. Eisner MD, Parsons P, Matthay MA, Ware L, Greene K. Plasma surfactant protein levels and clinical outcomes in patients with acute lung injury. *Thorax* 2003;**58**:983–8.
9. Cheng IW, Ware LB, Greene KE, Nuckton TJ, Eisner MD, Matthay MA. Prognostic value of surfactant proteins A and D in patients with acute lung injury. *Crit Care Med* 2003;**31**:20–7.
10. Sin DD, Pahlavan PS, Man SF. Surfactant protein D: a lung specific biomarker in COPD? *Ther Adv Respir Dis* 2008;**2**:65–74.
11. Sin DD, Man SF, Marciniuk DD, et al. The effects of fluticasone with or without salmeterol on systemic biomarkers of inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008;**177**:1207–14.
12. Ryan S, Taylor CT, McNicholas WT. Systemic inflammation: a key factor in the pathogenesis of cardiovascular complications in obstructive sleep apnoea syndrome? *Thorax* 2009;**64**: 631–6.
13. Chan KK, Ing AJ, Laks L, Cossa G, Rogers P, Birring SS. Chronic cough in patients with sleep-disordered breathing. *Eur Respir J* 2010;**35**:368–72.
14. Shore SA. Obesity and asthma: possible mechanisms. *J Allergy Clin Immunol* 2008;**121**:1087–93.
15. Marin JM, Soriano JB, Carrizo SJ, Boldova A, Celli BR. Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. *Am J Respir Crit Care Med* 2010;**182**:325–31.
16. Mermigkis C, Stagaki E, Tryfon S, et al. How common is sleep-disordered breathing in patients with idiopathic pulmonary fibrosis? *Sleep Breath* 2010;**14**:387–90.
17. Rechtschaffen A, Kales A. *A Manual of Standardized Terminology, techniques and Scoring system for sleep stages of human subjects*. Washington, DC: National Institutes of Health; 1968.
18. Iber C, Ancoli-Israel S, Chesson A, Quan S. *The AASM Manual for the Scoring of sleep and associated Events: Rules, Terminology and Technical Specifications*. Westchester, IL, USA: American Academy of Sleep Medicine; 2007.
19. Puig F, Rico F, Almendros I, Montserrat JM, Navajas D, Farre R. Vibration enhances interleukin-8 release in a cell model of snoring-induced airway inflammation. *Sleep* 2005;**28**:1312–6.
20. Stapleton RD, Dixon AE, Parsons PE, Ware LB, Suratt BT. The association between BMI and plasma cytokine levels in patients with acute lung injury. *Chest* 2010;**138**:568–77.
21. Collard P, Wilputte JY, Aubert G, Rodenstein DO, Frans A. The single-breath diffusing capacity for carbon monoxide in obstructive sleep apnea and obesity. *Chest* 1996;**110**:1189–93.
22. Rizzi M, Sergi M, Andreoli A, Pecis M, Bruschi C, Fanfulla F. Environmental tobacco smoke may induce early lung damage in healthy male adolescents. *Chest* 2004;**125**:1387–93.
23. Yokoyama A, Kohno N, Hamada H, et al. Circulating KL-6 predicts the outcome of rapidly progressive idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1998;**158**:1680–4.
24. Ohnishi H, Yokoyama A, Kondo K, et al. Comparative study of KL-6, surfactant protein-A, surfactant protein-D, and monocyte chemoattractant protein-1 as serum markers for interstitial lung diseases. *Am J Respir Crit Care Med* 2002;**165**: 378–81.
25. Lancaster LH, Mason WR, Parnell JA, et al. Obstructive sleep apnea is common in idiopathic pulmonary fibrosis. *Chest* 2009; **136**:772–8.
26. Taheri S, Austin D, Lin L, Nieto FJ, Young T, Mignot E. Correlates of serum C-reactive protein (CRP)—no association with

sleep duration or sleep disordered breathing. *Sleep* 2007;**30**: 991–6.
27. Ryan S, Nolan GM, Hannigan E, Cunningham S, Taylor C, McNicholas WT. Cardiovascular risk markers in obstructive sleep apnoea syndrome and correlation with obesity. *Thorax* 2007;**62**:509–14.
28. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. *JAMA* 1999;**282**:2131–5.
29. Mannino DM, Ford ES, Redd SC. Obstructive and restrictive lung disease and markers of inflammation: data from the Third National Health and Nutrition Examination. *Am J Med* 2003; **114**:758–62.
30. Takemura M, Matsumoto H, Niimi A, et al. High sensitivity C-reactive protein in asthma. *Eur Respir J* 2006;**27**:908–12.
31. Gan WQ, Man SF, Sin DD. The interactions between cigarette smoking and reduced lung function on systemic inflammation. *Chest* 2005;**127**:558–64.
32. Walter RE, Wilk JB, Larson MG, et al. Systemic inflammation and COPD: the Framingham Heart study. *Chest* 2008;**133**:19–25.
33. Shaaban R, Kony S, Driss F, et al. Change in C-reactive protein levels and FEV_1 decline: a longitudinal population-based study. *Respir Med* 2006;**100**:2112–20.
34. Leone N, Courbon D, Thomas F, et al. Lung function impairment and metabolic syndrome: the critical role of abdominal obesity. *Am J Respir Crit Care Med* 2009;**179**:509–16.
35. Lin FC, Chen YC, Chang SC. Clinical importance of bronchoalveolar lavage fluid and blood cytokines, surfactant protein D, and Kerbs von Lungren 6 antigen in idiopathic pulmonary alveolar proteinosis. *Mayo Clin Proc* 2008;**83**: 1344–9.
36. Janssen R, Sato H, Grutters JC, et al. Study of Clara cell 16, KL-6, and surfactant protein-D in serum as disease markers in pulmonary sarcoidosis. *Chest* 2003;**124**:2119–25.
37. Madsen J, Kliem A, Tornoe I, Skjodt K, Koch C, Holmskov U. Localization of lung surfactant protein D on mucosal surfaces in human tissues. *J Immunol* 2000;**164**:5866–70.
38. Bergeron C, Kimoff J, Hamid Q. Obstructive sleep apnea syndrome and inflammation. *J Allergy Clin Immunol* 2005;**116**: 1393–6.
39. Culla B, Guida G, Brussino L, et al. Increased oral nitric oxide in obstructive sleep apnoea. *Respir Med* 2010;**104**:316–20.
40. Ware LB, Koyama T, Billheimer DD, et al. Prognostic and pathogenetic value of combining clinical and biochemical indices in patients with acute lung injury. *Chest* 2010;**137**: 288–96.
41. Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc* 2008;**5**:136–43.
42. Botros N, Concato J, Mohsenin V, Selim B, Doctor K, Yaggi HK. Obstructive sleep apnea as a risk factor for type 2 diabetes. *Am J Med* 2009;**122**:1122–7.
43. Kemmer H, Mathes AM, Dilk O, Gröschel A, Grass C, Stöckle M. Obstructive sleep apnea syndrome is associated with overactive bladder and urgency incontinence in men. *Sleep* 2009; **32**:271–5.
44. Fleischmann G, Fillafer G, Matterer H, Skrabal F, Kotanko P. Prevalence of chronic kidney disease in patients with suspected sleep apnoea. *Nephrol Dial Transplant* 2010;**25**:181–6.

Advance Publication by J-STAGE

J Epidemiol 2012
doi:10.2188/jea.JE20110109

Original Article

Self-Reported Snoring Frequency and Incidence of Cardiovascular Disease: The Circulatory Risk in Communities Study (CIRCS)

Mako Nagayoshi[1,2], Takeshi Tanigawa[3], Kazumasa Yamagishi[2,4], Susumu Sakurai[3], Akihiko Kitamura[2], Masahiko Kiyama[2], Takeo Okada[2], Kenji Maeda[1,2], Tetsuya Ohira[1,2], Hironori Imano[1,2], Shinichi Sato[5], and Hiroyasu Iso[1], for the CIRCS Investigators

[1]Public Health, Department of Social and Environmental Medicine, Graduate School of Medicine, Osaka University, Suita, Japan
[2]Osaka Medical Center for Health Science and Promotion, Osaka, Japan
[3]Department of Public Health, Doctoral Program in Social Medicine, Ehime University Graduate School of Medicine, Toon, Japan
[4]Department of Public Health Medicine, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan
[5]Chiba Prefectural Institute of Public Health, Chiba, Japan

Received September 22, 2011; accepted December 15, 2011; released online March 10, 2012

ABSTRACT

Background: Although associations between snoring and cardiovascular disease have been reported in several prospective studies, there is limited evidence from Asian populations. The objective of this study was to determine if there is an association between self-reported snoring frequency and the incidence of cardiovascular disease in Japanese.

Methods: The subjects were 2350 men and 4163 women aged 40 to 69 years who lived in 3 communities in Japan. All subjects were participants in the Circulatory Risk in Communities Study (CIRCS) and were followed for 6 years. Incidence of cardiovascular disease during the follow-up period comprised events of myocardial infarction, angina pectoris, sudden cardiac death and stroke.

Results: During the 6-year follow-up period, 97 participants (56 men and 41 women) had cardiovascular events. After adjustment for potential confounding factors, self-reported snoring frequency was associated with an increased risk of cardiovascular events among women but not men. The hazard ratios (95% CI) for cardiovascular events were 0.9 (0.4–2.0) for sometimes snoring and 2.5 (1.0–6.1) for everyday snoring in women and 0.7 (0.3–1.3) and 1.0 (0.5–2.1), respectively, in men. Further adjustment for body mass index attenuated the association in women; the respective hazard ratios for cardiovascular events were 0.9 (0.4–1.9) and 2.1 (0.9–5.4).

Conclusions: Self-reported habitual snoring was associated with increased risk of cardiovascular events among Japanese women. Overweight may partly mediate this association.

