Sleep Breath (2013) 17:753–761
DOI 10.1007/s11325-012-0759-2

ORIGINAL ARTICLE

Measurement of dyspnea in patients with obstructive sleep apnea

Kensaku Aihara · Toru Oga · Chikara Yoshimura · Takefumi Hitomi · Yuichi Chihara · Yuka Harada · Kimihiko Murase · Yoshiro Toyama · Kiminobu Tanizawa · Tomohiro Handa · Tomomasa Tsuboi · Michiaki Mishima · Kazuo Chin

Received: 1 May 2012 / Revised: 9 July 2012 / Accepted: 23 July 2012 / Published online: 3 August 2012

Abstract
Purpose Patients with obstructive sleep apnea (OSA) frequently complain of exertional dyspnea. We aimed to assess its related factors and the significance of its measurement in OSA.
Methods We evaluated 301 subjects with suspected OSA for dyspnea during activities of daily living using the Medical Research Council (MRC) scale. We analyzed the relationships between MRC grades and various subjective and objective indices. Further, the relationship of disease severity based on the apnea/hypopnea index (AHI) with these indices was examined. Results were compared between those obtained using MRC grades and the AHI.
Results Of 301 subjects, 265 were diagnosed with OSA. Their MRC scores were worse than in non-OSA patients. Among OSA patients, 125 had MRC grade 1 (mild), 121 had MRC grade 2 (moderate), and 19 had MRC grade 3 or more (severe) dyspnea. Various measurements differed significantly between groups categorized according to the MRC scale although determinants between mild and moderate groups and between moderate and severe groups differed. AHI categorizations were not significantly related to patient-reported measurements such as the Medical Outcomes Study 36-item short form, Pittsburgh Sleep Quality Index, and Hospital Anxiety and Depression Scale scores, unlike categorization based on the MRC scale.
Conclusions Dyspnea is an important outcome in OSA although dyspnea in OSA patients is unrelated to the sleep disorder per se. Measurement of dyspnea in patients with OSA might provide further insights into the health of these patients and clinical manifestations of this disease.

Keywords Apnea/hypopnea index · Depression · Dyspnea · Health-related quality of life · Medical Research Council scale · Obstructive sleep apnea

Electronic supplementary material The online version of this article (doi:10.1007/s11325-012-0759-2) contains supplementary material, which is available to authorized users.

K. Aihara · Y. Chihara · Y. Harada · K. Murase · Y. Toyama · K. Tanizawa · T. Handa · M. Mishima
Department of Respiratory Medicine, Kyoto University Graduate School of Medicine,
54 Shogoin Kawahara-cho, Sakyo-ku,
Kyoto 606-8507, Japan

T. Oga (✉) · C. Yoshimura · T. Hitomi · K. Chin
Department of Respiratory Care and Sleep Control Medicine,
Kyoto University Graduate School of Medicine,
54 Shogoin Kawahara-cho, Sakyo-ku,
Kyoto 606-8507, Japan
e-mail: ogato@kuhp.kyoto-u.ac.jp

T. Tsuboi
Department of Respiratory Medicine, National Hospital Organization Minami-Kyoto Hospital,
11 Naka-ashihara,
Jōyō 610-0113, Japan

Introduction

Patients with obstructive sleep apnea (OSA) tend to complain of exertional dyspnea or exercise intolerance [1–3]. Snoring and observed apnea, which are characteristic manifestations of OSA, were correlated with dyspnea during activities of daily living [4]. However, whether exertional dyspnea is an outcome of OSA itself or of comorbid conditions with OSA is not known. Whether measurement of dyspnea is useful in OSA is also not known. Nocturnal intermittent hypoxia and hypercapnia due to OSA increases autonomic sympathetic activity and arterial vasoconstriction, which may elevate abnormal cardiac responses to exercise, possibly causing dyspnea [5]. On the other hand, obesity, a well-known risk factor for OSA, is a prevalent cause of dyspnea [6–8]. Other possible mechanisms related

to dyspnea as a comorbid condition with OSA may include pulmonary vascular diseases, comorbidities such as cardiovascular diseases or diabetes, systemic inflammation associated with decreased pulmonary function or muscle damage, poor physical condition, impaired health from various causes, and psychosocial problems [8–15].

Dyspnea can represent the overall systemic consequences of several diseases. Therefore, in respiratory diseases such as chronic obstructive pulmonary disease (COPD) or idiopathic pulmonary fibrosis, dyspnea during activities of daily living, in addition to pulmonary function, is an important outcome and represents disease severity associated with mortality [16–18]. Here we hypothesize that dyspnea in OSA would result from various pulmonary and systemic effects of OSA or comorbid conditions and would reflect disease severity, which might not be reflected by the apnea/hypopnea index (AHI) alone. Thus, in the present study, we assessed the relationships between dyspnea measurements and various subjective and objective indices in patients with OSA. We then compared the relationship of these indices with the AHI.

Methods

Study subjects

We recruited 457 consecutive outpatients with symptoms of habitual snoring, apnea during sleep, or daytime sleepiness from the Sleep Unit of Kyoto University Hospital. Exclusion criteria included (1) central sleep apnea, (2) other respiratory diseases, (3) uncontrolled comorbidities, (4) comorbid conditions causing dyspnea apparently unrelated to OSA, and (5) refusal or inability to complete questionnaires. This study was approved by the Ethics Committee of Kyoto University, and informed consent was obtained from all patients.

