睡眠時無呼吸症候群における不眠とその訴え

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abstract

睡眠時無呼吸症候群には無呼吸中に呼吸努力が存在する閉塞型と呼吸努力がみられない中枢型がある．また，心不全患者に多くみられるチェーンストークス型呼吸も中枢型の一つと考えられる．閉塞型無呼吸の場合，無呼吸による低酸素血症のほか，呼吸努力による胸腔内圧陰圧度の上昇が覚醒を誘導し，呼吸再開が起こることが多いが，チェーンストークス型呼吸の場合，覚醒は無呼吸解除後の過呼吸中に起こることが多いとされる．閉塞型無呼吸患者は短期覚醒があっても不眠を訴える頻度は，特に重症例では少ない．チェーンストークス型呼吸は一般的に不眠を訴えることが多い．閉塞型，チェーンストークス型呼吸とも夜間の頻回の覚醒は日中の過度の眠気などの症状を起こすことが多いが，それぞれ特徴的な症状を示すこともある．明らかな無呼吸を示さないが，いびきを伴う上気道症候群も不眠を訴え，日中の過度の眠気を訴えることが多いとされる．

I はじめに

睡眠時無呼吸には無呼吸中にも呼吸努力はあるが，気道閉塞または狭窄のため，無呼吸-低呼吸が起こる閉塞型睡眠時無呼吸（obstructive sleep apnea：OSA）と無呼吸中に呼吸努力がみられない中枢型睡眠時無呼吸（central sleep apnea：CSA）がある．通常，1時間に5回以上の睡眠時無呼吸-低呼吸があり，日中の過度の眠気（execessive daytime sleepiness：EDS）などの臨床症状があれば，睡眠時無呼吸症候群（sleep apnea syndrome：SAS）と診断される[1]．CSA後に呼吸が漸増，漸減するチェーンストークス型呼吸（Cheyne-Stokes Breathing：CSB）は米国睡眠アカデミーではCSAと別個に扱われているが[1]，本邦ではCSBもCSAの1種類として扱われることが多い．OSA，CSBともその呼吸に伴い覚醒を伴い不眠を訴えることがあり，いずれの無呼吸も共通症状を示すこともあるが，覚醒が起こる機序には違いもみられ，不眠に伴う訴えにも差異がみられることも多い．また，OSAは認めないが，いびきを伴うことが多い閉塞型呼吸が覚醒を誘発し，短期覚醒により日中の症状をきたす上気道症候群の存在を認める場合もある[2]．

II OSA

OSAは無呼吸時間が延びれば低酸素血症，高二酸化炭素血症も高度になる．また，同時に気道が閉塞しているため呼吸努力により無呼吸時間が延びれば胸腔内の陰圧度も強くなる．この血液ガスの悪化と呼吸努力（胸腔内陰圧度）の増加が覚醒反応（図1）を起こすと考えられている．なお，この胸腔内陰圧度の強さが日中の過度の眠気に関連するとも報告されている．OSAにみられる覚醒反応は短期覚醒（arousals）であることが多く（arousalsであっ

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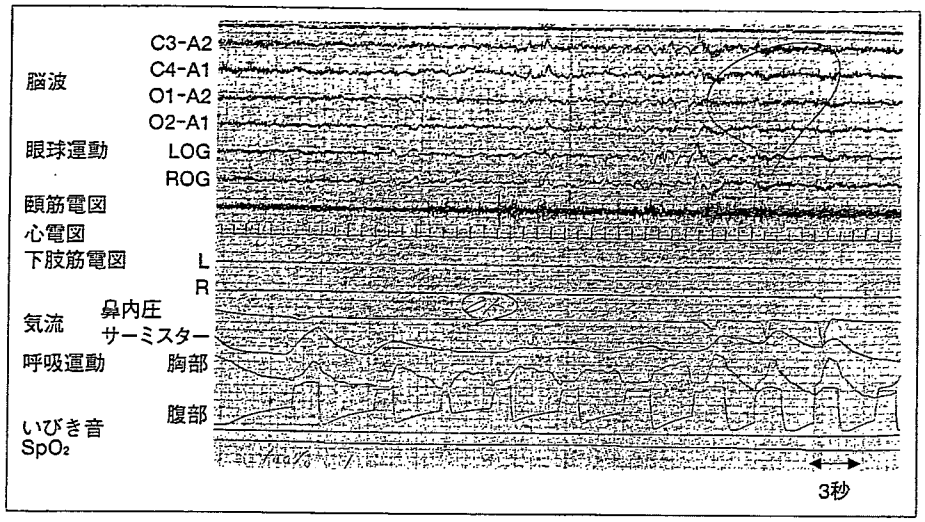

図1
閉塞型睡眠時無呼吸症候群患者のポリソムノグラフィー
閉塞型無呼吸（OA）に続いて短期覚醒（○印）がみられている．
（大阪回生病院提供）

表1　閉塞型睡眠時無呼吸症候群にみられる症状

よくみられる症状（60%以上の頻度）
1. 大きないびき
2. 日中の過度の傾眠
3. 家族による無呼吸の確認
4. 夜間の窒息感，息切れ
5. 睡眠中の多動
6. 睡眠後の壮快感の消失
7. 夜間の多尿

ときどきみられる症状（10～60%の頻度）
8. 性格の変化
9. 早朝の頭痛
10. 夜間の寝汗
11. 夜尿症
12. 性機能低下

まれにみられる症状（10%以下）
13. 頻回の覚醒と不眠
14. 夜間の咳
15. 逆流性食道炎の症状

〔参考文献4）より引用改変〕

てawakeningでない），特に重症例では不眠症状の頻度が高くならない原因となっている可能性がある．ただし，短期覚醒が増えると全睡眠時間（total sleep time）が減り，stage 1の睡眠が増えるとの報告がある[3]．一般的に重症患者では上記のように不眠の頻度は高くはないが，短期覚醒，無呼吸中の呼吸努力，無呼吸解除後の過大呼吸などの影響と考えられるEDSを含めたさまざまな症状（訴え）が出現すると考えられる（表1）[4, 5]．

CSB

心不全患者に伴うCSBは循環時間遅延とO_2，CO_2の化学受容体との関連によって説明されているが[6]，CSBに伴う覚醒はOSAのように呼吸再開直前ではなく，呼吸が再開された後の過呼吸期であるとされる[7, 8]．CSBの記述はHarrisonらによって最初に記述されている．彼らはCSBが睡眠開始時に最も高頻度に出現し，CSBの過呼吸時に覚醒が起こり，この覚醒時に患者はしばしば突然の呼吸困難に襲われる．また，日中に低酸素血症を示していなくてもCSB中には有意な程度に低酸素血症になると報告し，夜間の頻回の低酸素血症と突然の呼吸困難が心不全患者の疲労の伸展に関与しているとしている（図2）[9]．このようにCSB患者の睡眠は過呼吸中に覚醒し不眠を訴えることが多い．しかしながら，日中にEDSを訴える頻度はOSAに比較して低い．CSB患者の45%にいびきがあるとされ，心不全患者はOSAとCSBを合併していることが多い．この場合，睡眠開始時にはOSAが出て，睡眠時間の経過とともにCSBが出現してくるとの報告もある[10]．

CSB時にも無呼吸による低酸素血症などの血液ガスの悪化のほかに過呼吸中の覚醒時に交感神経の緊張が高まることが報告されている．心不全患者のCSBにおいて覚醒，不眠，浅睡眠期の増加が確認されている．このようなCSBによる夜間覚醒，不眠，交感神経緊張はEDS，日中の疲労感を増すばかりで