Key words: cardiovascular events; obstructive sleep apnea; population-based study; prospective cohort study

INTRODUCTION

Sleep-disordered breathing (SDB) is characterized by repeated episodes of apnea and hypopnea events during sleep.[1] Recently, SDB was identified as a risk factor for various disorders and diseases such as hypertension,[2–5] insulin and glucose abnormalities,[6] and cardiovascular disease.[7] Evidence has shown that self-reported snoring is a surrogate marker for SDB.[8] Associations of snoring and SDB with cardiovascular disease were examined cross-sectionally[9,10] in clinical and large-scale epidemiologic studies, most of which clearly showed an independent positive association between the 2 conditions, even after adjustment for potential confounding factors such as age, sex, and body mass index (BMI).[11]

This causal relationship has also been observed in studies of Western populations. As compared with non-snorers, the relative risk of developing cardiovascular disease among habitual snoring American women was 30% higher in the Nurses' Health Study,[12] and the risk among habitual and frequent snoring Finish men was 2.1-fold higher.[13] However, evidence from Asian populations is still very limited, and these results from Western studies cannot simply be extrapolated to Asian populations, because substantial differences exist between Asian and white populations, such

Address for correspondence. Hiroyasu Iso, MD, PhD, Public Health, Department of Social and Environmental Medicine, Graduate School of Medicine, Osaka University, 2-2 Yamada, Suita, Osaka 565-0871, Japan (e-mail: iso@pbhel.med.osaka-u.ac.jp).

as disparities in physique and prevalence of cardiovascular disease subtypes.[14]

In our previous large cross-sectional study,[15] we reported that the prevalence of snorers among Japanese men was about 70%, despite the low prevalence of obesity. The study revealed that alcohol consumption and cigarette smoking increased snoring risk among Japanese, especially among those who were not overweight. We also reported differences in the distribution of cardiovascular disease subtypes among Japanese versus whites, eg, among Japanese, the proportion of stroke was 2 times higher,[16] and the proportion of ischemic heart disease was one quarter, compared to the respective values reported in the United Kingdom and United States.[17] It is thus important to assess the risks of habitual snoring in Asians, because snoring is affected not only by obesity but also other factors, and Asian populations have different distributions of cardiovascular disease subtypes. We therefore examined the risk of cardiovascular events among habitual snorers compared with non-snorers in a large community-based prospective study of Japanese adults.

METHODS

Study subjects

Subjects were recruited from participants in the Circulatory Risk in Communities Study (CIRCS, see Appendix), a prospective community-based study of cardiovascular disease in 5 communities across Japan that was launched in 1963.[18] The subjects of the present sleep study comprised Japanese men and women aged 40 to 69, and none had previously received a diagnosis of SDB. Baseline data on snoring frequency and cardiovascular risk factors were obtained during annual surveys between 2001 and 2005 in the district of Yao City (midwestern suburban community, $n = 1994$), Ikawa (northeastern rural community, $n = 1446$), and between 2000 and 2004 in Kyowa (mideastern rural community, $n = 3209$). We excluded participants with incomplete data on sleep questionnaires ($n = 82$), those with missing data for BMI or other parameters ($n = 10$), and those with a history of ischemic heart disease ($n = 17$) or stroke ($n = 19$). A total of 2350 men and 4163 women were enrolled in the present study. All subjects had the protocol explained in detail and gave their informed consent for participation. The study protocol was approved by the Medical Ethics Committees of the University of Tsukuba.

Determination of endpoint

Follow-up lasted until the end of 2009 for Ikawa, until the end of 2008 for Yao, and until the end of 2006 for Kyowa. The criteria for ischemic heart disease were modified from those established by the World Health Organization (WHO) Expert Committee.[19] Definite myocardial infarction was defined as characteristic severe chest pain (lasting for ≥30 min) together with the appearance of new abnormal and persistent Q or QS waves and/or consistent changes in cardiac enzyme activity. Probable myocardial infarction was defined as characteristic chest pain in the absence of electrocardiographic findings or findings related to enzyme activity. Angina pectoris was defined as repeated episodes of chest pain during effort, especially when walking, that usually rapidly disappeared after cessation of effort or use of sublingual nitroglycerin. Sudden cardiac death was defined as death within 1 hour of symptom onset, a witnessed cardiac arrest, or abrupt collapse not preceded by symptoms persisting 1 hour or longer. Stroke was defined as a focal neurological disorder of rapid onset that persisted at least 24 hours or until death. Determination of incident strokes was conducted based on clinical criteria.[20] A panel of 3 or 4 physician-epidemiologists who were blinded to data from the risk factor surveys made the final diagnoses for these suspected cases of ischemic heart disease and stroke. Cardiovascular disease included events related to ischemic heart disease (definite and probable myocardial infarction, angina pectoris, and sudden cardiac death) and stroke during the follow-up period.

For case ascertainment, histories of cardiovascular events were obtained from annual cardiovascular risk surveys, national insurance claims, ambulance records, reports of local physicians, and public health nurses. To confirm the diagnosis, all living patients were telephoned or visited to obtain a medical history, and their medical records were reviewed. For deaths, we obtained histories from families and reviewed medical records. The protocol has been described in detail elsewhere.[20,21]

Risk factor measurements

At the annual cardiovascular surveys, each participant was asked about their snoring frequency. Answer options for the question "Did you snore during the past 3 months?" were almost every day, sometimes, never, and unknown. Information on smoking and drinking habits, menopausal status (for women), and measurements of blood pressure, serum glucose concentration, and physique were obtained according to the CIRCS protocol.[22] Hypertension was defined as systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or antihypertensive treatment; diabetes mellitus was defined as fasting blood glucose of 126 mg/dl or higher, non-fasting blood glucose of 200 mg/dl or higher, or antihyperglycemic treatment; and hypercholesterolemia was defined as serum total cholesterol of 220 mg/dl or higher or treatment with lipid-lowering medication.

Statistical analyses

Person-years for cardiovascular events were calculated as the sum of individual follow-up time until cardiovascular event, emigration, or the end of the follow-up period. Age- and community-adjusted and multivariable-adjusted hazard ratios (HRs) and 95% CIs for cardiovascular events were calculated according to baseline snoring frequency by using the Cox

proportional hazards model. The interaction of snoring with sex in relation to cardiovascular events was tested using their cross-product terms.

Confounding variables included age (continuous), BMI (continuous), alcohol consumption (never, ex-, <23 g and ≥23 g ethanol per day), cigarette smoking (never, ex-, <20 and ≥20 cigarettes per day), community (categorical), and menopausal status (for women; yes, no). To confirm the hypothesis that snoring induces cardiovascular events by increasing the risk of hypertension and metabolic disorders, we further adjusted for systolic blood pressure (continuous), use of antihypertensive medication (dichotomous), diabetes mellitus (dichotomous), and hypercholesterolemia (dichotomous). All statistical analyses were performed using SAS version 9.1 software (SAS Institute Inc., Cary, NC, USA). All statistical tests were 2-tailed, and P values less than 0.05 were regarded as statistically significant.

RESULTS

Demographic characteristics at baseline

The mean (± SD) age of participants was 56.3 ± 8.3 years, mean BMI was 23.5 ± 3.2 kg/m^2, mean systolic blood pressure was 132.3 ± 18.6 mm Hg, and mean diastolic blood pressure was 80.4 ± 11.1 mm Hg.

Analysis revealed that 42.5% of participants had hypertension, 17.5% were using antihypertensive medication, 5.9% had diabetes mellitus, 44.7% had hypercholesterolemia, 37.6% were current drinkers, 21.1% were current smokers, and 69.1% of women were post-menopausal. Baseline demographic characteristics, by sex, are shown in Table 1.

Table 1. Sex-specific mean values (SD) and prevalence of selected cardiovascular risk characteristics among 2350 men and 4163 women aged 40–69 years

	Men n = 2350	Women n = 4163	P value
Age (years)	57.5 (8.2)	55.6 (8.3)	<0.001
Body mass index (kg/m^2)	23.9 (3.0)	23.3 (3.3)	<0.001
Systolic blood pressure (mm Hg)	135.1 (17.6)	130.7 (18.9)	<0.001
Diastolic blood pressure (mm Hg)	83.3 (10.9)	78.7 (10.8)	<0.001
Antihypertensive use (%)	19.2	16.5	0.005
Hypertension (%)[a]	51.1	37.6	<0.001
Diabetes mellitus (%)[b]	9.1	4.1	<0.001
Hypercholesterolemia (%)[c]	34.5	50.5	0.28
Alcohol consumption (%)			
never	19.6	78.5	<0.001
ex-drinker	7.3	4.0	
<23 g ethanol per day	22.6	15.1	
≥23 g ethanol per day	50.6	2.4	
Cigarette smoking (%)			
never	17.0	90.5	<0.001
ex-smoker	35.4	3.3	
<20 cigarettes per day	13.2	4.4	
≥20 cigarettes per day	34.3	1.8	
Menopause (%)	—	69.1	—

[a]Hypertension was defined as blood pressure ≥140/90 mm Hg or current treatment.
[b]Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dl, non-fasting blood glucose ≥200 mg/dl, or current treatment.
[c]Hypercholesterolemia was defined as total cholesterol ≥220 mg/dl or current treatment.

Prevalence of snoring and its correlates

The distribution of snoring frequency was as follows: 14.0% (23.9% in men and 8.5% in women) reported snoring almost every day, 46.7% (48.7% in men and 45.6% in women) reported snoring sometimes, 28.9% (20.7% in men and 33.6% in women) reported never snoring, and 10.3% (6.8% in men and 12.3% in women) reported that their snoring frequency as unknown. Sex-specific, age-adjusted characteristics classified according to snoring frequency are shown in Table 2. The mean values and proportions of baseline risk characteristics tended to be higher with increasing snoring frequency, except for mean age in men and women and prevalence of diabetes mellitus in men. As compared with women who reported a snoring frequency, those who answered "unknown" were 2.6 years older ($P < 0.001$), 0.5 points lower in mean BMI ($P = 0.001$), and 4.3% higher in the mean proportion of current smokers ($P < 0.001$) in women. There was no significant difference among men.

Incidence of cardiovascular events

During the 6-year median follow-up duration, 97 participants (56 men and 41 women) experienced cardiovascular events, including 30 (22 in men and 8 in women) incident cases of ischemic heart disease and 67 (34 in men and 33 in women) strokes. The numbers of ischemic heart disease and stroke events, according to snoring frequency and sex, are shown in Table 3.