Hemoglobin (Hb) (anemia marker), fibrinogen and C-reactive protein (CRP) (inflammatory markers), B-type natriuretic peptide (cardiovascular marker), HbA1c (diabetic marker), and d-dimer (pulmonary vascular disease marker) were measured, using peripheral venous blood collected in the morning following polysomnography. Arterial blood gas analysis, including arterial partial pressure of oxygen (PaO_2) and arterial partial pressure of carbon dioxide ($PaCO_2$), was performed while patients were breathing room air at rest in the supine position. The alveolar–arterial oxygen pressure difference ($A\text{-}aDO_2$) was calculated according to the standard formula, using a respiratory exchange ratio of 0.8. Comorbidity was objectively evaluated by the Charlson comorbidity index [19]. Briefly, this system assigns to each disease a score of 1 to 6. A score of 1 is allocated to myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic lung disease, connective tissue disease, ulcer disease, mild liver disease, and diabetes. A score of 2 is allocated to advanced diabetes, hemiplegia, moderate or severe kidney disease, and malignancies. A score of 3 is allocated to moderate or severe liver disease, while a score of 6 is allocated to acquired immune deficiency syndrome or metastatic malignancies. The Charlson index score was calculated by the sum of all scores.

Polysomnography

The diagnosis of OSA was confirmed by polysomnography (SomnoStar pro, Cardinal Health, Dublin, OH, USA) as previously described in detail [11, 20]. Briefly, apnea was defined as the complete cessation of airflow and hypopnea as a clear decrease in airflow of 50 % or more lasting for 10 s or more accompanied by a decrease in arterial oxygen saturation of at least 3 %. All AHI values were expressed as the number of episodes of apnea and hypopnea per hour over the total sleep time. OSA severity was defined based on the AHI: non-OSA (AHI of less than 5), mild OSA (AHI of 5 to 15), moderate OSA (AHI of 15 to 30), and severe OSA (AHI of greater than 30) [21].

Pulmonary function

Pulmonary function tests were performed using CHESTAC (Chest M.I. Inc., Tokyo, Japan). Residual volume and total lung capacity were measured by the closed-circuit helium method, and diffusing capacity for carbon monoxide (DL_{CO}) was measured using the single-breath technique.

Patient-reported measurements

Dyspnea during activities of daily living was evaluated by the Japanese version of the five-point Medical Research Council (MRC) dyspnea scale [22] (Table 1). We then roughly placed the scale scores into three categories in an attempt to allow comparison with disease severity based on the AHI [23]: no or little dyspnea (mild) for MRC grade 1, dyspnea on exertion (moderate) for MRC grade 2, and dyspnea on any exertion or at rest (severe) for MRC grades 3 to 5.

Health-related quality of life (HRQoL) was assessed by the Japanese version of the Medical Outcomes Study 36-item short form (SF-36) [24, 25]. The SF-36 questionnaire contains 36 items that are aggregated into eight subscales: physical functioning, role—physical, bodily pain, general health, vitality, social functioning, role—emotional, and mental health. Scores were transformed into a score from 0 to 100, with 0 and 100 assigned the lowest (worst HRQoL) and highest (best HRQoL) possible scores, respectively.

Table 1 The MRC dyspnea scale

Grade	Degree of breathlessness related to activities
1	Not troubled by breathlessness except with strenuous exercise
2	Short of breath when hurrying or walking up a slight hill
3	Walks slower than contemporaries on level ground because of breathlessness or has to stop for breath when walking at own pace
4	Stop for breath after walking about 100 m or after a few minutes on level ground
5	Too breathless to leave the house or breathless when dressing or undressing

Daytime sleepiness was assessed by the Japanese version of the Epworth Sleepiness Scale (ESS) [26, 27]. With the ESS, individuals score themselves on a scale of 0 (not at all likely to fall asleep) to 3 (very likely to fall asleep) according to how easily they would fall asleep in eight different situations, with possible overall scores of 0 to 24. The higher the score is, the sleepier the individual is. Sleep quality was assessed by the Japanese version of the Pittsburgh Sleep Quality Index (PSQI) [28, 29]. Nineteen individual items generate seven component scores including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. Each dimension was scored from 0 to 3, and the seven component scores were then summed to yield a global PSQI score, ranging from 0 to 21, with a higher score indicating poorer sleep quality.

Psychological status was evaluated by the Japanese version of the Hospital Anxiety and Depression Scale (HADS) [30, 31]. The HADS consists of 14 items, seven for anxiety and seven for depression. Each item was scored from 0 to 3, where a score of 3 represents a worst state. The sum of these items produces anxiety and depression scores ranging from 0 to 21, respectively.

Statistics

Statistical analyses were performed using JMP version 9 (SAS Institute, Cary, NC, USA). Continuous variables are expressed as means ± standard deviation. A chi-square test (gender), Mann–Whitney's *U* tests (Charlson comorbidity index and MRC), and unpaired *t* tests (other continuous variables) were used to compare variables between non-OSA and OSA groups. The significance of intergroup differences based on the levels of dyspnea or the AHI was determined by an analysis of variance (ANOVA). When a significant difference was observed, we used the Fisher's protected least significant difference method to identify where the differences were significant. A chi-square test was used to compare a dichotomous variable. Stepwise logistic regression analyses were performed to indentify factors that were independently related to differences between groups classified by the levels of dyspnea, using variables that were significantly different on post hoc tests. A p value less than 0.05 was considered to indicate statistical significance.