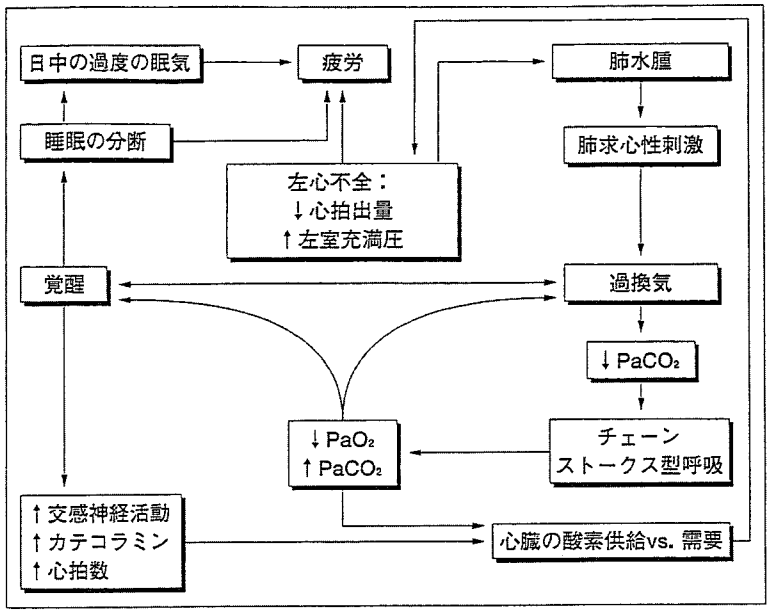

図2
心不全におけるチェーンストークス型呼吸（CSB）の病態生理図
心不全自体がCSBの発症の因子になっている．CSBは低酸素，交感神経活動亢進などにより，心筋に悪影響をもたらす．さらに，覚醒反応は睡眠を分断し，不眠をまねき，疲労をもたらす．

はなく，特に交感神経系の緊張は予後を悪化させると考えられている[7]．

Ⅳ 高齢化の問題

OSAの頻度は年齢とともに増加し，65歳以上での頻度は30～64歳に比して2～3倍になるとされている[11]．しかしながら，65歳以上で頻度の増加はみられないとされる．高齢者のそれ以下に比べて重症患者の頻度が低下し，高齢に伴いCSAの頻度が増すと報告されている．高齢者のSASの不眠にOSAの減少とCSAの増加が関与している可能性はあるが，詳細は明らかでない．

Ⅴ 上気道抵抗症候群[2]

上気道抵抗症候群は，睡眠中の上気道の狭窄により，①閉塞型の無呼吸はないが，気流制限があり，②酸素飽和度も変動するが，およそ92%以上は保たれ，③頻回の覚醒を伴い，④日中の過度の眠気と疲労を訴えるとされている[2), 12)]．OSAの一亜系と考えられ，その独立疾患としての異議を唱える意見もある[13]．最近のGuilleminaultらの報告では，94人（女性68人）の上気道抵抗症候群患者の初診時には睡眠開始時の不眠が5.3%，継続した不眠が32%，抑うつ気分（depressed mood）が7.4%であったが，未治療のまま平均54.2カ月（43～69カ月）経過後には，それぞれ，53.2%，85%，50%に著増したと報告されている[12]．

Ⅵ おわりに

OSAの短期覚醒（arousals）は不眠（awakening）につながる場合とつながらない場合があるが，不眠を訴えなくてもEDSなどの日中の症状が強い場合も多く，不眠の訴えと日中の症状の関連について明らかにできない場合も多い．心不全患者のCSBによる不眠が，経鼻持続陽圧呼吸（CPAP），酸素療法などによりいかに変化したかの知見は乏しい．また脳卒中後および高齢者不眠に対するSASの関与度およびこの睡眠呼吸障害による夜間の不眠が，日中の症状（訴え）の影響に関しての報告も乏しく，今後の臨床研究の課題と考えられる．

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Association of Sleep-Disordered Breathing and Ventricular Arrhythmias in Patients Without Heart Failure

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The prevalence and characteristics of sleep-disordered breathing (SDB) in patients with ventricular arrhythmias, such as premature ventricular complexes and ventricular tachycardia, are unknown. Therefore, this study was conducted to evaluate the prevalence of SDB in patients with severe ventricular arrhythmias and normal left ventricular (LV) function. Thirty-five patients (63% men, mean age 57.4 ± 13.8 years) underwent a sleep study. All patients had ventricular tachycardia or frequent premature ventricular complexes (≥300/hour) and had been referred to the cardiology department for medication, catheter ablation therapy, or the implantation of a cardioverter-defibrillator. Patients with heart failure with LV ejection fractions <50% were excluded; in the remaining patients, the mean LV ejection fraction was 63.9 ± 8.0%. Twenty-one patients (60%) had SDB with apnea-hypopnea indexes ≥5/hour, and the average apnea-hypopnea index was 22.7 ± 17.9/hour. Twelve patients (34%) had moderate to severe SDB, with an average apnea-hypopnea index of 33.6 ± 16.6/hour. Central dominant sleep apnea was evident in 3 patients with SDB. The average age and body mass index were significantly higher in patients with SDB than in those without SDB (age 62.0 ± 12.8 vs 50.6 ± 12.7 years, body mass index 26.3 ± 4.0 vs 21.2 ± 2.0 kg/m^2). In conclusion, this study found a high prevalence of SDB in patients with ventricular arrhythmias and normal LV function. **(Am J Cardiol 2008;xx:xxx)**

Some previously reported studies that analyzed the occurrence of sleep-disordered breathing (SDB) with ventricular arrhythmias involved only patients with heart failure.[1–3] In patients with heart failure, ventricular arrhythmias occur frequently not only because of SDB but also because of cardiac dysfunction itself, resulting in sympathetic nerve activity.[4] Other studies have reported a high occurrence of ventricular arrhythmias in patients with SDB.[5,6] We tested the hypothesis that patients with ventricular arrhythmias are more likely to have SDB even without heart failure. We studied 35 patients with ventricular arrhythmias who did not have major co-morbid disorders that could contribute to sleep disruption or desaturation. This study examined the prevalence and severity of SDB in patients having ventricular arrhythmias without heart failure.

Methods

Study population: We prospectively studied consecutive patients referred to the Cardiology Department of Tsukuba University Hospital, Tsukuba, Japan, from December 2005 and September 2007 who had ventricular tachycardia (VT) or frequent premature ventricular complexes (PVCs). Patients were referred for the following reasons: (1) the need for medication to control VT or frequent PVCs, (2) electrophysiologic study or catheter ablation therapy for VT or frequent PVCs, or (3) the implantation of a cardioverter-defibrillator for VT. Patients were excluded from enrollment if they had any of the following conditions: a left ventricular ejection fraction <50% by echocardiography, primary severe valvular heart disease, obstructive lung disease, pharyngeal disease, renal disorders, clinical signs of central or peripheral nervous system impairment, or history of stroke. Thirty-five patients (63% men, mean age 57 ± 14 years, mean ejection fraction 64 ± 8%) met the entry criteria. The initial assessment included routine blood tests, 12-lead electrocardiography, and echocardiography. Hypertension was defined as the presence of ≥1 of the following conditions: systolic blood pressure at rest ≥135 mm Hg, diastolic blood pressure at rest ≥80 mm Hg, or treatment with antihypertensive medication. Hyperlipidemia was defined as total cholesterol ≥220 mg/dl or low-density lipoprotein ≥150 mg/dl, the use of lipid-lowering therapy, or a documented diagnosis of hyperlipidemia. Diagnoses of diabetes mellitus and other prevalent chronic diseases were recorded according to clinical histories and the use of specific medications, as revealed by review of the patients' charts.

Written informed consent was obtained from all subjects, and the study protocol was approved by the ethics committee of the University of Tsukuba.

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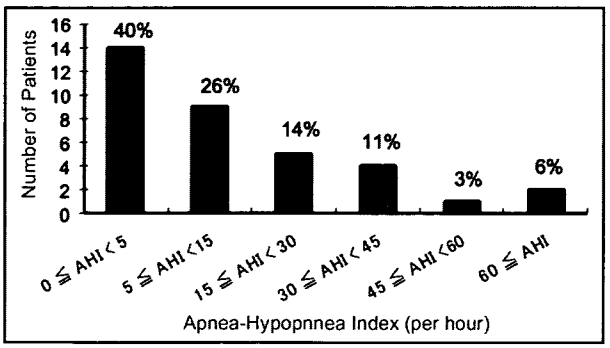

Figure 1. Frequency distribution of AHI in 5/hour- to 15/hour-unit intervals in 35 patients with ventricular arrhythmias. Fourteen patients (40%) showed no evidence of SDB, whereas 21 patients (60%) had SDB with AHIs ≥5/hour.