Association of snoring with cardiovascular events

As compared with never snorers, the age- and community-adjusted HR of ischemic heart disease and stroke combined was higher among female but not male everyday snorers; the HRs (95% CI) for cardiovascular events were 0.9 (0.5–2.0) for sometimes snoring and 2.6 (1.1–6.3) for everyday snoring in women and 0.7 (0.4–1.4) and 1.1 (0.5–2.2), respectively, in men (Table 3). These associations in men did not vary by age group (40–59 and 60–69 years), smoking status (current and non-current), or drinking status (current and non-current) (data not shown in table). After adjustment for age, community, and other confounding variables, the association between self-reported snoring frequency and cardiovascular events was unchanged in women: the HRs (95% CI) for cardiovascular events were 0.9 (0.4–2.0) for sometimes snoring and 2.5 (1.0–6.1) for everyday snoring in women (Table 3, Model 1). Further adjustment for BMI attenuated the association in women: the respective HRs for cardiovascular events were 0.9 (0.4–1.9) and 2.1 (0.9–5.4; Table 3, Model 2). To confirm

Table 2. Sex-specific, age-adjusted, mean values (standard error) and prevalence of selected cardiovascular risk characteristics according to snoring frequency among 2350 men and 4163 women aged 40–69 years

Snoring frequency	Men				Women			
	Never $n = 486$	Sometimes $n = 1144$	Daily $n = 561$	Unknown $n = 159$	Never $n = 1399$	Sometimes $n = 1900$	Daily $n = 352$	Unknown $n = 512$
Age (years)[a]	59.0 (0.4)	57.1 (0.2)	56.8 (0.3)	57.9 (0.6)	55.1 (0.2)	55.2 (0.2)	55.9 (0.4)	57.9 (0.4)
Body mass index (kg/m^2)	23.1 (0.1)	23.8 (0.1)	24.9 (0.1)	23.6 (0.2)	22.6 (0.1)	23.6 (0.1)	24.9 (0.2)	22.8 (0.1)
Systolic blood pressure (mm Hg)	133.4 (0.8)	135.1 (0.5)	136.5 (0.7)	135.0 (1.3)	128.3 (0.5)	132.4 (0.4)	133.5 (0.9)	129.0 (0.8)
Diastolic blood pressure (mm Hg)	81.9 (0.5)	83.0 (0.3)	85.3 (0.5)	83.2 (0.9)	77.0 (0.3)	79.6 (0.2)	80.8 (0.6)	78.6 (0.5)
Antihypertensive use (%)	18.6	17.6	22.1	22.8	13.3	18.1	22.3	15.0
Hypertension (%)[b]	48.3	49.3	56.8	52.2	31.5	41.4	46.0	34.8
Diabetes mellitus (%)[c]	9.2	9.2	8.8	9.3	3.4	4.3	6.2	3.8
Hypercholesterolemia (%)[d]	30.2	35.6	37.4	28.9	46.7	51.8	55.4	52.7
Cigarette smoking (%)								
never	22.4	15.6	15.0	18.2	92.5	91.1	87.4	84.8
ex-smoker	34.5	35.8	36.1	33.7	2.6	3.2	4.3	5.2
<20 cigarettes per day	13.6	14.1	10.9	13.7	3.9	4.2	4.6	6.2
≥20 cigarettes per day	29.5	34.6	38.1	34.3	1.0	1.6	3.7	3.8
Alcohol consumption (%)								
never	23.2	19.0	17.4	20.2	82.5	77.8	72.5	74.8
ex-drinker	10.5	6.2	6.1	9.9	3.1	3.8	6.6	5.1
<23 g ethanol per day	21.9	24.2	21.0	18.4	13.2	16.1	16.1	16.1
≥23 g ethanol per day	44.4	50.6	55.6	51.5	1.2	2.3	4.9	4.0
Menopause (%)	—	—	—	—	67.1	70.0	71.5	69.2

[a]Age was not included in the adjustment variables.
[b]Hypertension was defined as blood pressure ≥140/90 mm Hg or current treatment.
[c]Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dl, non-fasting blood glucose ≥200 mg/dl, or current treatment.
[d]Hypercholesterolemia was defined as total cholesterol ≥220 mg/dl or current treatment.

Table 3. Sex-specific age- and community-adjusted and multivariable-adjusted hazard ratios (95% CI) for incidence of cardiovascular events according to snoring frequency

Snoring frequency	Men				Women			
	Never	Sometimes	Daily	Unknown	Never	Sometimes	Daily	Unknown
Person-years	2792	7014	3427	951	8462	11 715	2119	3268
Subjects (n)	486	1144	561	159	1399	1900	352	512
Incident cardiovascular event (n)	15	22	16	3	13	16	8	4
Incident ischemic heart disease (n)	7	10	7	2	1	4	2	1
Incident stroke (n)	8	12	9	1	12	12	6	3
Age- and community-adjusted HR (95% CI)	(Reference)	0.7 (0.4–1.4)	1.1 (0.5–2.2)	0.7 (0.2–2.3)	(Reference)	0.9 (0.5–2.0)	2.6 (1.1–6.3)	0.8 (0.2–2.4)
Model 1 HR (95% CI)[a]	(Reference)	0.7 (0.3–1.3)	1.0 (0.5–2.1)	0.7 (0.2–2.3)	(Reference)	0.9 (0.4–2.0)	2.5 (1.0–6.1)	0.8 (0.2–2.4)
Model 2 HR (95% CI)[b]	(Reference)	0.6 (0.3–1.3)	1.0 (0.5–2.0)	0.6 (0.2–2.3)	(Reference)	0.9 (0.4–1.9)	2.1 (0.9–5.4)	0.8 (0.2–2.4)
Model 3 HR (95% CI)[c]	(Reference)	0.6 (0.3–1.2)	0.9 (0.4–1.9)	0.6 (0.2–2.1)	(Reference)	0.8 (0.4–1.7)	1.9 (0.8–4.9)	0.7 (0.2–2.2)

HR: hazard ratio; CI: confidence interval.
[a]Model 1 was adjusted for age, alcohol consumption, cigarette smoking, community, and, for women, menopausal status at baseline.
[b]Model 2 was adjusted for factors in Model 1 plus body mass index.
[c]Model 3 was adjusted for factors in Model 2 plus systolic blood pressure, antihypertensive medication use, diabetes mellitus, and hypercholesterolemia.

the hypothesis that snoring induces cardiovascular events by increasing the risk of hypertension and metabolic disorders, we further adjusted for systolic blood pressure, antihypertensive medication use, diabetes mellitus and hypercholesterolemia. The respective HRs (95% CI) for cardiovascular events were 0.8 (0.4–1.7) and 1.9 (0.8–4.9; Table 3, Model 3). The association between everyday snoring and risk of cardiovascular events was not significantly modified by sex (P for interaction = 0.12). The risk of cardiovascular events associated with unknown snoring was not increased and was similar to the risk associated with sometimes snoring in both men and women.

DISCUSSION

In the present prospective study, snoring frequency was associated with an increased incidence of cardiovascular events among community-dwelling middle-aged Japanese

women. This association was independent of age and other confounding factors. As compared with never snorers, 'everyday snoring' women had a 2.5-fold higher risk of cardiovascular events during 6 years of follow-up. The association of everyday snoring with cardiovascular events was attenuated after adjustment for BMI and after further adjustment for systolic blood pressure, antihypertensive medication use, diabetes mellitus, and hypercholesterolemia. This suggested that overweight partly mediated the association and that hypertension and metabolic abnormalities partly caused by snoring contribute to the risk of cardiovascular events in women who snore every day. This is the first study to show a relationship between habitual snoring and risk of cardiovascular events among a population in Asia, which has a low prevalence of obesity.

The biological mechanisms that link habitual snoring to the development of cardiovascular disease remain to be fully elucidated, but a number of mechanisms have been proposed. Habitual snoring is often accompanied by sleep apnea or hypopnea. Repetitive episodes of intermittent complete and partial airway collapse during sleep result in hypoxemia, hypercapnia, changes in intrathoracic pressure, and repeated arousal from sleep. Episodes of snoring and apneic events can cause acute hemodynamic changes[11] (such as increased cardiac output, enhanced cardiac arrhythmia, patent foramen ovale appearance,[23] increased intracranial pressure, and decreased cerebral blood flow),[24] increased platelet aggregation[25] and fibrinogen concentrations,[26] and decreased fibrinolysis, which directly affect the cardiovascular system. Abnormal metabolic conditions such as hypertension, diabetes mellitus, and hypercholesterolemia may also increase the risk of cardiovascular disease via elevation of sympathetic activation,[27,28] oxidative stress,[29] activation of the hypothalamic-pituitary-adrenal axis due to sleep fragmentation,[30,31] and endothelial dysfunction.[32]

In the present study, habitual snorers were more likely to be overweight, hypertensive, and diabetic than non-snorers, and the association between snoring frequency and the risk of cardiovascular events was attenuated when we further adjusted for these factors. This suggests that overweight partly mediates the association and that habitual snoring increases the risk of cardiovascular events partly through increasing the risk of hypertension and metabolic disorders.

The present results are consistent with those from studies of Western women[12] but not men[13]; however, this study is the first to note an independent association in a population with a different distribution of cardiovascular disease subtypes and a low prevalence of obesity. Among Japanese, 70% of cardiovascular events are strokes—whereas in Western countries ischemic heart disease is the largest cause of such events—and the risk factors for cardiovascular events among populations with low obesity are hypertension and metabolic abnormalities rather than overweight.[33]

In contrast to the significant association of habitual snoring with cardiovascular events in women, no such association was observed in men. Large population-based prospective studies of middle-aged men,[13] women,[12] and a population of men and women aged 20 years or older[34] have reported positive associations between habitual snoring and cardiovascular events. However, no study has reported a sex difference in the association. Recent reports from the Sleep Heart Health Study (a large population-based study of American residents aged 40 or older) have noted sex differences in the association between SDB, as defined by the apnea-hypopnea index (AHI), and the risk of coronary heart disease, heart failure, and stroke.[35,36] The multivariable HRs associated with a 10-unit increase in AHI were 1.1 (1.0–1.3) for incident heart failure in men and 1.1 (1.0–1.2) for incident coronary heart disease in men aged 70 years or younger, whereas no such associations were observed in women.[35] Similarly, the multivariable HR for ischemic stroke incidence was 2.9 (1.1–7.4) in men and 1.2 (0.7–2.2) in women for the highest (>19) as compared with the lowest (≤4) AHI quartiles.[36] The reasons for the present lack of association between habitual snoring and risk of cardiovascular events in men are unknown. We found no association in men when the analysis was stratified by age, smoking, or drinking status. Further research is necessary to elucidate this sex difference.

