惹起される．とくに，急性増悪時には負のエネルギーバランスが助長され，栄養障害がさらに進行する．REEの増大は肺過膨張や呼吸筋力の低下と相関しており，換気のメカニクスの障害に基づく呼吸筋酸素消費量の増大が主因とされている．また，COPD患者の骨格筋では酸素需要量が多いtypeⅡ繊維の比率が高いためにエネルギー消費が増大する可能性も指摘されている．

2. 全身性炎症

tumor necrosis factor(TNF)-αやinterleukin(IL)-6などの炎症性メディエータの血中濃度の上昇がみられ，これらの上昇はFMやFFMの減少と関連し，BMCが減少する一因ともなる．また，骨格筋における誘導型一酸化窒素合成酵素(iNOS)やnuclear factor kappa B(NF-κB)の発現が亢進しているために，筋細胞のタンパク合成の減少やアポトーシスをきたして筋肉量が減少することが示唆されている．炎症性サイトカインは摂食抑制に働くことや，栄養補給療法の効果を低下させる可能性もある．

3. 内分泌ホルモンの変化

1 異化因子/同化因子のバランス

炎症性サイトカインや内分泌ホルモンが異化因子や同化因子として栄養障害に関与している．体重減少患者では異化因子であるTNF-αやIL-6，ノルエピネフリンの血中濃度は高値を示し，成長ホルモンやインスリン様成長因子(IGF)-1，デヒドロエピアンドロステロンなどの同化因子よりも優位となっている．

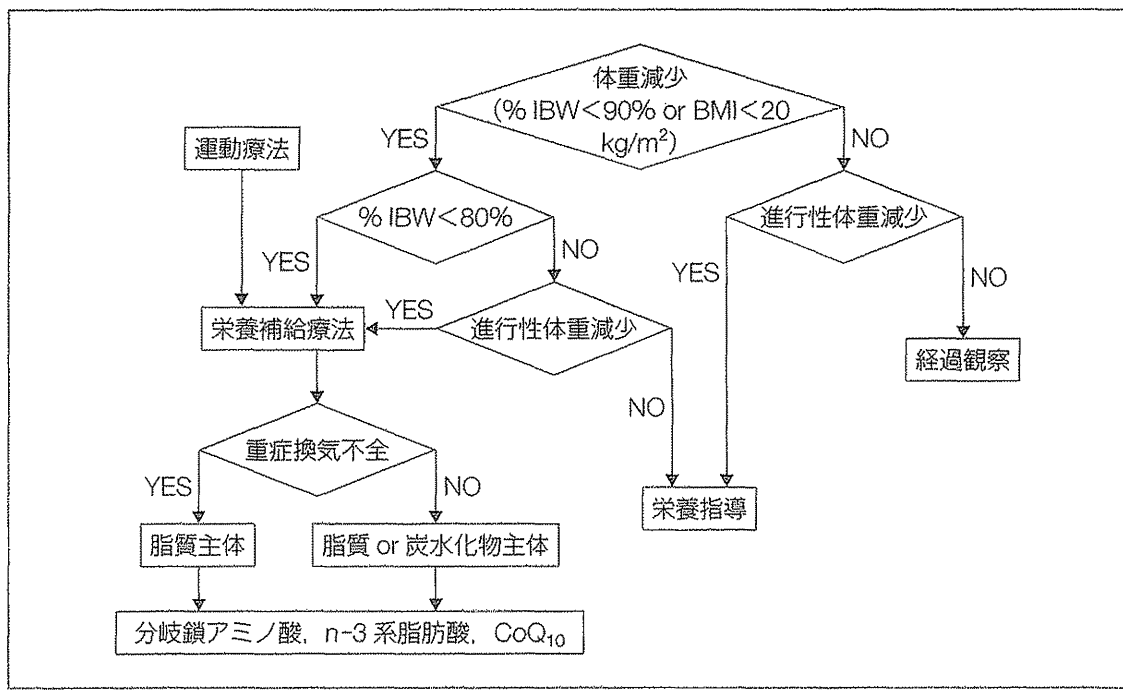
2 摂食調節因子

摂食行動を司る神経回路網の中心は視床下部であり，摂食促進因子と摂食抑制因子によって調節されている．体重減少を認めるCOPD患者では摂食促進因子であるグレリンの血漿中濃度は上昇しており，BMIと負の相関，肺過膨張の程度と正の相関を認める[9]．これらは，血漿グレリンは栄養障害や病態の進行に対して代償的に分泌が亢進しているものの，結果として十分に機能していないことを示唆している．また，摂食促進因子である血漿オレキシンA濃度が低下しており，BMIの低下やFMの減少と相関することが報告されている．