Arrhythmia analysis: Isolated and grouped ventricular ectopic activities were analyzed. VT was defined as ≥3 consecutive PVCs at a rate >100 beats/min. Frequent PVCs were defined as >300 PVCs/hour on 24-hour Holter electrocardiography. Day-night patterns of ventricular arrhythmias were evaluated by 24-hour Holter electrocardiography or bedside monitoring records in the hospital. Day was defined as 6 AM to 9 PM and night as 9 PM to 6 AM.

Polysomnography: Sleep evaluations of all 35 subjects were conducted by a sleep specialist at the Tsukuba University Hospital sleep disorder center. All subjects had undergone standard sleep studies, which were performed by monitoring of electroencephalography, electro-oculography, electromyography, electrocardiography, thoracoabdominal excursions, pulse oximetry, and naso-oral airflow with an Alice 4 (Respironics, Pittsburgh, Pennsylvania).

Apnea was defined as the cessation of inspiration for ≥10 seconds. All such events were counted irrespective of the degree of oxygen desaturation or presence of arousal. Obstructive apnea was defined as the absence of airflow in the presence of rib cage and/or abdominal excursions. Central apnea was defined as the absence of rib cage and abdominal excursions with the absence of airflow. Hypopnea was defined as a reduction in airflow of ≥30% with a decrease in oxygen saturation (SaO_2) of ≥4% for ≥10 seconds in the presence of thoracoabdominal ventilatory efforts. The apnea-hypopnea index (AHI) was calculated as the sum of apneic and hypopneic events per hour of sleep.[7] The diagnosis of central sleep apnea required an AHI ≥5/hour, with ≥50% of the events determined to be central rather than obstructive. We used an AHI of 5/hour as the threshold. Mild SDB was defined as 5/hour ≤AHI <15/hour, moderate SDB was defined as 15 ≤AHI <30/hour, and severe SDB was defined as AHI ≥30/hour.

Epworth sleepiness scale (ESS): The ESS is a frequently used, 8-item, self-administered subjective measure of sleepiness. A subject rates, on a scale of 0 to 3, the likelihood that he or she will doze off or fall asleep during 8 different situations commonly encountered in daily life. Scores are tallied across the 8 items to compute an ESS score; an ESS score ≥11 is considered indicative of subjective sleepiness. This scale has previously shown a high level of internal consistency among its 8 items, high test-retest reliability, and the ability to distinguish patients with excessive daytime sleepiness from normal subjects.

Statistical analysis: Results are expressed as mean ± SD. Comparisons of continuous variables between groups were made with unpaired Student's *t* tests when appropriate and otherwise with the Mann-Whitney test. Categorical variables were compared using Fisher's exact test or the chi-square test, depending on which was more appropriate. A p value <0.05 was considered significant.

Results

The frequency distribution of the AHI in 5/hour- to 15/hour-unit intervals for the 35 patients with ventricular arrhythmia is depicted in Figure 1. Twenty-one of 35 patients (60%) had SDB, with mild SDB noted in 26% of patients (mean AHI 8.2 ± 2.5/hour), moderate SDB in 14% (mean AHI 21.8 ± 3.7/hour), and severe SDB in 20% (mean AHI 45.5 ± 16.0/hour).

The clinical characteristics of the 2 groups are listed in Table 1. The gender difference between patients with and without SDB was not statistically significant. Patients with SDB were older than those without SDB, and their body mass indexes (BMIs) and waist circumferences were significantly higher than those of patients without SDB. No statistical differences were noted in rates of obesity (BMI ≥30 kg/m^2), hypertension, diabetes mellitus, hyperlipidemia, and cardiac disease between the 2 groups. The mean ESS score was <11 in the 2 groups and was not statistically different between the 2 groups.

There was no difference in the type of ventricular arrhythmias and the day-night pattern of the arrhythmias between the groups, as listed in Table 2. The results of the sleep study are listed in Table 3. Comparison of patients with and without SDB showed that those with SDB had significantly increased arousal indexes and percentage SaO_2 <90% and significantly decreased mean and lowest SaO_2.

The clinical characteristics of the 12 patients with moderate to severe SDB are listed in Table 4. Three of these patients had predominantly central sleep apnea (mean central apnea AHI 17.0 ± 6.6/hour). Three patients had ventricular arrhythmia occurring during night rather than day.

Discussion

The novel findings of the present study are that approximately 60% of patients with ventricular arrhythmias had SDB. This is the first report to show a strong association between SDB and ventricular arrhythmias in patients without heart failure. Among such patients, mild SDB was diagnosed in 26% and moderate to severe SDB in 34%. To our knowledge, no data are available regarding the prevalence of SDB in patients with ventricular arrhythmias occurring without heart failure, although several previous studies showed a relation between SDB and ventricular arrhythmia complicated by heart failure.[1–3] Because impaired heart function increases sympathetic activity, resulting in ventricular arrhythmia,[4] heart failure is thought to exacerbate ventricular arrhythmia. However, the contribution of SDB to sympathetic activity in patients with ventricular arrhythmia and normal cardiac function has not

Table 1
Patient characteristics

Variable	SDB		p Value
	Yes (n = 21)	No (n = 14)	
Age (yrs)	62 ± 13	51 ± 13	0.01
Men	15 (71%)	7 (50%)	0.4
BMI (kg/m^2)	26.3 ± 4.0	21.2 ± 2.0	0.0003
No. with BMI ≥30 kg/m^2	4 (19%)	0 (0%)	0.1
Waist circumference (cm)	91 ± 12	78 ± 8	0.003
Systolic blood pressure (mm Hg)	122 ± 12	118 ± 13	0.2
Diastolic blood pressure (mm Hg)	69 ± 10	66 ± 10	0.2
Heart rate (beats/min)	64 ± 10	69 ± 11	0.09
Echocardiographic characteristics			
Left ventricular ejection fraction (%)	64.0 ± 8.2	63.6 ± 8.0	0.4
Mitral valve E/A ratio	0.9 ± 0.4 (n = 19)*	1.2 ± 0.5 (n = 13)*	0.09
Deceleration time (ms)	253 ± 62	225 ± 38	0.09
Cardiovascular disease risk factors			
Hypertension	6 (29%)	2 (14%)	0.4
Diabetes mellitus	1 (5%)	0 (0%)	1
Hyperlipidemia	2 (10%)	2 (14%)	1
≥20 pack-year smoking history	10 (48%)	6 (43%)	0.9
Cardiac disease manifestations			
Myocardial infarction	3 (14%)	2 (14%)	1
Angina pectoris	3 (14%)	1 (7%)	0.6
Atrial fibrillation	4 (19%)	1 (7%)	0.6
Medications at discharge			
Amiodarone	4 (19%)	2 (14%)	1
β blockers	10 (48%)	4 (29%)	0.3
Disopyramide	0 (0%)	1 (7%)	0.4
Pyridine hydrochloride	1 (5%)	0 (0%)	1
Mexiletine hydrochloride	1 (5%)	0 (0%)	1
Sotalol hydrochloride	1 (5%)	0 (0%)	1
ESS score	7.1 ± 3.6	6.0 ± 4.5	0.2
No. with ESS score ≥11	6 (29%)	2 (14%)	0.4

* Mitral valve A-wave velocity could not be measured in 2 of the patients with SDB and 1 patient without SDB because of chronic atrial fibrillation.