The strengths of the present study include the use of systematic surveillance of cardiovascular events and complete data collection on incident stroke and ischemic heart disease, including sudden cardiac death. Our large population-based prospective cohort study enabled us to examine sex-specific associations between snoring frequency and risk of cardiovascular events and provides the first evidence of a positive association between these conditions in an Asian population.

The limitations of the present study are as follows: first, our data on snoring frequency were obtained from a self-reported questionnaire, so lack of awareness of snoring or the absence of a sleep partner may have resulted in misclassification. However, in our simultaneous subsample study (1564 men and 2806 women aged 40–69 years) using a 3% oxygen desaturation index (ODI) measured by pulse oxymetry (PULSOX-3Si; Minolta, Osaka, Japan) during 1 night of sleep at a participants' homes, we found that the proportion of SDB (ODI ≥5 events/hours) was 22% in never snorers, 36% in sometime snorers, and 50% in everyday snorers among men. The respective proportions for women were 9%, 19%, and 34%. Thus, self-reported snoring seemed to be reliable. Second, data on sleep duration were not obtained in this study. According to a recent meta-analysis, both short (≤5–6 hours per night in most studies) and long sleep duration (≥8–9 hours per night in most studies) were associated with increased risks of coronary heart disease and stroke.[37] Further studies of the effects of sleep quality and quantity on the risk of cardiovascular disease will be necessary to confirm an effect of habitual snoring.

In summary, the present large cohort study showed that habitual snoring was associated with an increased risk of cardiovascular events among community-dwelling middle-aged Japanese women and that overweight, snoring-related hypertension, and metabolic disorders may partly mediate the association. The present study provides epidemiologic evidence for physicians and other health professionals that habitual snoring should be considered in the prevention of cardiovascular disease among middle-aged Japanese.

ACKNOWLEDGMENTS

This was not an industry-funded study. This study was supported in part by grants from the Japanese Ministry of Education, Culture, Sports, Science and Technology (Grant-in-Aid for Research B, 14370132); a Health and Labor Sciences Research Grant (Clinical Research for Evidence Based Medicine, J060701211), Ministry of Health, Welfare and Labor; and a University Research Project Research Grant (B), University of Tsukuba.

Conflicts of interest: None declared.

APPENDIX

CIRCS investigators

The Circulatory Risk in Communities Study (CIRCS) is a collaborative study managed by the Osaka Medical Center for Health Science and Promotion, Osaka University, University of Tsukuba, and Ehime University. CIRCS investigators who contributed to this study are as follows: Hiroyasu Iso, Tetsuya Ohira, Hironori Imano, Renzhe Cui, Ai Ikeda, Hiroyuki Noda, Satoyo Ikehara, Isao Muraki, and Kotatsu Maruyama, Osaka University, Suita; Tomoko Sankai and Kazumasa Yamagishi, Mitsumasa Umesawa, Choy-Lye Chei, Kimiko Yokota, and Minako Tabata, University of Tsukuba, Tsukuba; Masamitsu Konishi, Yoshinori Ishikawa, Masakazu Nakamura, Akihiko Kitamura, Masahiko Kiyama, Takeo Okada, Kenji Maeda, Masatoshi Ido, Masakazu Nakamura, Takashi Shimamoto, Minoru Iida, and Yoshio Komachi, Osaka Medical Center for Health Science and Promotion, Osaka; Shinichi Sato, Chiba Prefectural Institute of Public Health, Chiba; Takeshi Tanigawa, Isao Saito, Susumu Sakurai, and Shinichi Hitsumoto Ehime University, Toon; Masayuki Yao, Ranryoen Hospital, Ibaraki.

REFERENCES

1. Krieger J, McNicholas WT, Levy P, De Backer W, Douglas N, Marrone O, et al. Public health and medicolegal implications of sleep apnoea. Eur Respir J. 2002;20:1594–609.
2. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. JAMA. 2000;283:1829–36.
3. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med. 2000;342:1378–84.
4. Tanigawa T, Tachibana N, Yamagishi K, Muraki I, Kudo M, Ohira T, et al. Relationship between sleep-disordered breathing and blood pressure levels in community-based samples of Japanese men. Hypertens Res. 2004;27:479–84.
5. Cui R, Tanigawa T, Sakurai S, Yamagishi K, Imano H, Ohira T, et al. Associations of sleep-disordered breathing with excessive daytime sleepiness and blood pressure in Japanese women. Hypertens Res. 2008;31:501–6.
6. Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R, Resnick HE; Sleep Heart Health Study Investigators. Sleep-disordered breathing, glucose intolerance, and insulin resistance: The Sleep Heart Health Study. Am J Epidemiol. 2004;160: 521–30.
7. Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Nieto FJ, et al. Sleep-disordered breathing and cardiovascular disease. Cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med. 2001;163:19–25.
8. Young T, Hutton R, Finn L, Badr S, Palta M. The gender bias in sleep apnea diagnosis. Are women missed because they have different symptom? Arch Intern Med. 1996;156:2445–51.
9. Koskenvuo M, Kaprio J, Partinen M, Langinvainio H, Sarna S, Heikkilä K. Snoring as a risk factor for hypertension and angina pectoris. Lancet. 1985;1:893–6.
10. Dunai A, Keszei AP, Kopp MS, Shapiro CM, Mucsi I, Novak M. Cardiovascular disease and health-care utilization in snorers: a population survey. Sleep. 2008;31:411–6.
11. Yaggi H, Mohsenin V. Obstructive sleep apnoea and stroke. Lancet Neurol. 2004;3:333–42.
12. Hu FB, Willett WC, Manson JE, Colditz GA, Rimm EB, Speizer FE, et al. Snoring and risk of cardiovascular disease in women. J Am Coll Cardiol. 2000;35:308–13.
13. Koskenvuo M, Kaprio J, Telakivi T, Partinen M, Heikkilä K, Sarna S. Snoring as a risk factor for ischaemic heart disease and stroke in men. Br Med J (Clin Res Ed). 1987;294:16–9.
14. Haslam DW, James WP. Obesity. Lancet. 2005;366:1197–209.
15. Nagayoshi M, Yamagishi K, Tanigawa T, Sakurai S, Kitamura A, Kiyama M, et al; CIRCS Investigators. Risk factors for snoring among Japanese men and women: a community-based cross-sectional study. Sleep Breath. 2011;15:63–9.
16. Kitamura A, Nakagawa Y, Sato M, Iso H, Sato S, Imano H, et al. Proportions of stroke subtypes among men and women > or =40 years of age in an urban Japanese city in 1992, 1997, and 2002. Stroke. 2006;37:1374–8.
17. Saito I, Folsom AR, Aono H, Ozawa H, Ikebe T, Yamashita T. Comparison of fatal coronary heart disease occurrence based on population surveys in Japan and the USA. Int J Epidemiol. 2000;29:837–44.
18. Imano H, Kitamura A, Sato S, Kiyama M, Ohira T, Yamagishi K, et al. Trends for blood pressure and its contribution to stroke incidence in the middle-aged Japanese population. The Circulatory Risk in Communities Study (CIRCS). Stroke. 2009;40:1571–7.
19. WHO Expert Committee. Arterial hypertension and ischemic heart disease, preventive aspect. Geneva: World Health Organization; 1962 (WHO technical report series no. 231).

20. Shimamoto T, Komachi Y, Inada H, Doi M, Iso H, Sato S, et al. Trends for coronary heart disease and stroke and their risk factors in Japan. Circulation. 1989;79:503–15.
21. Iso H, Sato S, Kitamura A, Imano H, Kiyama M, Yamagishi K, et al. Metabolic syndrome and the risk of ischemic heart disease and stroke among Japanese men and women. Stroke. 2007; 38:1744–51.
22. Muraki I, Tanigawa T, Yamagishi K, Sakurai S, Ohira T, Imano H, et al; CIRCS Investigators. Nocturnal intermittent hypoxia and metabolic syndrome; the effect of being overweight: the CIRCS study. J Atheroscler Thromb. 2010;17:369–77.
23. Shanoudy H, Soliman A, Raggi P, Liu JW, Russell DC, Jarmukli NF. Prevalence of patent foramen ovale and its contribution to hypoxemia in patients with obstructive sleep apnea. Chest. 1998;113:91–6.
24. Franklin KA. Cerebral haemodynamics in obstructive sleep apnoea and Cheyne-Stokes respiration. Sleep Med Rev. 2002; 6:429–41.
25. Bokinsky G, Miller M, Ault K, Husband P, Mitchell J. Spontaneous platelet activation and aggregation during obstructive sleep apnea and its response to therapy with nasal continuous positive airway pressure. A preliminary investigation. Chest. 1995;108:625–30.
26. Wessendorf TE, Thilmann AF, Wang YM, Schreiber A, Konietzko N, Teschler H. Fibrinogen levels and obstructive sleep apnea in ischemic stroke. Am J Respir Crit Care Med. 2000;162:2039–42.
27. Narkiewicz K, van de Borne PJ, Montano N, Dyken ME, Phillips BG, Somers VK. Contribution of tonic chemoreflex activation to sympathetic activity and blood pressure in patients with obstructive sleep apnea. Circulation. 1998;97:943–5.
28. Nonogaki K. New insights into sympathetic regulation of glucose and fat metabolism. Diabetologia. 2000;43:533–49.
29. Ciftci TU, Kokturk O, Bukan N, Bilgihan A. The relationship between serum cytokine levels with obesity and obstructive sleep apnea syndrome. Cytokine. 2004;28:87–91.
30. Follenius M, Brandenberger G, Bandesapt JJ, Libert JP, Ehrhart J. Nocturnal cortisol release in relation to sleep structure. Sleep. 1992;15:21–7.
31. Stamatakis KA, Punjabi NM. Effects of sleep fragmentation on glucose metabolism in normal subjects. Chest. 2010;137: 95–101.
32. Atkeson A, Jelic S. Mechanisms of endothelial dysfunction in obstructive sleep apnea. Vasc Health Risk Manag. 2008;4: 1327–35.
33. Noda H, Iso H, Saito I, Konishi M, Inoue M, Tsugane S; JPHC Study Group. The impact of the metabolic syndrome and its components on the incidence of ischemic heart disease and stroke: the Japan public health center-based study. Hypertens Res. 2009;32:289–98.
34. Zamarrón C, Gude F, Otero Otero Y, Rodríguez-Suárez JR. Snoring and myocardial infarction: a 4-year follow-up study. Respir Med. 1999;93:108–12.
35. Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the Sleep Heart Health Study. Circulation. 2010;122:352–60.
36. Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O'Connor GT, Resnick HE, et al. Obstructive sleep apnea-hypopnea and incident stroke: the Sleep Heart Health Study. Am J Respir Crit Care Med. 2010;182:269–77.
37. Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. Eur Heart J. 2011;32:1484–92.