Results

Among the 457 patients, we excluded patients for the following reasons: refusal or inability to complete questionnaires (n=19), asthma (n=33), COPD (n=11), bronchiectasis (n=1), interstitial lung disease (n=7), congestive heart failure (CHF) (n=3), collagen vascular disease (n=26), cancer (n=34), severe liver disease (n=3), severe kidney disease (n=5), neuromuscular disease (n=4), and central sleep apnea (n=10). Then, 301 patients were examined further.

Of the 301 subjects in the final study group, 265 (88 %) were diagnosed as having OSA. Among them, 57 (22 %), 82 (31 %), and 126 patients (47 %) had mild, moderate, and severe OSA, respectively. When comparing the baseline data between non-OSA subjects (n=36) and OSA subjects (n=265), there were some differences in the background measurements (Table E1). MRC scores were significantly higher in subjects with OSA (1.6±0.7) than in those without OSA (1.4±0.6) (p=0.04). Regarding the dyspnea severity, 125 (47 %), 121 (46 %), and 19 patients (7 %) had mild, moderate, and severe dyspnea, respectively.

Patient characteristics categorized according to the MRC dyspnea scale

Table 2 shows patient characteristics of the three groups of OSA patients categorized according to the MRC grade. First of all, the AHI and ESS did not differ significantly among the three groups (p=0.49 and 0.94, respectively), indicating that there is no relationship between dyspnea severity and measures of sleep disorder. Secondly, significant differences among the groups were observed in sex, body mass index (BMI), neck circumference, and waist circumference, which are well-known important factors in determining OSA severity. There were also significant differences in the Charlson comorbidity index and, regarding blood parameters, in Hb, fibrinogen, CRP, and HbA1c. With regard to pulmonary function and arterial blood gas, significant differences were observed in vital capacity (VC), forced vital capacity (FVC), DL_{CO}, PaO_2, and A-aDO_2.

Regarding patient-reported measurements, all SF-36 subscale scores were significantly different between groups (ANOVA, $p<0.05$). Between the mild and moderate dyspnea groups, there were significant differences in the six subscales but no significant differences were shown with the two subscales, which were vitality and social functioning,

Table 2 Patient characteristics categorized according to MRC dyspnea scale

	MRC grade 1 (n=125)	MRC grade 2 (n=121)	MRC grades 3–5 (n=19)	p value
Sex, male/female	107/18	88/33*	12/7*	0.01
Age, years	54.6±13.6	59.7±13.4*	58.3±12.8	0.01
BMI, kg/m^2	25.8±4.5	26.9±5.5	29.6±8.4*,**	0.01
Neck circumference, cm	39.6±3.7	39.4±4.5	39.5±2.9	0.95
Waist circumference, cm	92.1±10.7	95.5±13.1*	100.5±14.3*	0.008
Smoking (pack years)	16.4±22.5	22.0±30.0	32.5±33.5*	0.03
Charlson comorbidity index	0.3±0.5	0.4±0.7*	0.9±1.2*,**	<0.001
Hemoglobin, g/dl	15.0±1.5	14.3±1.7*	13.8±1.7*	<0.001
Fibrinogen, mg/dl	277.4±64.5	282.6±56.8	302.7±67.4	0.24
CRP, mg/dl	0.1±0.3	0.1±0.2	0.2±0.2	0.64
D-dimer, μg/ml	0.4±0.4	0.5±0.5	0.7±1.0*	0.03
HbA1c, %	5.6±1.0	5.8±1.0	6.4±1.5*,**	0.009
BNP, pg/ml	22.3±29.3	34.9±50.8	24.5±40.8	0.053
AHI, events/h	33.5±22.6	33.5±21.3	39.9±29.9	0.49
VC, % predicted	114.9±15.2	110.6±16.0*	102.7±17.2*,**	0.003
FVC, % predicted	113.2±15.4	107.9±16.5*	101.2±17.5*	0.002
FEV_1, % predicted	107.7±15.9	103.3±17.9	100.5±18.8	0.06
FRC, % predicted	107.2±26.4	111.0±54.8	111.7±41.6	0.76
RV, % predicted	112.5±36.2	113.4±44.1	115.4±45.4	0.96
TLC, % predicted	102.7±21.0	102.6±23.7	103.0±27.6	0.99
DL_{CO}, % predicted	89.7±15.6	80.7±16.4*	82.3±11.3	<0.001
$PaCO_2$, mmHg	42.2±3.5	41.6±3.7	41.3±5.9	0.40
PaO_2, mmHg	85.4±10.8	81.6±10.0*	83.5±15.4	0.03
A-aDO_2, mmHg	11.9±11.2	16.4±10.1*	14.9±12.1	0.006
Global PSQI score	6.3±2.8	7.2±3.2*	8.4±3.9*	0.004
ESS score	9.3±5.0	9.5±4.9	9.2±5.4	0.94
HADS—anxiety	4.5±3.3	5.6±3.8*	6.7±2.6*	0.006
HADS—depression	4.7±3.3	6.3±3.6*	7.8±3.4*	<0.001

Data presented as number or mean ± standard deviation

BMI body mass index, *CRP* C-reactive protein, *BNP* B-type natriuretic peptide, *AHI* apnea/hypopnea index, *VC* vital capacity, *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 pressure of carbon dioxide, *PaO_2* arterial partial pressure of oxygen, *A-aDO_2* alveolar–arterial oxygen pressure difference, *PSQI* Pittsburgh Sleep Quality Index, *ESS* Epworth Sleepiness Scale, *HADS* Hospital Anxiety and Depression Scale

*p<0.05 versus patients with mild dyspnea (MRC grade 1); **p<0.05 versus patients with moderate dyspnea (MRC grade 2)

and in the moderate and severe dyspnea groups, there were also significant differences in the six subscales, but no significant differences were shown in general health and mental health (Fig. 1). Although ESS scores did not differ among the groups, global PSQI and HADS scores were worse as the severity of dyspnea increased (Table 2).