Table 2
Relation between ventricular arrhythmias and sleep-disordered breathing

Variable	SDB		p Value
	Yes (n = 21)	No (n = 14)	
Type of ventricular arrhythmia			
PVCs ≥300/hour	16 (76%)	10 (71%)	0.9
Couplet	3 (10%)	1 (7%)	0.6
VT	19 (91%)	14 (100%)	0.5
Day-night pattern of ventricular arrhythmia			
Day >night	12 (57%)	7 (50%)	0.7
Day = night	6 (29%)	5 (36%)	0.7
Day <night	3 (14%)	2 (14%)	1

Table 3
Polysomnographic characteristics in 30 ventricular arrhythmia patients with or without sleep-disordered breathing

Variable	SDB	
	Yes (n = 21)	No (n = 14)
AHI (n/h)	22.7 ± 17.9	1.3 ± 1.0
Central apnea (n/h)	3.3 ± 6.2	0.3 ± 0.4
Obstructive apnea (n/h)	7.5 ± 9.7	0.2 ± 0.4
Arousal index (n/h)	26.8 ± 12.0	12.3 ± 6.1
Nocturnal SaO_2	(n = 18)*	(n = 14)
Mean SaO_2 (%)	93 ± 3	96 ± 2
Lowest SaO_2 (%)	81 ± 9	89 ± 3
Percentage SaO_2 <90%	9 ± 16	0

* SaO_2 could not be detected in 3 patients with SDB because of frequent PVCs with bigeminal cycle through most of the night. Therefore, these patients were excluded from SaO_2 calculations.

been extensively discussed. In this study, all participants had clinically severe ventricular arrhythmias without heart failure.

Interestingly, there was no difference either in ESS score or the number of patients with ESS scores ≥11. This result showed that patients had no symptoms of daytime sleepiness even with SDB. Among subjects participating in the Sleep Heart Health Study (SHHS), although there was a strong association of AHI with self-reported sleepiness, most subjects with AHIs ≥5/hour did not report excessive sleepiness,[8] indicating that self-report measures may underestimate the severity of sleepiness in the setting of hypersomnolence.

Another novel finding of this study involved BMI in the patients with SDB; our patients had a mean BMI of 26.3 ±

Table 4
Demographics, left ventricular ejection fractions, and disordered breathing events in patients with ventricular arrhythmia with moderate to severe sleep-disordered breathing

Patient	Age (yrs)	Gender	BMI (kg/m^2)	Left Ventricular Ejection Fraction (%)	Day-Night Pattern of Arrhythmias	ESS	AHI (n/h)	Central Apnea (n/h)	Obstructive Apnea (n/h)	Arousal Index (n/h)	Mean SaO_2 (%)	Lowest SaO_2 (%)	Percentage SaO_2 <90%
1	36	M	34.7	75	Day < night	8	64	6	11	60	89	54	42
2	45	M	32.3	53	Day < night	12	24	1	6	18	88	75	6
3	49	M	22.4	62	Day = night	5	31	24	2	29	95	87	0
4	51	M	30.1	75	Day < night	6	33	1	22	30	95	75	8
5	62	M	28.0	62	Day > night	6	28	0	6	24	94	85	2
6	64	F	21.6	66	Day > night	12	23	1	6	31	89	82	5
7	68	F	23.7	52	Day > night	3	18	1	1	9	89	77	58
8	71	M	22.6	57	Day > night	7	19	11	1	25	94	82	2
9	74	F	27.8	80	Day = night	12	19	1	11	30	94	75	4
10	75	M	28.7	67	Day > night	5	30	15	7	32	97	89	0
11*	78	M	26.8	69	Day > night	11	61	3	34	47	—	—	—
12	78	M	25.5	62	Day = night	3	53	1	31	33	94	72	8

* SaO_2 in patient 11 could not be detected precisely because of frequent PVCs.

4.0 kg/m^2, with 19% having BMIs ≥30 kg/m^2. Compared with previous reports[9–11] from Western nations, data from patients with SDB in the present study revealed lower BMIs and a low rate of obesity. One report estimated the prevalence of obstructive sleep apnea in an Asian population.[12] Kim et al[13] reported that the prevalence of SDB in Korea was 27% in men and 16% and women, and the mean BMI was 26.5 ± 2.9 kg/m^2 in men and 26.9 ± 4.1 kg/m^2 in women. These are provocative results because obesity, a strong risk factor for SDB, is prevalent in white populations but is relatively uncommon in Asian countries.

In addition, 3 of the patients with SDB experienced ventricular arrhythmia more often at night than during the day, suggesting that conditions associated with SDB may lead to ventricular arrhythmias. Gami et al[14] reported that patients with SDB have a peak in sudden death from cardiac causes during the sleeping hours, which contrasts strikingly with the nadir of sudden death from cardiac causes during this period in subjects without SDB. In the present study, 1 of the patients without SDB was also found to have ventricular arrhythmia more often at night than during the day. This patient had an arousal index of 28.1/hour and an AHI of 18.1/hour when we estimated hypopnea as the occurrence of a ≥50% reduction in airflow lasting ≥10 seconds with an arousal. Interestingly, PVCs in this patient stopped synchronizing with arousal. No previous report has shown a relation between nocturnally occurring PVCs and arousal. This finding suggests that not only arterial desaturation but also arousal may be related to the occurrence of ventricular arrhythmias.

Previous studies have shown a relation between repetitive intermittent hypoxia and ventricular arrhythmias.[15,16] Alexander[17] reported that at high altitude, normal elderly subjects experienced increased heart rate and greater frequency of PVCs and VT when arterial SaO_2 reached 70%. Shepard et al[18] reported that in patients with SDB with SaO_2 <60%, a significant increase in PVC frequency was detected with decreasing SaO_2. In patients with SDB, they suggested that repetitive obstructions to normal breathing during sleep induce hypoxemia and hypercapnia, which (acting through the chemoreflexes) elicit increased sympathetic activity that induces ventricular arrhythmias.

Altered cardiovascular variability affects predominantly patients with moderate to severe sleep apnea.[19–24] In patients with SDB, ventilation and blood pressure increase substantially during hypoxic breathing. Peripheral chemoreceptors, which primarily respond to blood oxygen, are detected with high sensitivity in SDB. In patients with SDB, the chemoreflex appears to be a potent mechanism for sympathetic activation, overriding the combined restraining influences of increased blood pressure and increased ventilation. Enhanced chemoreflex sensitivity in SDB may explain the exaggerated sympathetic response during hypoxemic episodes, resulting in autonomic activity–dependent arrhythmias.[24–26]

Our study had several limitations. First, because of technical limitations, SaO_2 monitoring results of the patients with frequent PVCs were excluded because these data were thought to be underestimated. However, hypopnea could be analyzed by the occurrence of a ≥50% reduction in airflow lasting ≥10 seconds with an arousal. Second, the diagnosis

of sleep apnea was provided by a study based on a single night in a sleep laboratory. However, this is the standard procedure followed for the diagnosis of sleep apnea in the clinical setting. Third, there was no control group. However, compared with the previous epidemiologic studies,[12,13] the prevalence of SDB was revealed to be significantly high in this study.

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ORIGINAL ARTICLE

Demographic characteristics of 3,659 Japanese patients with obstructive sleep apnea–hypopnea syndrome diagnosed by full polysomnography: associations with apnea–hypopnea index

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Abstract Information on obstructive sleep apnea–hypopnea syndrome (OSAHS) in Japan has been limited. The purposes of this clinical study were to evaluate the demographic characteristics of Japanese OSAHS patients and to assess how demographic factors are associated with OSAHS severity. We analyzed 3,659 OSAHS patients who underwent polysomnographic evaluation between January 2000 and December 2004 at 11 hospitals in Niigata

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Prefecture, Japan. Data consisted of apnea–hypopnea index (AHI) and demographic characteristics, including sex, age, and body-mass index, for statistical analysis. Levels of obesity were classified according to the WHO criteria. The male-to-female patient ratio for OSAHS was 4.6, and male patients presented more severe OSAHS than female patients. High AHI and a high proportion of moderate to serious OSAHS (AHI≥15) were found among the patients in their 30s, as well as female patients in their 70s and male patients in their 80s. The AHI and the proportion of moderate-to-serious OSAHS (AHI≥15) were greater in patients classified as underweight than in normal weight patients. In conclusion, there is a higher male predominance in the prevalence of OSAHS, and in both sexes, the results suggest different pathophysiological mechanisms of deteriorating OSAHS between adults under age 55 and adults 55 years or over. In addition, underweight patients exhibit more severe OSAHS than normal weight patients.