CHEST

Original Research

SLEEP DISORDERS

Differences in Breathing Patterning During Wakefulness in Patients With Mixed Apnea-Dominant vs Obstructive-Dominant Sleep Apnea

Motoo Yamauchi, MD, PhD; Shinji Tamaki, MD, PhD; Masanori Yoshikawa, MD, PhD; Yoshinobu Ohnishi, MD, PhD; Hiroshi Nakano, MD, PhD; Frank J. Jacono, MD; Kenneth A. Loparo, PhD; Kingman P. Strohl, MD; and Hiroshi Kimura, MD, PhD, FCCP

Background: **Mixed apneas share both central and obstructive components and are often treated as if they are obstructive events. The hypothesis is that patients with obstructive sleep apnea syndrome (OSAS) who exhibit a majority of mixed apneas will differ in ventilatory control from those with predominantly obstructive apneas during wakefulness; moreover, this difference could affect nasal continuous positive airway pressure (CPAP) adherence.**

Methods: **In a retrospectively derived case-control study, 5 min of respiratory inductance plethysmography signals during wakefulness prior to sleep onset were extracted from a diagnostic polysomnogram in these groups: (1) mixed apnea-dominant OSAS (mix-OSAS) (n = 36), (2) obstructive apnea-dominant OSAS (pure-OSAS) (n = 20), (3) central apnea-dominant sleep apnea syndrome (pure-CSAS) (n = 6), and (4) control subjects (n = 10). Breathing patterning was compared between the groups using the coefficient of variation (CV) for breath-to-breath inspiration time (T_I), expiration time (T_E), $T_I + T_E$ (Ttot), and tidal volume, and an information theory-based metric of signal pattern variability (sample entropy). Subsequent CPAP adherence over 12 months was determined in OSAS groups.**

Results: **Breath-to-breath CV parameters and sample entropy in the mix-OSAS group were significantly greater as compared with the pure-OSAS and control groups. In a subanalysis, CV and sample entropy were similar in the mix-OSAS and the pure-CSAS groups. CPAP adherence was significantly poorer in mix-OSAS compared with pure-OSAS.**

Conclusions: **During wakefulness, both breath patterning and sample entropy in mix-OSAS are similar to pure-CSAS and more variable than in pure-OSAS. In addition, CPAP adherence was decreased in patients with mix-OSAS, which may be related to basic differences in respiratory control.**

CHEST 2011; 140(1):54–61

Abbreviations: AHI = apnea-hypopnea index; CompSAS = complex sleep apnea syndrome; CPAP = continuous positive airway pressure; CV = coefficient of variation; EMG = electromyogram; ESS = Epworth sleepiness scale; mix-OSAS = mixed apnea-dominant obstructive sleep apnea syndrome; OSA = obstructive sleep apnea; OSAS = obstructive sleep apnea syndrome; pure-CSAS = central apnea-dominant sleep apnea syndrome; pure-OSAS = obstructive apnea-dominant obstructive sleep apnea syndrome; RIP = respiratory inductance plethysmography; T_E = expiration time; T_I = inspiration time; Ttot = inspiration time + expiration time

Obstructive sleep apnea syndrome (OSAS) is a major public health problem with a prevalence estimated at approximately 4% of adults in both Western and Asian countries.[1,2] Nasal continuous positive airway pressure (CPAP) therapy for OSAS has been the most effective and widely used treatment.[3-5] However, approximately 25% to 50% of patients with OSA will either refuse to try or will not tolerate CPAP therapy.[6] Furthermore, some patients do not respond to CPAP treatment, either without symptom improvements or without reductions in overall respiratory events. Finally, central apneas can emerge with initiation of CPAP therapy, a condition that has been called "complex sleep apnea."[7] Taken together, these facts indicate significant variability of the OSAS phenotype.

Mixed apneas are characterized by a relative lack of respiratory effort during the initial event period followed by efforts against an occluded upper airway. According to the American Academy of Sleep Medicine Task Force in 1999, mixed apneas are pathophysiologically considered to be a part of obstructive apneas.[8] Thus, patients whose apneas are mostly mixed receive the clinical diagnosis of OSAS, even though respiratory events in these patients may be primarily central as opposed to obstructive. This may contribute to the fact that some patients with OSAS do not show benefit from CPAP therapy.

In this study, we hypothesized that even before sleep onset there would be a fundamental difference in the breathing pattern between patients with mixed apnea-dominant OSAS (mix-OSAS) and those with obstructive apnea-dominant OSAS (pure-OSAS); moreover, this difference may affect CPAP acceptance and compliance. To examine these hypotheses, the breathing pattern during wakefulness was analyzed using conventional (linear) analysis of tidal volume and frequency, as well as nonlinear analysis of the respiratory signal, an approach that does not depend on breath identification. In addition, subsequent CPAP compliance was compared between OSAS groups.

The Bottom Line

How does this work advance the field?

Patients with mostly mixed apneas are diagnosed with and treated for obstructive sleep apnea syndrome. More irregular breathing during wakefulness and poor adherence to continuous positive airway pressure in patients with primarily mixed apneas identifies clinically important variability in the obstructive sleep apnea syndrome phenotype.

What are the clinical implications?

Patients with mixed apneas may have fundamental differences in respiratory control, which manifest as increased breathing pattern variability during wakefulness. An assessment of resting breathing pattern variability during wakefulness may be able to identify these patients who are less likely to adhere to subsequent continuous positive airway pressure therapy.

Materials and Methods

Subjects

Subjects were selected from 987 patients referred to a sleep laboratory with suspected sleep-disordered breathing who underwent diagnostic polysomnography between 2003 and 2008. The research database held values for the total number of apneas according to the each type (obstructive, central, and mixed) for each patient and measures of sleep latency, length, and state. Forty-four patients with mix-OSAS (4.4% of the sample) were identified and compared with patients with pure-OSAS (n = 20) and control subjects (n = 10) randomly extracted from the same database. A group with central apnea-dominant sleep apnea syndrome (pure-CSAS) (n = 7) was also identified. Data were collected on the Epworth sleepiness scale (ESS), medical history, and current medications.

Inclusion Criteria

Mix-OSAS was defined as an apnea-hypopnea index (AHI) > 20, in which the number of mixed apneas during the diagnostic study was > 30% of the total number of apneic events. Pure-OSAS was defined by an AHI > 20 in a patient in whom all of the apneas were obstructive apneas. The definition of pure-CSAS was a central apnea index > 5, where the total number of central apneas was greater than the number of obstructive apneas, or the presence of Cheyne-Stokes respiration. Patients with AHI < 5 were defined as control subjects.

Analysis of the Respiratory Signal

Approximately 5 min of stable respiratory signal data before sleep onset were extracted from the diagnostic polysomnography. Respiratory signals were generated by the sum of chest and abdominal signals using respiratory inductance plethysmography (RIP). The stable respiratory signal was identified using the respiratory signal itself as well as electromyogram (EMG) (chin and limb) to detect any body movements. When the amplitude of the EMG signal was high, that part of the signal was considered to be during movement and inappropriate for analysis. In the analytic phase of the study, investigators were blinded to the group assignment, and each 5-min record of respiratory signal during EEG staging of wakefulness was analyzed for breath-to-breath inspiration time (T_I), expiration time (T_E), $T_I + T_E$ (T_{tot}), and tidal volume. To assess breathing irregularity, the coefficient of variation (CV) ([SD/mean] × 100) for each parameter was calculated.

Sample entropy is calculated from the same data sample (RIP-sum signals) but is not dependent on information of tidal volume or frequency per se. Rather, it is a statistical measure of the predictability or regularity of the data set and is defined as the logarithm of the difference between the probability that a vector X is within a chosen distance r in m-dimensional space and the probability that the vector X is within the same chosen distance r in

Manuscript received April 26, 2010; revision accepted February 14, 2011.
Affiliations: From the Second Department of Internal Medicine, Department of Respiratory Medicine, (Drs Yamauchi, Tamaki, Yoshikawa, and Kimura), Nara Medical University, Kashihara; the Department of Internal Medicine (Dr Ohnishi), Tenri City Hospital, Tenri; and the Department of Pulmonology (Dr Nakano), Fukuoka National Hospital, Fukuoka, Japan; the Division of Pulmonary, Critical Care, and Sleep Medicine (Drs Jacono and Strohl), Case Western Reserve University and Louis Stokes Cleveland VA Medical Center; and the Department of Electrical Engineering and Computer Science (Dr Loparo), Case Western Reserve University, Cleveland, OH.
Funding/Support: This study was supported in part by Grant-in-Aid for Young Scientists (B) [21790781] from The Ministry of Education, Culture, Sports, Science and Technology, Japan; National Institutes of Health, National Heart, Lung, and Blood Institute [Grant R33HL087340-01]; and the Veterans Affairs Research Service.
Correspondence to: Motoo Yamauchi MD, PhD, Second Department of Internal Medicine, Department of Respiratory Medicine, Nara Medical University, 840 Shijo-cho, Kashihara, Nara, 634-8522, Japan; e-mail: motoo@naramed-u.ac.jp

DOI: 10.1378/chest.10-1082

m + 1-dimensional space.[9] The probability densities are normally estimated using the method suggested by Grassberger and Procaccia.[10] In the present study, sample entropy of the raw respiratory signal (sampled at 10 Hz) was calculated using standard parameters ($m = 2$ and $r = 0.2 \times SD$).[9] This information theory-based metric reflects linear and nonlinear determinants of temporal pattern variability with high values denoting less self-similarity and greater complexity. Comparisons of sample entropy of the original time series were made with the sample entropy of surrogate data sets ($n = 19$) to provide a statistical comparison between the surrogate data sets as well as to provide a means for comparing results of analyzing surrogate data and surrogate and original data through computational algorithms. Surrogate data were computed using the iterated amplitude-adjusted Fourier transform by moving the data into the frequency domain for adjustment and then back into the time domain while ensuring that both the frequency distribution (power spectrum/autocorrelation function) and the amplitude distribution are maintained.[11,12] Sample entropy was computed over multiple time delays from unity up to one cycle length.[13] Values were averaged across time lags excluding those with high linear correlations as defined by the first minimum of the mutual information function. Average sample entropy (excluding small lags) was reported for the surrogate and original data for each group.