Factors associated with MRC grades

To identify the determinants of the differences in the severity of dyspnea, we performed two stepwise logistic regression analyses between the mild and moderate dyspnea groups and between the moderate and severe dyspnea groups using factors based on the post hoc tests, respectively, because factors determining the differences between two groups might vary [32]. Waist circumference, DL_{CO}, physical functioning of the SF-36, and depression of the HADS were significant factors associated with differences between mild and moderate groups, whereas the Charlson comorbidity index and physical functioning and social functioning of the SF-36 were significantly related to the difference between the moderate and severe groups (Table 3).

Patient characteristics categorized according to the severity of OSA

For comparison of categories of dyspnea severity with those of the severity of OSA, we categorized the patients into

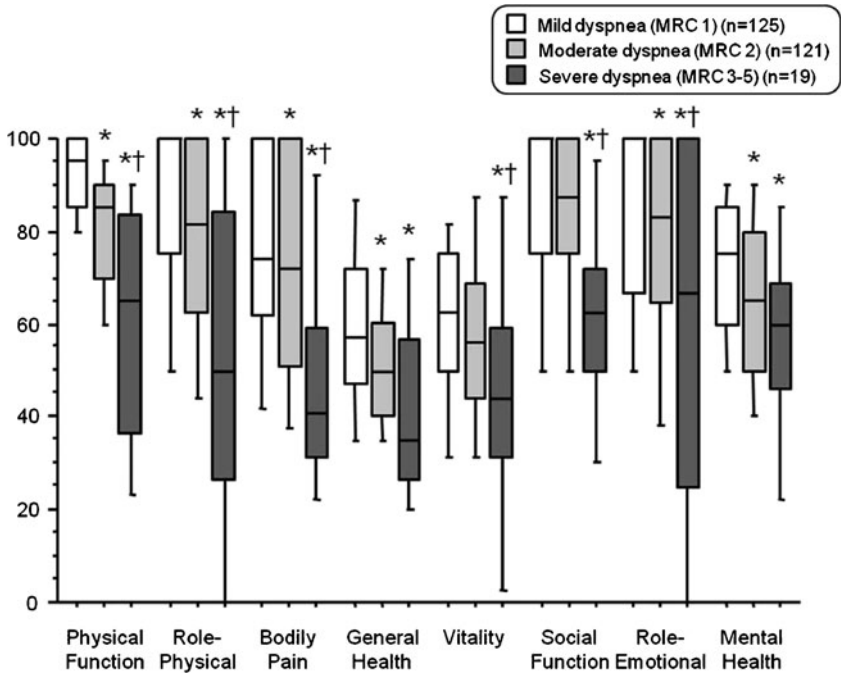

Fig. 1 *Box and whisker plots* representing the score distributions on the SF-36 between groups, based on the MRC dyspnea scale. The *boxes* show the first to third quartile, the *horizontal line* represents the median, and the *vertical bars* indicate the 10th to 90th percentiles. *Asterisk*, significant differences in the scores as compared with patients with mild dyspnea; *dagger*, significant differences in the scores as compared with patients with moderate dyspnea (Fisher's protected least significant difference method)

three groups based on the severity of OSA (Table 4). Significant differences among the groups were observed in sex, BMI, neck circumference, waist circumference, and the Charlson comorbidity index and, regarding blood parameters, in Hb, fibrinogen, CRP, and HbA1c. With regard to pulmonary function and arterial blood gas, significant differences were observed in PaO_2 and A-aDO_2. Regarding patient-reported measurements, there were no significant differences in the SF-36 (Fig. 2), ESS, global PSQI, and HADS scores.

Discussion

MRC scores of patients with OSA were poorer than those of individuals who did not have OSA. There were significant differences in various measurements between mild, moderate, and severe dyspnea groups categorized by the MRC scale, although there were differences in the factors that were independently related to differences in dyspnea between mild and moderate groups and between moderate and severe groups. The categorization based on the AHI did not significantly show a relationship with patient-reported measurements of the SF-36, PSQI, and HADS scores, unlike the categorization based on the MRC scale.

OSA patients had a greater degree of dyspnea than non-OSA patients, with 46 % of OSA patients having moderate dyspnea and 7 % severe dyspnea. Although in patients with respiratory diseases, dyspnea is a common distressing symptom that limits the activities of daily living, the significance of its severity has not been assessed in OSA. A wide variety of clinical conditions such as pulmonary, cardiovascular, psychogenic, neuromuscular, and other conditions, including obesity, can cause dyspneic symptoms [8]. OSA is a condition with the potential to cause dyspnea associated with these multiple clinical and pathophysiological characteristics. In the present study, categorization based on MRC scores identified many variables with significance including patient characteristics (sex, age, smoking, and obesity), comorbidities or secondary clinical conditions (including anemia, diabetes, and possible pulmonary vascular diseases), pulmonary function impairment, HRQoL, and

Table 3 Regression analysis of variables between MRC grades: odds ratios, 95 % confidence intervals, and levels of significance