Keywords Apnea–hypopnea index · Body-mass index · Demographic characteristics · Japanese · Obstructive sleep apnea–hypopnea syndrome · Polysomnography

Introduction

Obstructive sleep apnea–hypopnea syndrome (OSAHS) is a disorder characterized by repeated apneas and/or hypopneas and is known to increase the risk of hypertension, cardiovascular diseases, stroke, and mortality [1–4]. Waking after apnea or hypopnea disrupts the quality of sleep at night. Chronic sleep disturbance causes daytime sleepiness and decreased concentration associated with increased risk of motor-vehicle accidents [5, 6] and occupational accidents [7]. For these reasons, OSAHS is an issue of great concern in both clinical medicine and public health.

The severity of OSAHS is an important aspect of the disorder. The apnea–hypopnea index (AHI) reflects the severity of OSAHS. A person with AHI greater than or equal to 5 is diagnosed as having OSAHS, and a patient with AHI of 15 or over is considered to have a disorder associated with significant morbidities and should be treated with continuous positive airway pressure or surgery [8].

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Epidemiologic studies have found obesity to be a critical factor associated with the development or severity of OSAHS [2]. While most previous studies had been conducted in white populations, a few studies of Asian populations have suggested that the contribution of obesity to OSAHS may differ between whites and Asians [9], indicating the need for further epidemiologic and clinical research.

The aims of this clinical study were to examine the demographic characteristics of Japanese OSAHS patients and to assess how demographic factors, including sex, age, and body-mass index (BMI), are associated with severity of OSAHS.

Materials and methods

Patients

We targeted a total of 4,561 patients who were suspected to suffer from SAHS and underwent polysomnographic evaluation between January 2000 and December 2004 at 11 hospitals in Niigata Prefecture (population, 2.5 million), Japan. The 11 hospitals were the only hospitals in which polysomnography was available in Niigata Prefecture, a geographically defined area [10], and consequently almost all suspected SAHS patients in Niigata Prefecture were examined during the study period. Many of the 4,561 patients were referred to the selected hospitals from other hospitals and clinics in Niigata Prefecture. Of the 4,561 patients suspected of having SAHS, 3,788 were diagnosed with the sleep-disordered breathing with a comprehensive polysomnographic examination. Of the 3,788 SAHS patients, 60 patients were diagnosed with central SAHS (CSAHS), which is distinguished from OSAHS by a different pathophysiological mechanism, and excluded from the study. Of the 3,728 OSAHS patients, 50 patients under the age of 16, 18 patients whose age was unknown, and an abnormally undersized patient, were also excluded for the same reason. Ultimately, 3,659 OSAHS patients aged 16 and over were statistically analyzed for the study. The protocol for this study was approved by the Ethics Committee of Niigata University School of Medicine.

Diagnostic procedure

All patients underwent overnight polysomnographic evaluation (Sandman, Nellcor Puritan Bennett, Ottawa, Ontario, Canada, in four hospitals; Somnostar Pro, SensorMedics, Yorba Linda, CA, USA, in four hospitals; Somnostar Alpha, SensorMedics, Yorba Linda, CA, USA, in three hospitals; E series, Compumedics, Abbotsford, Victoria, Australia, in one hospital), which included electroenceph-

alogram (EEG), electromyogram, electrooculogram, electrocardiogram, airflow by oronasal thermistor, chest and abdominal wall movements, oxygen saturation (SaO_2) by pulse oximeter, snoring sounds by tracheal microphone, and body position. Patients were examined by a trained clinical technologist at each hospital using a standardized procedure. Sensors were attached to a patient before going to sleep at each hospital, and real-time data were collected overnight until the patient awoke in the morning. Using the Chicago Criteria [11], apnea was defined as the complete absence of oronasal airflow for at least 10s, and hypopnea was defined as a <50% decrease in oronasal airflow accompanied by a 3% fall in SaO_2 from baseline or an EEG arousal from sleep. Sleep-disordered breathing was assessed with the AHI, and lowest SaO_2 levels and cumulative percentage of sleep time with an SaO_2 level less than 90% (CT90%). A person with an AHI greater than or equal to 5 is generally diagnosed as having OSAHS. Patients with $5 \leq AHI < 15$, $15 \leq AHI < 30$, and AHI greater than or equal to 30 were classified as having mild, moderate, and serious OSAHS, respectively. Polysomnographic data of all patients obtained from each hospital were collected and entered in the database used for this study.

Other information

Information on sex, age, height, and weight was added to the database from patient medical charts. BMI was calculated by dividing weight (kilograms) by the square of height (square meters) for each patient. Levels of obesity were classified according to the WHO criteria [12] as follows: "underweight", $BMI < 18.5$; "normal weight", $18.5 \leq BMI < 25$; "preobese", $25 \leq BMI \leq 30$; class I, $30 \leq BMI < 35$; class II, $35 \leq BMI < 40$; and class III, $BMI \geq 40$. We further divided "normal weight" into "lower normal weight", $18.5 \leq BMI < 21.75$, and "upper normal weight", $21.75 \leq BMI < 25$, because too many (56%) OSAHS patients were classified as normal weight.

Statistical methods

Means and standard deviations were used to characterize continuous variables. AHI scores were skewed to higher values, and thus they were logarithmically transformed for statistical tests. Sex was coded as a dichotomous variable with "0" for male and "1" for female. Student *t* tests were performed to test for statistically significant differences between the mean values of two groups. The chi-square test was used to test independence of categorical data. Multiple linear regression analysis was used to test associations between log-transformed AHI as an outcome variable and predictor variables, including sex, age (a continuous variable), and BMI (a continuous variable). Statistical tests were performed using the SAS statistical package (release 8.02, SAS Institute, Cary, NC, USA). *P*-values of less than 0.05 were considered to be statistically significant.

Results

Demographic characteristics and AHI by sex are shown in Table 1. Male patients were significantly younger and had significantly higher average values in height, weight, and log-transformed AHI than female patients. The male-to-female patient ratio was 4.6. The database was incomplete, with some missing values for height, weight, and BMI. AHI ranged from 5 to 158 events per hour. Mean values of lowest SaO_2 and CT90% were 77.3% (SD 12.9, median 81.0) and 16.0% (SD 24.9, median 4.0), respectively. Mean values of apnea and hypopnea episodes were 25.7 events per hour (SD 24.7, median 16.6) and 8.6 events per hour (SD 9.0, median 6.4), respectively.