Sleep Study

Data acquisition started from 9:00 PM and continued until 6:00 AM on the following morning. Polysomnography was performed using a polygraph system (EEG7414; Nihon Kohden; Tokyo, Japan). EEG (C3-A2, C4-A1), bilateral electrooculogram, submental EMG, ECG, and bilateral anterior tibial EMG were recorded. Airflow was monitored using an oronasal thermal sensor and/or nasal air pressure transducer. Thoracic and abdominal respiratory movements were monitored using RIP (Respitrace; Ambulatory Monitoring Inc; Ardsley, New York). Oxyhemoglobin saturation and pulse rate were monitored using pulse oximetry with a finger probe (OLV-3100; Nihon Kohden). All the signals were digitized and stored on a personal computer. Apneas were defined as an episode of complete airflow cessation measured from the thermal sensor lasting > 10 s. Hypopneas were defined by ≥ 30% reduction in amplitude of the RIP-sum signal lasting > 10 s with ≥ 3% oxygen desaturation. AHI was calculated as the average number of apnea-hypopnea events per hour over the total sleep period.

Continuous Positive Airway Pressure

Patients who had an AHI > 20 and any symptoms related to OSAS were initiated on nasal CPAP (REMstar Auto; Respironics; Pittsburgh, Pennsylvania, or GoodKnight 420E; Tyco Mallinckrodt; Plaisir, France) with auto-titrating mode. All patients treated with CPAP visited our sleep laboratory every month, and CPAP compliance was monitored every month using data extracted from the memory of the CPAP equipment for at least 12 months. At the monthly visit to the laboratory, CPAP settings, including pressure range or CPAP mode (auto or fix mode), were modified by an expert physician if it was necessary. Eventually, most of the patients used CPAP with auto-titrating mode during the follow-up period. Good CPAP compliance was defined by use in > 75% of days with > 4 h usage each night; otherwise, it was considered to be poor compliance. CPAP acceptance was defined by whether a patient refuses CPAP within 1 month after CPAP administration.

Statistical Analysis

The differences in age, sleep-disordered parameters, and CV values between three groups (mix-OSAS, pure-OSAS, and control subjects) were detected by one-way analysis of variance. When the analysis of variance was significant, probing of differences within the model was done by t tests of estimated marginal means (simple main effects) with adjustments for multiple comparisons made via the Bonferroni correction. The difference in categorical variables between the three groups and the difference in CPAP acceptance and compliance were detected by χ^2 test for independence. For the subanalysis, comparison between pure-OSAS and mix-OSAS was done by t test. Differences with $P < .05$ were considered significant. All results were expressed as means ± SD. Statistical analysis was done with SPSS, version 10.0 for Windows software (SPSS Inc; Chicago, Illinois).

RESULTS

Subject Characteristics

Among 44 patients with mix-OSAS, eight were excluded from the analysis because sufficient respiratory signal data could not be extracted because of noise; thus, 36 patients with mix-OSAS were enrolled in the study. Table 1 shows subject characteristics for each group. Significant differences in ESS were not observed. There were significant differences in age, AHI, and BMI between the three groups; however, a post hoc test did not indicate significant differences between mix-OSAS and pure-OSAS groups. In addition, four subjects suffered from arrhythmias, including chronic atrial fibrillation (n = 3) and atrioventricular block (n = 1), in the mix-OSAS group. Another two patients in the mix-OSAS group had a past history of cerebral infarction. In contrast, no patients had a history of arrhythmias or cerebral infarction in the pure-OSAS and control groups. The use of medications for hypertension, hyperlipidemia, and diabetes mellitus were similar between groups. No patients were using opioid or hypnotic medications.

Table 1—*Subject Characteristics*

Characteristic	Mix-OSAS (n = 36)	Pure-OSAS (n = 20)	Control Subjects (n = 10)	*P* Value
Age, y	56.8 ± 13.9	49.9 ± 11.9	42.5 ± 9.6[a]	< .01
AHI, per h	65.8 ± 17.8	59.1 ± 15.8	3.2 ± 1.3[a]	< .001
ESS	11.2 ± 4.8	11.7 ± 7.0	8.0 ± 3.8	NS
BMI, kg/m²	28.2 ± 3.8	27.7 ± 4.0	24.4 ± 3.7[b]	< .05
Arrhythmia	4/36 (11.1)	0/20 (0)	0/10 (0)	NS
Hypertension	15/36 (41.7)	7/20 (35)	2/10 (20)	NS
Hyperlipidemia	8/36 (22.2)	3/20 (15)	1/10 (10)	NS
Diabetes mellitus	6/36 (16.7)	2/20 (10)	1/10 (10)	NS
Past history of cerebral infarction	2/36 (5.6)	0/20 (0)	0/10 (0)	NS

Data are shown as mean ± SD or No. (%). AHI = apnea-hypopnea index; ESS = Epworth Sleepiness Scale; mix-OSAS = mixed apnea-dominant obstructive sleep apnea syndrome; NS = not significant; pure-OSAS = obstructive apnea-dominant obstructive sleep apnea syndrome.

[a]Significant difference from mix-OSAS, $P < .01$.

[b]Significant difference from mix-OSAS, $P < .05$.

Breathing Irregularity During Rest Before Sleep Onset

Figure 1 shows examples of RIP-sum signals during wakefulness for two subjects with mix-OSAS and two subjects with pure-OSAS. These tracings highlight the more irregular breathing pattern prior to sleep onset in mix-OSAS as compared with pure-OSAS. The average interval between the end of the extracted respiratory signal and sleep onset time in mix-OSAS, pure-OSAS, and control subjects was 10.0 ± 18.2, 7.5 ± 7.1, and 18.5 ± 32.8 min, respectively (data are not shown). This suggests that the irregularity of the extracted respiratory signal was not affected by drowsiness or an oscillation to sleep state. The CV values for TI, TE, and Ttot in patients with mix-OSAS were significantly higher than in pure-OSAS and control subjects (TI: 31.5 ± 18.8, 14.5 ± 10.2, 15.9 ± 7.5; TE: 41.9 ± 23.5, 18.5 ± 8.1, 19.5 ± 6.0; Ttot: 29.7 ± 16.6, 13.0 ± 6.5, 14.3 ± 6.0, respectively). Moreover, the CV of tidal volume in the mix-OSAS group was significantly higher than in pure-OSAS and control groups (37.0 ± 13.3, 18.8 ± 8.6, 23.1 ± 10.4, respectively) (Fig 2). Sample entropy for the respiratory signal in the mix-OSAS group was greater than that in both the pure-OSAS and control groups (1.42 ± 0.15, 1.20 ± 0.16, 1.19 ± 0.25, respectively). These findings suggest that there is greater complexity, less predictability, and thus greater variability in the mix-OSAS group as compared with both the control and pure-OSAS groups. However, this difference between groups remained when sample entropy of surrogate data were measured, suggesting that this difference may come from linear determinants of pattern variability in these two groups (Fig 3).

CPAP Acceptance and Compliance

In the mix-OSAS group (n = 36), all patients were treated with CPAP; however, one subject's data for CPAP usage were not recorded. Excluding this subject, only 17 out of 35 patients with mix-OSAS (48.6%) had acceptable compliance and acceptance. On the other hand, in the pure-OSAS group (n = 20), three patients chose other treatments, including oral appliance, lateral positional sleep, and weight loss, rather than CPAP; thus 17 patients were treated with CPAP. One subject's data for CPAP usage were not recorded. Thus, 16 patients with pure-OSAS were eligible for analysis of CPAP compliance. Among them, 13 patients (81%) had a good compliance and acceptance, whereas only three patients refused or could not tolerate CPAP within 1 month (Table 2). The main reasons for poor CPAP acceptance and compliance were an uncomfortable feeling with CPAP and having a sensation of it being hard to breathe and fall asleep. Some reported removing CPAP without awareness during sleep. Also, none of the three patients who refused or could not tolerate CPAP treatment felt any improvement in symptoms such as excessive daytime sleepiness, morning headache, and sleep quality.

Comparison of Mix-OSAS and Pure-CSAS Groups

Among subjects with pure-CSAS, six patients were suitable for the analysis, as one patient did not have a sufficient length of stable respiratory signal for the analysis. The central apnea index for the pure-CSAS group was 15.3 ± 12.1. Their age and BMI were 64.7 ± 10.2 years and 25.3 ± 2.4, respectively, which were similar to the mix-OSAS group. Moreover, the

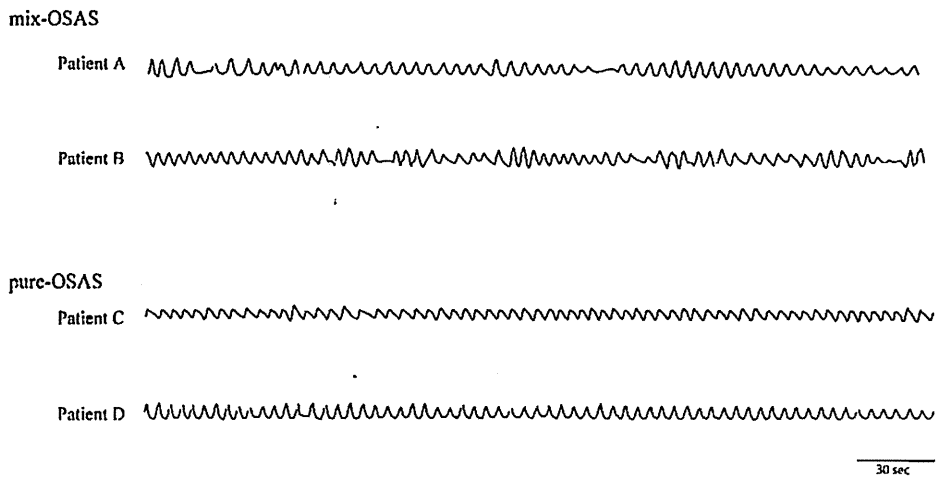

FIGURE 1. Respiratory inductance plethysmography (RIP)-sum tracings prior to sleep onset in two patients with mix-OSAS and two patients with pure-OSAS. Respiratory patterns are more irregular in mix-OSAS as compared with pure-OSAS. mix-OSAS = mixed apnea-dominant obstructive sleep apnea syndrome; pure-OSAS = obstructive apnea-dominant obstructive sleep apnea syndrome.