Outcome variable	Explanatory variable	Odds ratio (95 % CI)	*p* value
MRC 1 versus MRC 2	Waist circumference, cm	1.04 (1.01–1.06)	0.008
	DL_{CO}, % predicted	0.96 (0.94–0.98)	<0.001
	SF-36, physical function	0.96 (0.93–0.98)	<0.001
	HADS—depression	1.14 (1.04–1.24)	0.004
MRC 2 versus MRC 3-5	Charlson comorbidity index	1.89 (1.02–3.50)	0.044
	SF-36, physical function	0.96 (0.94–0.99)	0.01
	SF-36, social function	0.98 (0.96–1.00)	0.049

DL_{CO} diffusing capacity for carbon monoxide, *SF-36* Medical Outcomes Study 36-item short form, *HADS* Hospital Anxiety and Depression Scale

Table 4 Patient characteristics categorized according to the severity of OSA

	Mild OSA (n=57)	Moderate OSA (n=82)	Severe OSA (n=126)	p value
Sex, male/female	38/19	63/19	106/20*	0.03
Age, years	54.6±13.6	59.7±13.4	58.3±12.8	0.61
BMI, kg/m^2	24.9±3.8	25.3±4.9	28.2±5.8*,**	<0.001
Neck circumference, cm	37.9±3.1	38.3±3.5	40.9±4.2*,**	<0.001
Waist circumference, cm	90.2±10.6	91.2±12.6	97.9±11.9*,**	<0.001
Smoking (pack years)	16.0±25.4	22.2±32.2	20.6±24.4	0.41
Charlson comorbidity index	0.3±0.5	0.3±0.5	0.5±0.8*,**	0.04
Hemoglobin, g/dl	14.4±2.0	14.3±1.4	14.9±1.6*,**	0.02
Fibrinogen, mg/dl	275.8±55.8	267.7±64.4	293.0±60.0**	0.01
CRP, mg/dl	0.1±0.2	0.1±0.2	0.2±0.3**	0.04
D-dimer, μg/ml	0.5±0.7	0.4±0.4	0.4±0.5	0.81
HbA1c, %	5.5±0.8	5.5±0.8	6.0±1.2*,**	<0.001
BNP, pg/ml	16.4±14.6	30.3±37.5	32.2±50.6	0.052
AHI, events/h	9.7±2.7	22.3±3.9*	52.5±18.9*,**	<0.001
VC, % predicted	112.2±16.5	113.6±15.9	111.0±15.9	0.53
FVC, % predicted	110.4±16.1	111.6±16.6	108.5±16.5	0.40
FEV_1, % predicted	105.4±15.9	105.8±19.0	104.7±16.7	0.91
FRC, % predicted	108.0±25.5	110.6±43.3	108.9±47.9	0.93
RV, % predicted	117.6±39.6	108.6±37.4	114.0±42.6	0.42
TLC, % predicted	106.6±26.7	101.2±22.6	101.8±20.5	0.33
DL_{CO}, % predicted	82.1±14.8	83.6±17.9	87.4±15.6	0.08
$PaCO_2$, mmHg	41.5±3.4	42.3±3.6	41.7±4.1	0.37
PaO_2, mmHg	85.8±11.9	85.7±9.6	81.1±10.8*,**	0.002
A-aDO_2, mmHg	12.3±12.4	11.4±10.4	16.8±10.1*,**	<0.001
Global PSQI score	7.6±3.0	6.6±3.1	6.7±3.2	0.10
ESS score	10.1±5.0	9.4±4.5	9.1±5.2	0.45
HADS—anxiety	5.7±3.3	5.1±3.7	5.0±3.6	0.44
HADS—depression	5.7±3.6	5.6±3.8	5.6±3.4	0.99

Data presented as number or mean ± standard deviation

OSA obstructive sleep apnea, *BMI* body mass index, *CRP* C-reactive protein, *BNP* B-type natriuretic peptide, *AHI* apnea/hypopnea index, *VC* vital capacity, *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 pressure of carbon dioxide, *PaO_2* arterial partial pressure of oxygen, *A-aDO_2* alveolar–arterial oxygen pressure difference, *PSQI* Pittsburgh Sleep Quality Index, *ESS* Epworth Sleepiness Scale, *HADS* Hospital Anxiety and Depression Scale

*p<0.05 versus patients with mild OSA; **p<0.05 versus patients with moderate OSA

psychosocial issues such as sleep quality, depression, and anxiety, although the AHI and ESS did not differ between the three patient groups (Table 2). Therefore, dyspnea in OSA is unrelated to a sleep disorder per se and may reflect a composite of clinical aspects of OSA that cannot be evaluated by the AHI.

Multiple logistic regression analyses indicated differences in the contributive factors for the increasing severity of dyspnea between mild, moderate, and severe groups, which were similarly observed in patients with COPD [32]. Firstly, abdominal obesity, gas exchange derangement, and self-ratings of physical functioning and depression were significantly associated with the difference between MRC grades 1 and 2. They are all important clinical features in OSA [11, 13–15, 33–35]. Recently, work from our group [11] and others [36] suggested OSA as a cause of subclinical lung injury and gas exchange derangement. In addition to obesity, which is a prevalent cause of dyspnea [6–8], subclinical lung injury in OSA might also have a clinically significant impact on respiratory symptoms. Secondly, regarding the differences between MRC grade 2 and grades 3 or more, comorbidities and self-ratings of physical and social functioning were the significant determinants. As OSA is associated with multiple comorbidities including cardiovascular diseases, metabolic syndrome, and diabetes [37], the presence of those comorbidities was related to dyspnea even