Distributions of patients' age by sex are shown in Fig. 1. The mode of the distributions was the 50- to 59-year age group in both sexes. The age distribution of females tended to shift to the right, and there were fewer female patients under 50 years of age than those aged 50 years or over. The percent frequency distributions of male and female patients

Table 1 Characteristics of 3,659 patients (≥16 years of age) with obstructive sleep apnea–hyponea syndrome (OSAHS)

	Male patients		Female patients	
	n	Mean (SD)	*n*	Mean (SD)
Age (years)	3,000	51.8 (13.5)	659	57.4 (12.8)
Height (cm)	2,811	168.0 (7.0)	611	153.0 (7.0)
Weight (kg)	2,805	75.6 (15.1)	612	63.0 (14.6)
Body-mass index (kg/m^2)	2,803	26.7 (4.5)	610	26.9 (5.9)
Apnea–hypopnea index (events/hour)	3,000	36.1 (25.1)	659	27.0 (23.9)
	Median	30.0	Median	18.8

Male patients were significantly younger ($P<0.0001$) and had significantly higher average values in height, weight, and log-transformed AHI than female patients ($P<0.0001$)

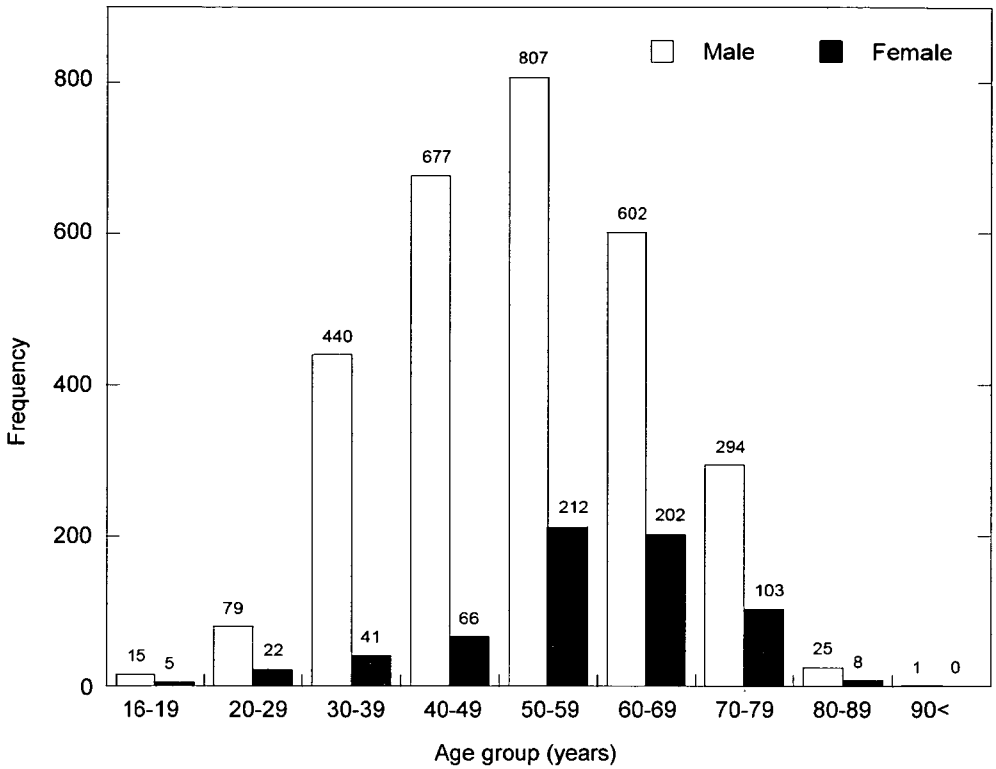

Fig. 1 Distributions of patients' age by sex. The mode of the distributions was the 50- to 59-year age group in both sexes. The percent frequency distributions of male and female patients were significantly different (χ^2=126.0, *df*=8, *P*<0.0001)

were significantly different (χ^2=126.0, *df*=8, *P*<0.0001). Distributions of patients' BMI by sex are shown in Fig. 2. The distributions for males tended to have higher kurtosis than females, and the percent frequency distributions of male and female patients were significantly different (χ^2=67.2, *df*=6, *P*<0.0001).

The numbers of OSAHS patients diagnosed at each of the three levels of AHI by sex are shown in Table 2. An

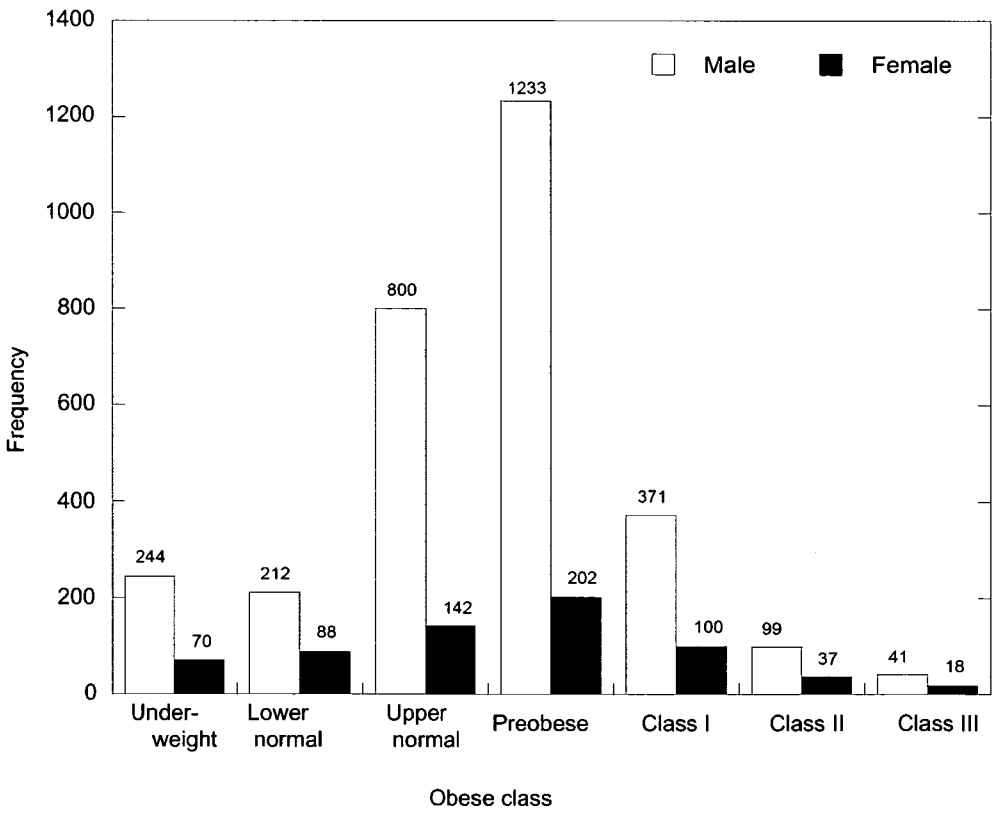

Fig. 2 Distributions of patients' body-mass index (BMI) by sex. Obesity was evaluated based on the WHO classification of BMI (underweight, <18.5; lower normal, 18.5≤BMI<22.25; upper normal, 22.25≤BMI<25; preobese, 25≤BMI<30; class I, 30≤BMI<35; class II, 35≤BMI<40; and class III, BMI≥40). The mode of the distributions was in the "preobese" group in both sexes

Table 2 Number of patients with obstructive sleep apnea–hypopnea syndrome according to levels of apnea–hypopnea index (AHI) by sex

Sex	5≤AHI<15	15≤AHI<30	30≤AHI	Total	Proportion of 15≤AHI (%)
Male	757	740	1,503	3,000	74.8
Female	277	184	198	659	58.0

$\chi^2=103.2$, $df=2$, $P<0.0001$

AHI greater than or equal to 15 was found in 74.8% of male patients, in 58.0% of female patients, and in 71.8% of patients overall. The percent frequency of patients with AHI greater than or equal to 30 was higher in males than in females, whereas the proportion of patients with AHI less than 15 was significantly lower for males than females ($\chi^2=103.2$, $df=2$, $P<0.0001$). Absolute numbers of OSAHS patients grouped according to the three levels of AHI and age group by sex are shown in Table 3. The proportion of patients with AHI greater than or equal to 15 tended to be lower in the 16- to 19-year age group (60.0%) than the other age groups (70.9–100%) among male patients ($\chi^2=37.6$, $df=16$, $P=0.0017$), and lower in the 16- to 19-year age group (20.0%) and 80- to 89-year age group (25.0%) than the other age groups (40.9–69.9%) among female patients ($\chi^2=26.5$, $df=14$, $P=0.0223$). The frequency of moderate-to-serious OSAHS (AHI≥15) did not increase with increasing years of age. The numbers of OSAHS patients according to the three levels of AHI and obese class by sex are shown in Table 4. The proportion of patients with AHI greater than or equal to 15 increased with higher obese class with the exception of the "underweight" group for both male and female patients.