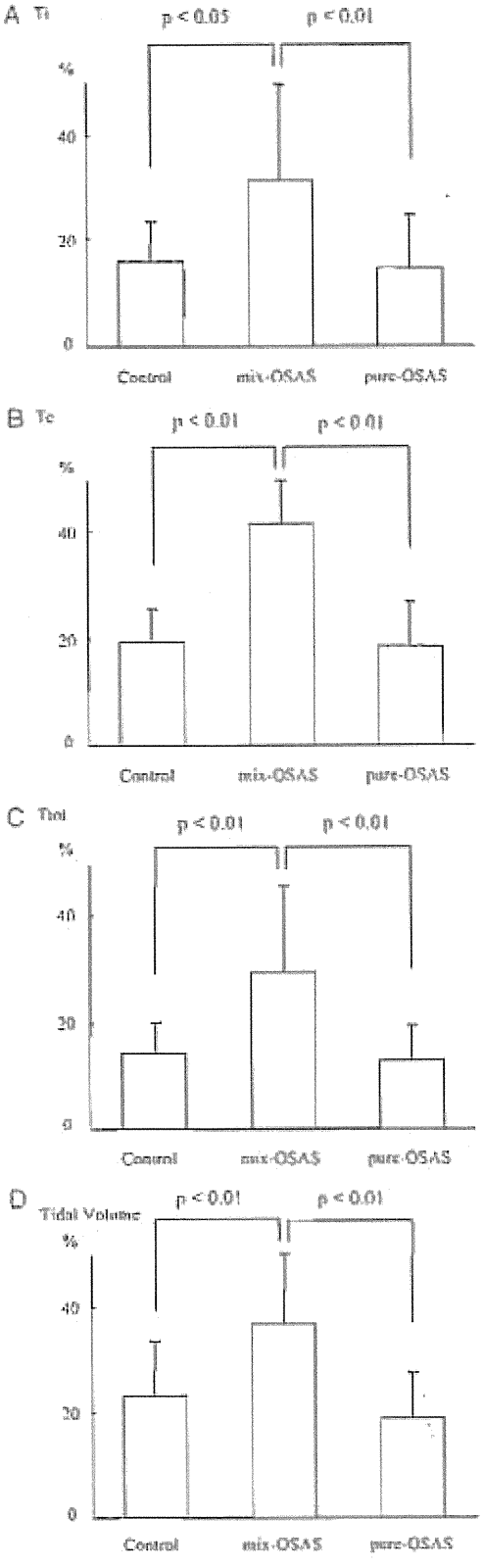

FIGURE 2. Coefficients of variation (CV) for breath-to-breath respiratory variables during resting breathing before sleep onset. Values are mean ± SD. A, Ti. B, Te. C, Ttot. D, Tidal volume. Resting breathing during wakefulness was more irregular in patients with mix-OSAS than in those with pure-OSAS and control subjects as expressed by higher CV values in all respiratory variables. Te = expiration time; Ti = inspiration time; Ttot = Ti + Te. See Figure 1 legend for expansion of other abbreviations.

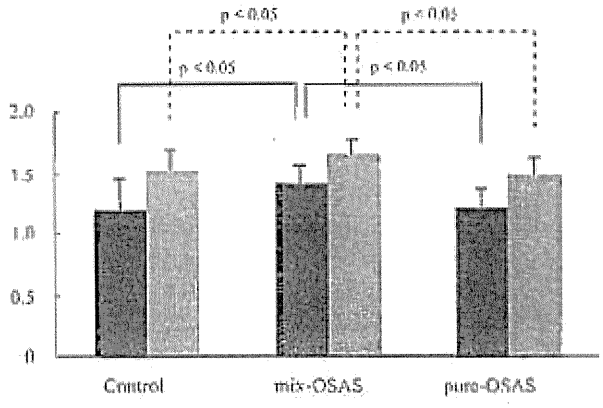

FIGURE 3. Sample entropy values for original data set (black bar) and surrogate data set (gray bar). Values are mean ± SD. See Figure 1 legend for expansion of abbreviations.

CV of Ti, Te, Ttot, and tidal volume in pure-CSAS were 24.6 ± 6.5, 33.8 ± 9.2, 23.9 ± 7.6, and 34.6 ± 8.5, respectively, which were similar to the values for the mix-OSAS group. In addition, the sample entropy of the pure-CSAS group was 1.34 ± 0.17 bits, which was comparable to that observed in the mix-OSAS group ($P = .24$). However, the sample entropy of the surrogate data were 1.46 ± 0.20 bits in the pure-CSAS group, which was lower than that observed in the mix-OSAS group ($P < .05$). Taken together, these data suggest that the overall complexity and variability of the breathing pattern is similar between the pure-CSAS and the mix-OSAS groups, but that there are some differences in linear determinants of pattern variability.

Discussion

The present study suggests breathing irregularity during wakefulness, as quantified by both linear and nonlinear metrics, is greater in patients with mix-OSAS as compared with patients with pure-OSAS and control subjects. Additionally, a secondary comparison indicated that breathing irregularity in patients with mix-OSAS is similar to those with pure-CSAS. This finding suggests an intrinsic pathophysiology in the respiratory control system for breathing rhythm and depth in patients with mix-OSAS. Furthermore, this instability of breathing at rest might have some predictive importance in regard to CPAP acceptance and compliance, as there was significantly poorer CPAP adherence in the mix-OSAS group as compared with the pure-OSAS group.

Breathing irregularity during wakefulness is associated with genetic diseases such as Rett syndrome,[14,15] with certain environments such as high altitude,[16,17]

Table 2—*CPAP Compliance and Acceptance*

CPAP Usage	Mix-OSAS (n = 35)[a]	Pure-OSAS (n = 16)[b]	*P* Value
Good compliance	17	13	<.01
Poor compliance	16	1	<.01
Poor acceptance	2	2	NS

CPAP = continuous positive airway pressure. See Table 1 legend for expansion of other abbreviations.

[a]One patient was excluded from the analysis because of loss of CPAP compliance data.

[b]Four patients were excluded from the analysis because three patients were given other treatments and one patient's CPAP data were lost.

with treatment with opioid medications,[18,19] and with medical conditions including heart failure[20-22] and cerebral infarction.[23,24] These phenomena reflect particular features of the respiratory control system involving respiratory rhythm generation and/or central and peripheral chemoreception. In the present study, we observed greater respiratory variability (as measured by CV of respiratory intervals) in the mix-OSAS group as compared with the pure-OSAS and control groups. This increase in breathing pattern variability was observed during a period of wakefulness, when it is rare for scoreable apnea and/or hypopnea events to occur. This finding suggests that the central respiratory control system in patients with mix-OSAS is different from those with pure-OSAS. To further investigate this difference, we quantified the morphology of the breathing pattern using sample entropy. This analysis identified a greater complexity and less predictability in the mixed group as compared with the control and obstructive groups. If this increased variability in the mixed group were due to nonlinear relationships in the data, we would expect that differences in sample entropy to be lost when looking at the surrogates. However, since these differences between the mixed and control and obstructive groups persisted on analysis of the surrogates, we concluded that the variability differences between the groups were primarily due to linear (stochastic) relationships in the data. The presence of these differences in the awake breathing patterns in these patients further supports the idea that there are fundamental differences in the respiratory control system in patients with mix-OSAS.

The pathogenesis for obstructive sleep apnea has been the focus of much study across the world. Anatomic features are key, but the neuromuscular control system also contributes to the pathogenesis of upper airway obstruction.[25-27] In this regard, OSA is already a fairly complex disease. Moreover, it has been proposed that the interaction of respiratory output to the upper airway and diaphragm may determine the expression of apnea types, such as central and obstructive.[28] Thus, individuals may manifest apneas with both obstructive and central components. The relative proportion of these components would depend on individual factors, which may be genetic or secondary to a medical condition. Taken together with our findings, we speculate that mixed apneas are closer to central apneas than to obstructive apneas. Although one can score each apnea as a mixed or obstructive apnea, the diagnosis must be OSAS because in the current American Academy of Sleep Medicine definition set a mixed apnea is considered as an obstructive apnea,[8] and "mixed sleep apnea syndrome" has not been defined. The present findings also suggest that variability in the OSAS phenotype may be one reason for the variability in CPAP treatment effectiveness for this group.

Poor CPAP compliance in the mix-OSAS group compared with the pure-OSAS group suggests that just opening the upper airway with a pressure splint is not always effective in patients with mix-OSAS. Among 36 patients with mix-OSAS, none had nasal disease; however, four patients had arrhythmias including chronic atrial fibrillation and two patients had a past history of cerebral infarction. As arrhythmias as well as cerebral infarction could affect respiration, the analyses were also performed in a subgroup excluding the six patients with these conditions. However, the significant differences in CV values between the mix-OSAS and pure-OSAS groups remained, suggesting that the presence of the arrhythmias and past history of cerebral infarction might be a surrogate marker and not necessarily the main reason for the respiratory irregularity observed in the mix-OSAS group.

Complex sleep apnea syndrome (CompSAS) is a novel category of sleep-disordered breathing that describes patients with obstructive apneas who develop frequent central apneas or Cheyne-Stokes respiration after successful application of CPAP.[29] It has been demonstrated that spectral analysis of ECG-based cardiopulmonary coupling distinguishes pure obstructive apnea from central or complex sleep apnea.[30] Moreover, patients with CompSAS show poor CPAP adherence.[31] Our study focused on mix-OSAS breathing detected during diagnostic PSG (before CPAP application). Although mixed-OSAS is distinct from CompSAS, similarities to CompSAS are relevant to our findings. Our study indicates that breath-to-breath analysis of breathing during wakefulness, which may be easier than spectral analysis of ECG-based cardiopulmonary coupling during sleep, might be able to not only distinguish mixed apnea dominant from pure obstructive sleep apnea but also predict CPAP adherence.