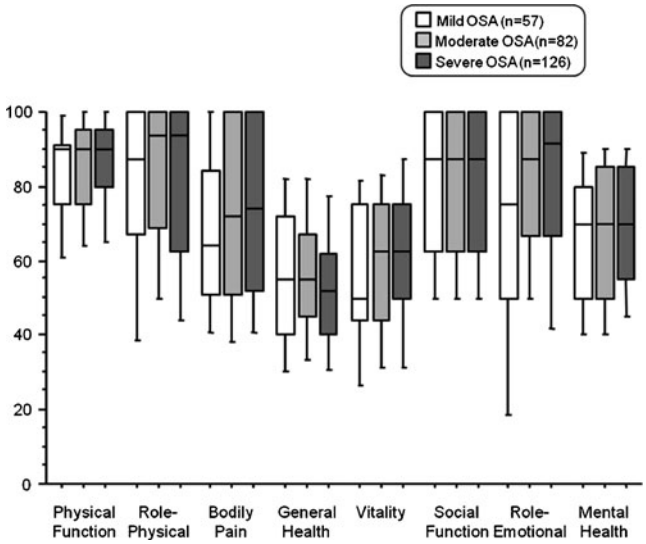

Fig. 2 *Box and whisker plots* representing the score distributions on the SF-36 between groups, based on the level of the AHI. The *boxes* show the first to third quartile, the *horizontal line* represents the median, and the *vertical bars* indicate the 10th to 90th percentiles

after excluding subjects with uncontrolled comorbidities or comorbid conditions unrelated to OSA.

HRQoL is impaired in patients with OSA, and the SF-36 is a recommended measurement of generic HRQoL [14]. SF-36 scores that involved both physical and mental aspects were clearly separated according to the categorization based on the MRC. Significant differences were observed in six of the eight subscales between mild and moderate dyspnea groups and between moderate and severe groups. A similar relationship was observed in patients with COPD who had clear separations in HRQoL according to the MRC dyspnea scale [23]. This may not be surprising in diseases where dyspnea is demonstrated to be a main determinant of HRQoL [38, 39]. However, as the significance of dyspnea as an impairment in the health of OSA patients remains to be addressed, our current finding is novel.

We compared categories based on MRC grades and AHI. HRQoL, sleep quality, and psychological status differed significantly between groups based on the levels of dyspnea, but not on the AHI. Presently, the severity of OSA has been assessed solely by the AHI. However, previous studies suggested that self-perceptions of general health [34, 40], sleep quality [41], or psychological status [42–44] in patients with OSA were not significantly related to the AHI. Thus, particularly from the viewpoint of patient-reported outcomes, assessment of dyspnea, in addition to the AHI, would be useful in patients with OSA.

The categorization based on MRC scores, but not on the AHI showed clear separations for pulmonary function (VC, FVC, and DL_{CO}) according to the level of dyspnea, but the results for systemic inflammation biomarkers (fibrinogen and CRP) were not clearly separated according to the level of dyspnea. Decreased pulmonary function and increased systemic inflammation, respectively, are known to be associated with cardiovascular mortality [45, 46]. In addition, the trends of Hb levels across subgroups were opposite between patient categories based on the MRC score and AHI. The trend toward lower Hb levels in proportion to the severity of dyspnea might have been dependent on values from the female subjects. However, as relationships between anemia and adverse clinical outcomes are often reported in chronic diseases [47, 48], a relationship between anemia and dyspnea in patients with OSA might not be unexpected. Furthermore, d-dimer was elevated in the subjects with severe dyspnea, but its values did not differ between groups based on the AHI. OSA is known as an underlying disease causing pulmonary vascular diseases [8, 9], in which d-dimer is a candidate biomarker [49, 50]. Thus, although the severity of OSA has been determined based on the AHI particularly in relation with a future risk of cardiovascular diseases, the combined assessment of both the AHI and the results of the simple and brief MRC scale might be more useful in assessing disease severity, the degree of which would otherwise be overlooked based only on the frequency of nocturnal respiratory events.

The present study has some limitations. First, few patients had severe dyspnea (7 %). That may be partly due to the blunted ventilatory responsiveness that is commonly seen in patients with OSA [51–53]. In addition, although we used the simple five-point MRC scale, a more discriminative multidimensional measure like the Baseline Dyspnea Index (0–12) [54] might have been more useful. Second, since this is a cross-sectional study, the direction of causality and causality itself cannot be definitively established from the present study. The purposes of measuring dyspnea include differentiation between patients with greater and lesser degrees of dyspnea, evaluation of changes in dyspnea after medical interventions, and prediction of future outcomes [17, 55]. Further study may be warranted to evaluate the level of dyspnea after treatment of OSA and to investigate whether assessment of dyspnea in OSA is also useful for evaluative and predictive purposes. Third, we did not evaluate cardiac function by catheterization or echocardiography. To reduce sampling bias, we excluded patients with CHF, severe kidney disease, or other uncontrolled diseases and measured several blood biomarkers instead of performing catheterization or echocardiography.

In conclusion, dyspnea is an important outcome in OSA, although dyspnea in OSA patients is unrelated to the sleep disorder per se. Patient-reported outcomes such as quality of life and psychological status were not related to the severity of the sleep disorder but were significantly related to the severity of dyspnea. Categorizing OSA patients based on their level of dyspnea in addition to the present categorization by the AHI alone might provide further insights into the health of these patients and the clinical manifestations of OSA.

Acknowledgments This work was supported in part by grants from the Japanese Ministry of Education, Culture, Sports, Science and Technology (nos. 22249031, 22590860, 22590862, and 23659109) and the Respiratory Failure Research Group and Health Science Research Grants (Comprehensive Research on Life-Style Related Diseases including Cardiovascular Diseases and Diabetes Mellitus) from the Japanese Ministry of Health, Labor and Welfare.