Table 3 Number of patients with obstructive sleep apnea–hypopnea syndrome according to levels of apnea–hypopnea index (AHI) and age group by sex

Age group	5≤ AHI<15	15≤ AHI<30	30≤ AHI	Proportion of 15≤AHI (%)
Male ($\chi^2=37.6$, $df=16$, $P=0.0017$)				
16–19	6	5	4	60.0
20–29	40	30	9	71.2
30–39	99	87	254	77.5
40–49	168	155	354	75.2
50–59	235	209	363	70.9
60–69	143	165	294	76.2
70–79	63	80	151	78.6
80–89	3	8	14	88.0
>90	0	1	0	100.0
Female ($\chi^2=26.5$, $df=14$, $P=0.0223$)				
16–19	4	1	0	20.0
20–29	13	3	6	40.9
30–39	13	12	16	68.3
40–49	29	19	18	56.1
50–59	107	53	52	49.5
60–69	74	61	67	63.4
70–79	31	34	38	69.9
80–89	6	1	1	25.0

Associations between demographic variables and AHI as a continuous variable were analyzed. Mean values of log-transformed AHI according to age groups were plotted by sex in Fig. 3. In both sexes, separate peaks in the log-transformed AHI occurred before and after the 50- to 59-year age group. Among males, these peaks occurred in the 30- to 39- and 80- to 89-year age groups, and peaks appeared among female patients in the 30- to 39- and 70- to 79-year age groups. Mean values of log-transformed AHI according to obese class were plotted by sex in Fig. 4. Beginning with the "upper normal" group, the log-transformed AHI increased as obese class rose in both sexes. Multiple linear regression analysis showed that sex ($\beta=0.394$, $R^2=0.035$, $P<0.0001$), age ($\beta=0.00509$, $R^2=0.003$, $P<0.0001$), and BMI ($\beta=0.0662$, $R^2=0.138$, $P<0.0001$) were independently associated with the log-transformed AHI.

Because two peaks of the log-transformed AHI were seen before and after the 50- to 59-year age group (Fig. 3), we supposed that patients above and below 55 years of age might have different pathophysiological mechanisms and thus chose to analyze the relative contributions of sex, age, and BMI to the log-transformed AHI for the two groups separately. The results of multiple linear regression analysis are shown in Table 5. The R^2 value of BMI for this was 2.6 times larger than that for patients' age 55 years and over.

Discussion

This study revealed interesting demographic findings in relation to AHI. We found two peaks in the log-transformed AHI and in the proportion of moderate-to-serious OSAHS (AHI≥15) associated with age. These findings suggest that different pathophysiological mechanisms may be at work in patients under and over 55 years of age. Obesity is known to be an important causal factor of OSAHS [2]. Our data showed that the contribution of BMI to AHI was lower in older patients than in younger patients, suggesting that OSAHS in the elderly may be associated less with BMI and more with other unknown factors as compared with younger populations. Tishler et al. [13] similarly found that

Table 4 Number of patients with obstructive sleep apnea–hypopnea syndrome according to levels of apnea–hypopnea index (AHI) and obese class (WHO classification) by sex

Obese class	5≤AHI<15	15≤AHI<30	30≤AHI	Proportion of 15≤AHI (%)
Male (χ^2=309.6, *df*=12, *P*<0.0001)				
Underweight (BMI<18.5)	82	65	97	66.4
Lower normal (18.5≤BMI<21.75)	90	70	52	57.5
Upper normal (21.75≤BMI<25)	271	250	279	66.1
Preobese (25≤BMI<30)	261	284	688	78.2
Class I (30≤BMI<35)	41	57	273	88.9
Class II (35≤BMI<40)	12	12	75	87.9
Class III (40≤BMI)	0	1	40	100.0
Female (χ^2=75.6, *df*=12, *P*<0.0001)				
Underweight (BMI<18.5)	29	18	23	58.6
Lower normal (18.5≤BMI<22.25)	49	31	8	44.3
Upper normal (22.25≤BMI<25)	74	39	29	47.9
Preobese (25≤BMI<30)	90	54	58	55.4
Class I (30≤BMI<35)	28	30	42	72.0
Class II (35≤BMI<40)	4	8	25	89.2
Class III (40≤BMI)	2	4	12	88.9

the effects of BMI on the incidence of sleep-disordered breathing diminish with increasing age.

In this study, we propose a few hypotheses on factors that might explain OSAHS in elderly people. First, coexisting central apnea/hypopnea may contribute to OSAHS as some patients diagnosed with OSAHS by polysomnography have central and mixed apnea/hypopnea events. Bixler et al. [14] showed that central events are observed exclusively in middle-aged and elderly people (reflecting a normal aging process). When we compared the proportion of patients with 10% or more nonobstructive events in polysomnographic data, patients 55 years and older had a significantly higher proportion (*P*=0.0022) than those less than 55 years (36.4 vs 31.6%, data not shown in the "Results" section). Therefore, latent central apnea/hypopnea may influence the severity of OSAHS in the elderly. Secondly, a relative increase in mouth breathing to nasal breathing in the elderly may contribute to progression of OSAHS. Gleeson et al. [15] reported that an age-related decrease in nasal ventilation due to nasal obstruction was

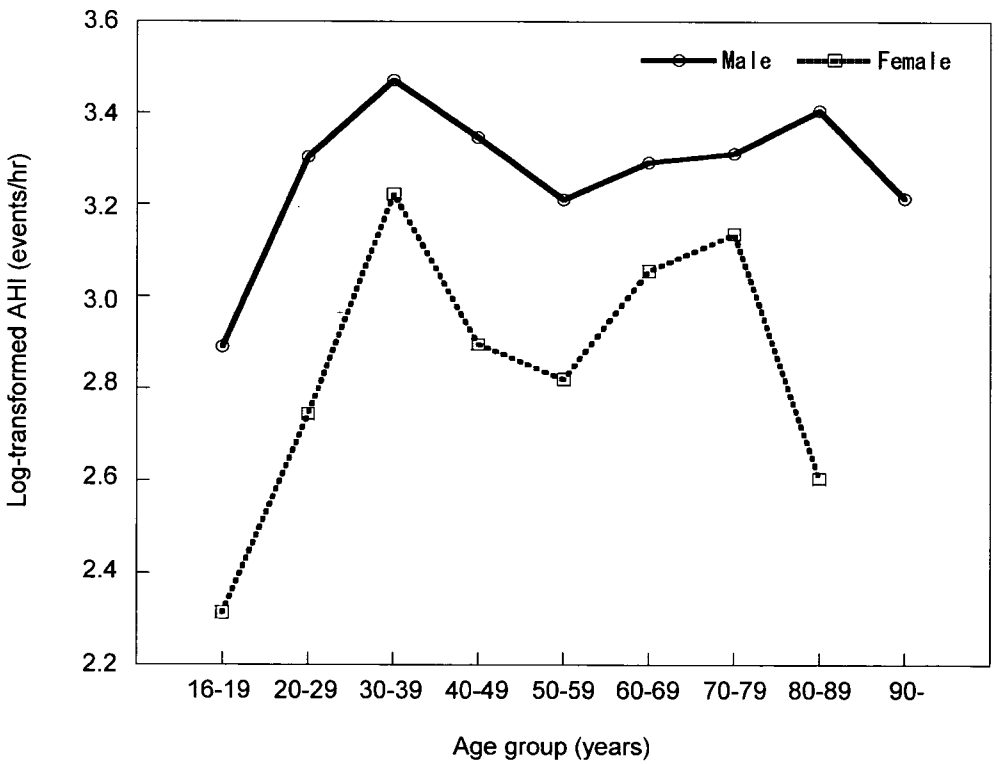

Fig. 3 Mean values of log-transformed apnea–hypopnea index (AHI, events/hour) in 10-year age groups were plotted by sex. Overall, the mean values of log-transformed AHI were higher in male patients than in female patients. Two peaks of the log-transformed AHI are seen before and after the 50- to 59-year age group in both sexes