7 栄養療法

1. 栄養療法の原則

食事指導を含めた早期の栄養学的介入および栄養サポートチーム(NST)によるチーム医療が望ましい．体重減少患者(% IBW<90% あるいはBMI<20 kg/m^2)で，食事摂取量を増やすことが困難な場合や進行性の体重減少が認められれば経腸栄養剤による経口栄養補給療法を考慮すべきである．とくに，FFMの減少が予測される中等度以上の体重減少



図Ⅲ-104　栄養治療の適応に関するアルゴリズム
（吉川ら，2007[8]より転載）

患者（% IBW<80%）では栄養補給療法が必須となる（**図Ⅲ-104**）[8]．増大したエネルギー消費量にみあう十分なエネルギー摂取が最も重要であり，総エネルギー摂取量の目標を実測 REE の 1.5 倍または予測 REE の 1.7 倍とする[5]．運動療法施行時には負のエネルギーバランスの増悪による栄養障害の進行を抑制し，運動療法の効果を高める目的で栄養補給療法を併用する必要がある[3]．

2．栄養指導のポイント

高タンパク・高熱量食を基本として食事指導を行う．食後に腹部膨満感や呼吸困難を訴えることが多いため，食事は 4〜6 回の分食として 1 回あたりの食事量を少なくする．消化管でガスを発生しやすい食物や炭酸系飲料水の摂取は避けるように指導する．肺性心の合併による浮腫があれば，塩分は 7〜8 g/日に制限する．筋タンパク量の保持には，十分なエネルギーに加え，十分なタンパク源の摂取が必要となる．プロテインスコアの高い良質のタンパク質や，BCAA の含有率が高い食品（牛肉，鶏肉，牛乳，チーズなどの乳製品など）の摂取が勧められる．

カリウム，カルシウム，リン，マグネシウム，鉄などの電解質や微量元素は呼吸筋や四肢運動筋の収縮力保持に重要であり十分な摂取を指導する．骨粗鬆症の合併頻度が高いことからもカルシウム摂取が重要である．食事のみで摂取が困難であれば，必要に応じてサプリメントによる補給も考慮する．

3. 経口栄養法

1 経腸栄養剤の投与法

十分なエネルギー量の摂取を最優先し，少なくとも3か月以上の継続を目標とする．明らかな栄養状態の改善が得られない場合でも，栄養障害の進行を抑制する目的で可能な限り継続する．また，食事摂取量の維持や腹部膨満感の軽減のために，栄養剤の分割摂取や夕食以降の摂取を指導する．

2 経腸栄養剤の選択

a. 換気能からみた選択

換気不全による高炭酸ガス血症を伴う場合は，呼吸商の小さい脂肪を主体とする栄養剤が有用と考えられる[10]．一方，安定期COPD患者において，低炭水化物・高脂肪の栄養剤の有用性に対する否定的な見解もある[11]．原則的には，著しい換気障害がなければ炭水化物，脂質にかかわらず，十分な熱量補給を最優先してよいと考えられる．

b. 抗炎症作用からみた選択

抗炎症性作用を有するn-3系脂肪酸が全身性炎症の抑制および栄養障害や運動耐容能の改善に有用と考えられる．最近，n-3系脂肪酸およびビタミンAの含有率の高い栄養剤と低強度運動療法の併用による抗炎症効果が報告された[12]．また，n-3系脂肪酸に加えて抗酸化作用を有するコエンザイムQ_{10}(CoQ_{10})を強化したライフロン®-QLによる栄養状態，呼吸筋力の改善がみられている．

c. アミノ酸組成からみた選択

BCAAには異化抑制やタンパク合成促進作用があり，運動時に骨格筋での利用が高まる．COPD患者では血漿BCAA濃度の低下がみられることから，BCAAを強化した栄養剤の効果が期待される．BCAAを8～16 g強化したエレンタール®(300～600 kcal/日)を12か月間投与し，体重，lean body mass(LBM)，内臓タンパクの増加および呼吸筋力，握力の改善や呼吸困難の軽減が認められた[5]．また，呼吸リハビリテーションとBCAAの含有率が高いヘパス®(200 kcal/日)との併用がリハビリテーション後の栄養状態の維持に有用であることが報告されている(ヘパス®は現在発売中止)[13]．

d. 摂食調節からみた選択

オクタン酸の含有量が多い栄養剤によって，摂食促進因子であるアシルグレリンの血中濃度の上昇とともに，BMIや内臓タンパクの増加，食欲の改善が認められている[14]．