Conflict of interest The Department of Respiratory Care and Sleep Control Medicine is funded by endowments from Philips-Respironics, Teijin Pharma, and Fukuda Denshi to Kyoto University.

References

1. Lin CC, Hsieh WY, Chou CS, Liaw SF (2006) Cardiopulmonary exercise testing in obstructive sleep apnea syndrome. Respir Physiol Neurobiol 150:27–34
2. Alameri H, Al-Kabab Y, BaHammam A (2010) Submaximal exercise in patients with severe obstructive sleep apnea. Sleep Breath 14:145–151
3. Pendharkar SR, Tsai WH, Eves ND, Ford GT, Davidson WJ (2011) CPAP increases exercise tolerance in obese subjects with obstructive sleep apnea. Respir Med 105:1565–1571
4. Ekici M, Ekici A, Keles H, Akin A, Karlidag A, Tunckol M, Kocyigit P (2008) Risk factors and correlates of snoring and observed apnea. Sleep Med 9:290–296
5. Kaleth AS, Chittenden TW, Hawkins BJ, Hargens TA, Guill SG, Zedalis D, Gregg JM, Herbert WG (2007) Unique cardiopulmonary exercise test responses in overweight middle-aged adults with obstructive sleep apnea. Sleep Med 8:160–168
6. Sin DD, Jones RL, Man SF (2002) Obesity is a risk factor for dyspnea but not for airflow obstruction. Arch Intern Med 162:1477–1481
7. Bowden JA, To TH, Abernethy AP, Currow DC (2011) Predictors of chronic breathlessness: a large population study. BMC Public Health 11:33
8. Niven A, Weisman IM (2005) Diagnosis of unexplained dyspnea. In: Mahler D, O'Donnell DE (eds) Dyspnea: mechanisms, measurement and management. Taylor & Francis, Boca Raton, pp 207–263
9. Minai OA, Ricaurte B, Kaw R, Hammel J, Mansour M, McCarthy K, Golish JA, Stoller JK (2009) Frequency and impact of pulmonary hypertension in patients with obstructive sleep apnea syndrome. Am J Cardiol 104:1300–1306
10. Lopez-Jimenez F, Sert Kuniyoshi FH, Gami A, Somers VK (2008) Obstructive sleep apnea: implications for cardiac and vascular disease. Chest 133:793–804
11. Aihara K, Oga T, Harada Y, Chihara Y, Handa T, Tanizawa K, Watanabe K, Tsuboi T, Hitomi T, Mishima M, Chin K (2011) Comparison of biomarkers of subclinical lung injury in obstructive sleep apnea. Respir Med 105:939–945
12. Aihara K, Oga T, Chihara Y, Harada Y, Tanizawa K, Handa T, Hitomi T, Uno K, Mishima M, Chin K (2012) Analysis of systemic and airway inflammation in obstructive sleep apnea. Sleep Breath. doi:10.1007/s11325-012-0726-y
13. Quan SF, O'Connor GT, Quan JS, Redline S, Resnick HE, Shahar E, Siscovick D, Sherrill DL (2007) Association of physical activity with sleep-disordered breathing. Sleep Breath 11:149–157
14. Reimer MA, Flemons WW (2003) Quality of life in sleep disorders. Sleep Med Rev 7:335–349
15. Sateia MJ (2009) Update on sleep and psychiatric disorders. Chest 135:1370–1379
16. Nishimura K, Izumi T, Tsukino M, Oga T (2002) Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. Chest 121:1434–1440
17. Oga T, Nishimura K, Tsukino M, Hajiro T, Mishima M (2006) Dyspnoea with activities of daily living versus peak dyspnoea during exercise in male patients with COPD. Respir Med 100:965–971
18. Nishiyama O, Taniguchi H, Kondoh Y, Kimura T, Kato K, Kataoka K, Ogawa T, Watanabe F, Arizono S (2010) A simple assessment of dyspnoea as a prognostic indicator in idiopathic pulmonary fibrosis. Eur Respir J 36:1067–1072
19. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40:373–383
20. Aihara K, Oga T, Harada Y, Chihara Y, Handa T, Tanizawa K, Watanabe K, Hitomi T, Tsuboi T, Mishima M, Chin K (2012) Analysis of anatomical and functional determinants of obstructive sleep apnea. Sleep Breath 16:473–481
21. The Report of an American Academy of Sleep Medicine Task Force (1999) 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 22:667–689
22. National Institute for Clinical Excellence (NICE) (2004) Chronic obstructive pulmonary disease. National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. Thorax 59(Suppl 1):1–232
23. Hajiro T, Nishimura K, Tsukino M, Ikeda A, Oga T, Izumi T (1999) A comparison of the level of dyspnea vs disease severity in indicating the health-related quality of life of patients with COPD. Chest 116:1632–1637
24. Ware JE Jr, Sherbourne CD (1992) The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 30:473–483
25. Fukuhara S, Suzukamo Y (2004) Manual of SF-36v2 Japanese version. Institute for Health Outcomes & Process Evaluation Research, Kyoto
26. Johns MW (1991) A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 14:540–545
27. Takegami M, Suzukamo Y, Wakita T, Noguchi H, Chin K, Kadotani H, Inoue Y, Oka Y, Nakamura T, Green J, Johns MW, Fukuhara S (2009) Development of a Japanese version of the Epworth Sleepiness Scale (JESS) based on item response theory. Sleep Med 10:556–565
28. Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ (1989) The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 28:193–213
29. Hayashino Y, Yamazaki S, Takegami M, Nakayama T, Sokejima S, Fukuhara S (2010) Association between number of comorbid conditions, depression, and sleep quality using the Pittsburgh Sleep Quality Index: results from a population-based survey. Sleep Med 11:366–371
30. Zigmond AS, Snaith RP (1983) The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 67:361–370
31. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T, Mishima M (2007) Analysis of longitudinal changes in the psychological status of patients with asthma. Respir Med 101:2133–2138
32. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA (1999) Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 54:581–586
33. Chin K, Shimizu K, Nakamura T, Narai N, Masuzaki H, Ogawa Y, Mishima M, Nakamura T, Nakao K, Ohi M (1999) Changes in intra-abdominal visceral fat and serum leptin levels in patients with obstructive sleep apnea syndrome following nasal continuous positive airway pressure therapy. Circulation 100:706–712
34. Akashiba T, Kawahara S, Akahoshi T, Omori C, Saito O, Majima T, Horie T (2002) Relationship between quality of life and mood or depression in patients with severe obstructive sleep apnea syndrome. Chest 122:861–865