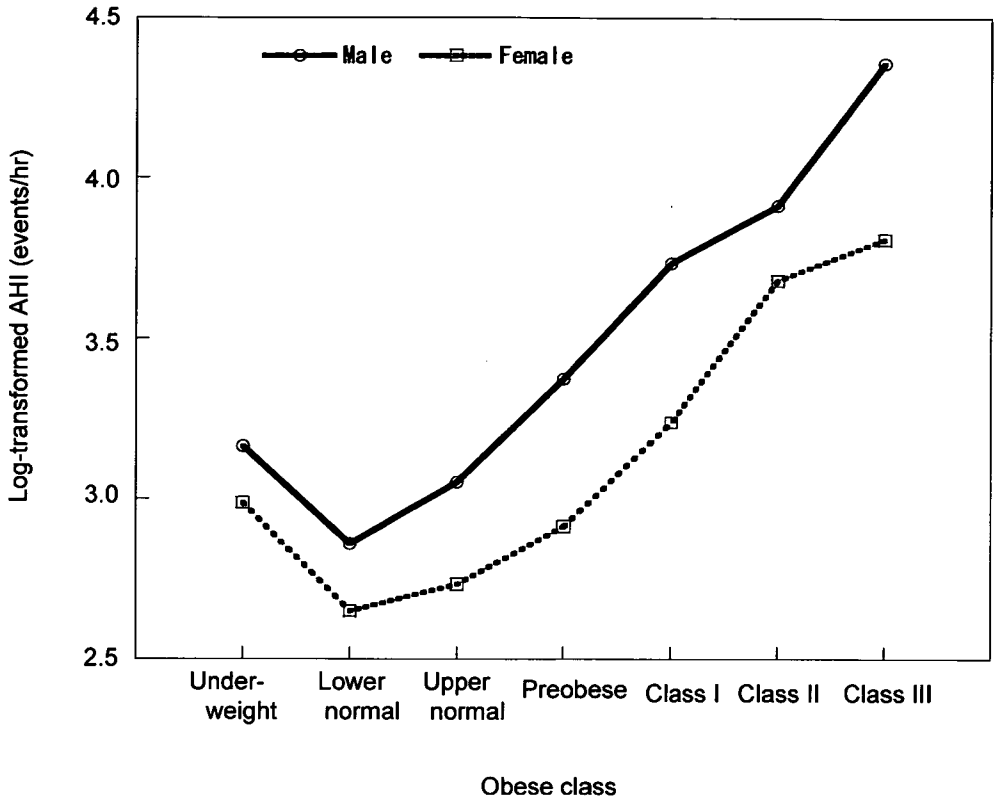

Fig. 4 Mean values of log-transformed apnea–hypopnea index (AHI, events/hour) in obese classes were plotted by sex. Obesity was evaluated using the WHO classifications for BMI (underweight, <18.5; lower normal, 18.5≤BMI<22.25; upper normal, 22.25≤BMI<25; preobese, 25≤BMI<30; class I, 30≤BMI<35; class II, 35≤ BMI<40; and class III, BMI≥ 40). The log-transformed AHI rises as obese class becomes higher beginning from the upper normal group in both sexes

associated with apneic episodes during sleep. Finally, Worsnop et al. [16] reported that falls in ventilation and activities of upper airway muscle functions and a rise in upper airway resistance during a transition from wakefulness to sleep are greater in older men than in younger men, and these age-related changes in upper airway physiology may be possible candidates for the "unknown" factor associated with OSAHS in the elderly. Further research is necessary to isolate factors contributing to OSAHS in the elderly.

Asians are generally slimmer than North American and European whites, and Asian OSAHS patients are reported to be less obese than white patients [17]. Nevertheless, our data showed that BMI remained a leading factor associated with high AHI. We also showed that the "underweight" group had higher AHI and a higher proportion of moderate-to-serious OSAHS (AHI≥15) patients of both sexes than the normal weight groups. This finding may be unique to Asian OSAHS patients, as nonobese Asian patients have been reported to exhibit relative narrowing of the upper airway due to craniofacial bony structure and the soft tissue of the naso- and oro-pharynx, which may be associated with the development of OSAHS [18, 19].

Among the demographic variables analyzed in this study, BMI can be lowered through lifestyle change, which in turn has the potential of lowering the AHI of OSAHS patients. A recent cohort study observed that weight loss in sleep-disordered patients decreased their AHI [20]. Our data suggest that weight loss could decrease the proportion of OSAHS patients with AHI greater than or equal to 15 in any obese-class group, with the exception of "underweight" and "normal weight" groups.

It is also known that OSAHS patients are predominantly male. In this study, the male-to-female patient ratio was 4.6:1, and male patients experienced more severe OSAHS than female patients, i.e., the proportion of OSAHS patients with AHI of 15 or above was significantly higher in males (74.8%) than in females (58.0%). Previous studies reported male-to-female patient ratios of 8:1 or more in clinic populations, and lower ratios of 2–3:1 in community samples [21–23], suggesting that there may be a disparity between clinic and community populations. The true male-

Table 5 The results of multiple linear regression analysis in patients above and below 55 years of age with the log-transformed apnea–hypopnea index (AHI) as the dependent variable

Independent variable	Regression coefficient	Standard error	R^2	*P*-value
Patients <55 years				
Sex	−0.484	0.053	0.035	<0.0001
Age	0.00373	0.00201	0.001	0.0633
BMI	0.0706	0.0034	0.182	<0.0001
Patients ≥55 years				
Sex	−0.315	0.041	0.034	<0.0001
Age	0.0108	0.0026	0.008	0.0340
BMI	0.0560	0.0045	0.071	0.0196

to-female patient ratio in the Japanese population may be lower than that obtained in this study, although accurate techniques were used to diagnose patients with OSAHS.

The age distribution of male OSAHS patients approximated a normal distribution with a mode of 50–59 years, yet most (80%) female patients were 50 years of age or older. This finding has been reported by several researchers. Young et al. [24] reported that changes in sex hormone economy during the menopausal transition increased incidence of sleep-disordered breathing in perimenopausal women. Shahar et al. [25] found that the incidence of sleep-disordered breathing in postmenopausal women who received hormone replacement therapy (HRT) was half of that in postmenopausal women who did not receive HRT. These data suggest that decreased estrogen levels may explain the increase of OSAHS patients among postmenopausal women.

A strength of this study was the use of full polysomnographic examination as the standard diagnostic tool of OSAHS. Moreover, we identified almost all OSAHS cases within a geographically defined area. Therefore, the subjects in this study were correctly classified, and selection bias was minimized. However, some limitations were observed in the study. First, we were not able to collect data for all OSAHS patients in Niigata Prefecture because there may have been patients with OSAHS who did not visit hospitals or clinics during the study period. For example, given the disparity between clinic and community populations, we may have underestimated female OSAHS patients and thus may have overestimated the male-to-female ratio. In addition, elderly OSAHS patients are less likely to visit hospitals or clinics, and thus we may have missed more elderly OSAHS patients as compared with younger patients. In our data, there were fewer elderly OSAHS patients compared to middle-aged patients even when a distribution of the population of Niigata Prefecture is taken into account. We calculated the period prevalence of OSAHS for males in their 30s, 40s, 50s, 60s, 70s, and 80s that would be calculated as 294, 423, 435, 412, 262, and 66 /100,000, respectively, although the prevalence of OSAHS has been reported to be similar between the middle-aged and the elderly ones in population-based studies [2]. This problem is a major limitation of the clinical study. There were also limitations in diagnostic procedure, which could lead to misclassification in the case definition. We used thermistors instead of nasal pressure transducers for polysomnography, and quality control over multiple centers was difficult to achieve. Finally, this study did not evaluate risk factors other than the specified demographic characteristics for OSAHS. Well-designed, population-based epidemiologic studies are needed to address these limitations.

Based on this study of 3,659 Japanese OSAHS patients, we conclude that: (1) the male-to-female patient ratio was 4.6:1, (2) different pathophysiological mechanisms of developing OSAHS are active in adults under 55 years as compared with adults 55 years and older, and (3)OSAHS in this population is more severe in underweight patients than in normal weight patients.

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