There are several potential limitations of the present work. First, arterial blood gas analysis was not

performed. Thus, a possible effect of hypocapnia on the irregular breathing during wakefulness in mix-OSAS or in those with central apneas cannot be excluded. However, if such a difference were present it would be another reason to suggest that the root cause for breathing irregularity is different. Second, repeat polysomnography with CPAP was not performed at follow-up. Of note, three patients with mix-OSAS had relatively high AHI (roughly around 10.0) during routine CPAP use as documented in the adherence report generated by CPAP equipment and obtained from CPAP memory. Thus, it is possible that patients with mix-OSA may be more likely to develop CPAP-emergent central apneas. Third, this was a retrospective clinical sample. Given the 4% to 5% prevalence of mix-OSAS, it would be difficult to do a prospective study to examine this issue. However, we point out that the recordings were extracted before a sleep study, and the matching to other groups was randomly done and analyzed in the same manner. In this regard there may be a bias that the recordings were acquired before sleep. Although all records were scored for state (in this case wakefulness using standard criteria) by investigators blinded to the group assignment, there may be differences in cortical control of breathing in patients with mix-OSAS and central apneas as compared with those with purely obstructive events. Whether the structure of breathing is also different at other times of the day during quiet wakefulness would need to be studied separately.

In summary, we conclude that irregular breathing during wakefulness and poor adherence to CPAP in the mix-OSAS group suggest distinct features of mix-OSAS as compared with pure-OSAS and control subjects. Mixed apneas may be part of central apneas rather than obstructive apneas, and specific or additional treatment using CPAP may be needed to treat patients with mixed apnea-dominant sleep apnea. Furthermore, an assessment of resting breathing pattern variability during wakefulness might be not only a window to explore the central respiratory control system but also a new tool to distinguish clinically important OSAS phenotypes.

Acknowledgments

Author contributions: *Dr Yamauchi:* contributed to study concept and design; data acquisition, analysis, and interpretation; and drafting and revising the manuscript.
Dr Tamaki: contributed to study concept and design, data interpretation, and drafting and revising the manuscript.
Dr Yoshikawa: contributed to study concept and design, data interpretation, and drafting and revising the manuscript.
Dr Ohnishi: contributed to data acquisition and drafting and revising the manuscript.
Dr Nakano: contributed to data acquisition and drafting and revising the manuscript.
Dr Jacono: contributed to data analysis and drafting and revising the manuscript.
Dr Loparo: contributed to data analysis and drafting and revising the manuscript.
Dr Strohl: contributed to study concept and design and data interpretation and drafting and revising the manuscript.
Dr Kimura: contributed to study concept and design and data interpretation and drafting and revising the manuscript.
Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
Role of sponsors: The content is entirely the responsibility of the authors, and sponsors had no role in design or conduct of the study.
Other contributions: We thank Kaoru Senzaki, RPSGT, for her help with polysomnogram scoring.

References

1. Ip MS, Lam B, Lauder IJ, et al. A community study of sleep-disordered breathing in middle-aged Chinese men in Hong Kong. *Chest*. 2001;119(1):62-69.
2. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med*. 1993;328(17):1230-1235.
3. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet*. 2005; 365(9464):1046-1053.
4. Dhillon S, Chung SA, Fargher T, Huterer N, Shapiro CM. Sleep apnea, hypertension, and the effects of continuous positive airway pressure. *Am J Hypertens*. 2005;18(5 pt 1): 594-600.
5. Babu AR, Herdegen J, Fogelfeld L, Shott S, Mazzone T. Type 2 diabetes, glycemic control, and continuous positive airway pressure in obstructive sleep apnea. *Arch Intern Med*. 2005;165(4):447-452.
6. Zozula R, Rosen R. Compliance with continuous positive airway pressure therapy: assessing and improving treatment outcomes. *Curr Opin Pulm Med*. 2001;7(6):391-398.
7. Morgenthaler TI, Kagramanov V, Hanak V, Decker PA. Complex sleep apnea syndrome: is it a unique clinical syndrome? *Sleep*. 2006;29(9):1203-1209.
8. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep*. 1999;22(5):667-689.
9. Richman JS, Moorman JR. Physiological time-series analysis using approximate entropy and sample entropy. *Am J Physiol Heart Circ Physiol*. 2000;278(6):H2039-H2049.
10. Grassberger P, Procaccia I. Measuring the strangeness of strange attractors. *Physica D*. 1983;9(1-2):189-208.
11. Schreiber T, Schmitz A. Surrogate time series. *Physica D*. 2000;142(3-4):346-382.
12. Theiler J, Eubank S, Longtin A, et al. Testing for nonlinearity in time series: the method of surrogate data. *Physica D*. 1992;58(1-4):77-94.
13. Kaffashi F, Foglyano R, Wilson CG, et al. The effect of time delay on approximate & sample entropy calculations. *Physica D*. 2008;237(23):3069-3074.
14. Kerr AM. A review of the respiratory disorder in the Rett syndrome. *Brain Dev*. 1992;14(suppl):S43-S45.
15. Ogier M, Katz DM. Breathing dysfunction in Rett syndrome: understanding epigenetic regulation of the respiratory network. *Respir Physiol Neurobiol*. 2008;164(1-2):55-63.
16. Netzer NC, Strohl KP. Sleep and breathing in recreational climbers at an altitude of 4200 and 6400 meters: observational study of sleep and patterning of respiration during sleep

in a group of recreational climbers. *Sleep Breath*. 1999;3(3):75-82.
17. Eckert DJ, Jordan AS, Merchia P, Malhotra A. Central sleep apnea: pathophysiology and treatment. *Chest*. 2007;131(2):595-607.
18. Teichtahl H, Wang D. Sleep-disordered breathing with chronic opioid use. *Expert Opin Drug Saf*. 2007;6(6):641-649.
19. Pattinson KT. Opioids and the control of respiration. *Br J Anaesth*. 2008;100(6):747-758.
20. Leung RS, Bradley TD. Sleep apnea and cardiovascular disease. *Am J Respir Crit Care Med*. 2001;164(12):2147-2165.
21. Bradley TD, Floras JS. Sleep apnea and heart failure: part II: central sleep apnea. *Circulation*. 2003;107(13):1822-1826.
22. Caples SM, Garcia-Touchard A, Somers VK. Sleep-disordered breathing and cardiovascular risk. *Sleep*. 2007;30(3):291-303.
23. Hardavella G, Stefanache F, Ianovici N. Cheyne stokes respiration in stroke patients. *Rev Med Chir Soc Med Nat Iasi*. 2006;110(1):82-87.
24. Cherniack NS, Longobardo G, Evangelista CJ. Causes of Cheyne-Stokes respiration. *Neurocrit Care*. 2005;3(3):271-279.
25. Ayappa I, Rapoport DM. The upper airway in sleep: physiology of the pharynx. *Sleep Med Rev*. 2003;7(1):9-33.
26. Patil SP, Schneider H, Marx JJ, Gladmon E, Schwartz AR, Smith PL. Neuromechanical control of upper airway patency during sleep. *J Appl Physiol*. 2007;102(2):547-556.
27. Younes M. Contributions of upper airway mechanics and control mechanisms to severity of obstructive apnea. *Am J Respir Crit Care Med*. 2003;168(6):645-658.
28. Cherniack NS. Respiratory dysrhythmias during sleep. *N Engl J Med*. 1981;305(6):325-330.
29. Gilmartin GS, Daly RW, Thomas RJ. Recognition and management of complex sleep-disordered breathing. *Curr Opin Pulm Med*. 2005;11(6):485-493.
30. Thomas RJ, Mietus JE, Peng CK, et al. Differentiating obstructive from central and complex sleep apnea using an automated electrocardiogram-based method. *Sleep*. 2007;30(12):1756-1769.
31. Pusalavidyasagar SS, Olson EJ, Gay PC, Morgenthaler TI. Treatment of complex sleep apnea syndrome: a retrospective comparative review. *Sleep Med*. 2006;7(6):474-479.

解　説

閉塞性睡眠時無呼吸症候群の病態生理と診断

The pathophysiology of obstructive sleep apnea

特集

山内　基雄　　木村　弘*
YAMAUCHI Motoo　　*KIMURA Hiroshi*

睡眠呼吸障害と全身性疾患　Key words　閉塞性睡眠時無呼吸症候群　病態生理　上気道虚脱性　ループゲイン

上気道が虚脱することが閉塞型無呼吸の基本病態である．しかしながら一般的に上気道の虚脱は覚醒時には起こらず，睡眠することで観察される事象である．覚醒相から睡眠相に移行することによって増す上気道の虚脱性に対し，解剖学的な上気道形態はもちろんのこと，上気道開大筋群の代償機構，反射機構，さらには呼吸中枢の不安定性などが複雑に絡み合い，上気道の開存性が決定される．そしてその複雑性は個々の遺伝的背景や併存する疾患などによって異なる．また近年，繰り返される無呼吸による間歇的低酸素曝露がこのような上気道開存の代償機構や調節機構を修飾することも報告されている．このように，多面的にOSASの病態生理の研究が積み重ねられてきているものの，その病態生理はいまだ完全には理解されていない．さらに経鼻的持続陽圧呼吸療法(CPAP)の登場以来，OSASの治療効果は飛躍的に向上したが，いまだ十分であるとは言い難い．OSASの病態生理の完全な解明なくして，OSASの完全な治療コントロールは不可能である．ここでは，最新の知見を含めながらOSASの病態生理とその診断について概説する．

OSASの病態生理

1．解剖学的上気道形態

一般的に，健常人に比較してOSASでは解剖学的上気道径が小さい[1]．その原因として，上気道周囲の軟部組織沈着，頭蓋顔面形態，舌容積などが考えられている．なかでも肥満による咽頭周囲への軟部組織の沈着は，上気道径に影響する最も重要な因子である．非肥満者に多く見られるOSASはわが国の特徴であるが，その場合は頭蓋顔面形態が重要な因子となる．これらは，アジアと欧米諸国では肥満度が明らかに違うのにもかかわらずOSASの有病率はほぼ同じであることを説明しうる[2][3]．

2．上気道虚脱性

一般的に無呼吸は覚醒時には観察されず，睡眠時にのみ観察されることから考えても，解剖学的な上気道狭小化だけでOSASの病態が説明できないことは明らかである．すなわち，吸気時に伴

奈良県立医科大学内科学第二講座　*教授

0371-1900/11/¥50/頁/JCOPY