35. Harris M, Glozier N, Ratnavadivel R, Grunstein RR (2009) Obstructive sleep apnea and depression. Sleep Med Rev 13:437–444
36. Lederer DJ, Jelic S, Basner RC, Ishizaka A, Bhattacharya J (2009) Circulating KL-6, a biomarker of lung injury, in obstructive sleep apnoea. Eur Respir J 33:793–796
37. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP (2010) Pathophysiology of sleep apnea. Physiol Rev 90:47–112
38. Hajiro T, Nishimura K, Tsukino M, Ikeda A, Koyama H, Izumi T (1998) Comparison of discriminative properties among disease-specific questionnaires for measuring health-related quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 157:785–790
39. Nishiyama O, Taniguchi H, Kondoh Y, Kimura T, Ogawa T, Watanabe F, Nishimura K (2005) Health-related quality of life in patients with idiopathic pulmonary fibrosis. What is the main contributing factor? Respir Med 99:408–414
40. Bennett LS, Barbour C, Langford B, Stradling JR, Davies RJ (1999) Health status in obstructive sleep apnea: relationship with sleep fragmentation and daytime sleepiness, and effects of continuous positive airway pressure treatment. Am J Respir Crit Care Med 159:1884–1890
41. Kezirian EJ, Harrison SL, Ancoli-Israel S, Redline S, Ensrud K, Goldberg AN, Claman DM, Spira AP, Stone KL (2009) Behavioral correlates of sleep-disordered breathing in older men. Sleep 32:253–261
42. Sforza E, de Saint HZ, Pelissolo A, Rochat T, Ibanez V (2002) Personality, anxiety and mood traits in patients with sleep-related breathing disorders: effect of reduced daytime alertness. Sleep Med 3:139–145
43. Jackson ML, Stough C, Howard ME, Spong J, Downey LA, Thompson B (2011) The contribution of fatigue and sleepiness to depression in patients attending the sleep laboratory for evaluation of obstructive sleep apnea. Sleep Breath 15:439–445
44. Rey de Castro J, Rosales-Mayor E (2012) Depressive symptoms in patients with obstructive sleep apnea/hypopnea syndrome. Sleep Breath. doi:10.1007/s11325-012-0731-1
45. Sin DD, Wu L, Man SF (2005) The relationship between reduced lung function and cardiovascular mortality: a population-based study and a systematic review of the literature. Chest 127:1952–1959
46. Tice JA, Browner W, Tracy RP, Cummings SR (2003) The relation of C-reactive protein levels to total and cardiovascular mortality in older U.S. women. Am J Med 114:199–205
47. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Borenstein J (2002) Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. J Am Coll Cardiol 39:1780–1786
48. Cote C, Zilberberg MD, Mody SH, Dordelly LJ, Celli B (2007) Haemoglobin level and its clinical impact in a cohort of patients with COPD. Eur Respir J 29:923–929
49. Bounameaux H, de Moerloose P, Perrier A, Reber G (1994) Plasma measurement of D-dimer as diagnostic aid in suspected venous thromboembolism: an overview. Thromb Haemost 71:1–6
50. Shitrit D, Bendayan D, Bar-Gil-Shitrit A, Huerta M, Rudensky B, Fink G, Kramer MR (2002) Significance of a plasma D-dimer test in patients with primary pulmonary hypertension. Chest 122:1674–1678
51. Garay SM, Rapoport D, Sorkin B, Epstein H, Feinberg I, Goldring RM (1981) Regulation of ventilation in the obstructive sleep apnea syndrome. Am Rev Respir Dis 124:451–457
52. Gold AR, Schwartz AR, Wise RA, Smith PL (1993) Pulmonary function and respiratory chemosensitivity in moderately obese patients with sleep apnea. Chest 103:1325–1329
53. Han F, Chen E, Wei H, He Q, Ding D, Strohl KP (2001) Treatment effects on carbon dioxide retention in patients with obstructive sleep apnea–hypopnea syndrome. Chest 119:1814–1819
54. Mahler DA, Weinberg DH, Wells CK, Feinstein AR (1984) The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. Chest 85:751–758
55. Mahler D (2005) Measurement of dyspnea: clinical ratings. In: Mahler D, O'Donnell DE (eds) Dyspnea: mechanisms, measurement and management. Taylor & Francis, Boca Raton, pp 157–165