4. その他の治療

グレリンの経静脈投与により栄養状態および呼吸筋力や運動耐容能が改善する可能性が報告されている[15]．タンパク同化ステロイドおよび成長ホルモンの投与を栄養療法や運動療法と組み合わせる試みが行われてきたが，体重とFFMは増加するが，呼吸筋力や運動耐容能に対する有効性は確立されていない．テストステロンと下肢筋力トレーニングの併用による，FFMの増加と運動能の改善が報告されている．

8 増悪時の栄養管理

呼吸器感染症などによる急性増悪時にはしばしば重症呼吸不全状態となり，経口摂取が困難な状況となる場合も多い．全身性炎症反応症候群(systemic inflammatory response syndrome；SIRS)を呈するような重症患者においても，循環動態が安定していれば24～48時間以内の早期に経腸栄養(enteral nutrition；EN)を開始することが推奨されている[16]．実測REEや推算式から目標投与エネルギー量を設定し，タンパク質投与量は1.2～2.0 g/kg/日に調整する．急性肺損傷(ALI)/急性呼吸窮迫症候群(ARDS)を呈する患者に投与する経腸栄養剤として，n-3系脂肪酸などの抗炎症脂質を含有し抗酸化作用を有する経腸栄養剤の投与が強く推奨されている．一方，呼吸商の調節や炭酸ガス産生の減少を目的とした高脂質・低炭水化物製剤をルーチンに投与することは推奨されていない．逆流による誤嚥の危険性が高い場合や胃内の投与が困難な場合には，小腸内に経腸栄養チューブを留置する．

ENが不可能な場合やENのみで必要エネルギー量の投与が困難な場合には静脈栄養(parenteral nutrition；PN)を検討する．急性増悪時では右心負荷が強いため，過剰輸液による右心不全の誘発に留意する．急性期には設定エネルギー投与量の80%をゴールとし，過剰なエネルギー投与を避けるべきである[16]．これらの事項は重症患者における栄養管理の原則となるが，最終的には個々の患者の重症度や病態に適した栄養治療を考慮する必要がある．

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Sleep Breath
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ORIGINAL ARTICLE

Measurement of dyspnea in patients with obstructive sleep apnea

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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

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

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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

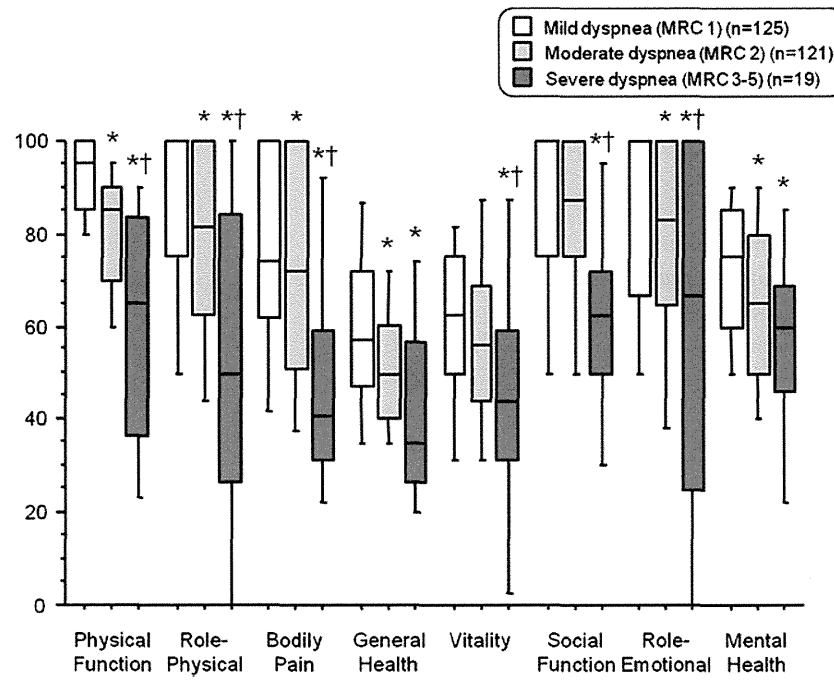

Fig. 1 *Box and whisker plots* representing the score distributions on the SF-36 between groups, based on the MRC dyspnea scale. The *boxes* show the first to third quartile, the *horizontal line* represents the median, and the *vertical bars* indicate the 10th to 90th percentiles. *Asterisk*, significant 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

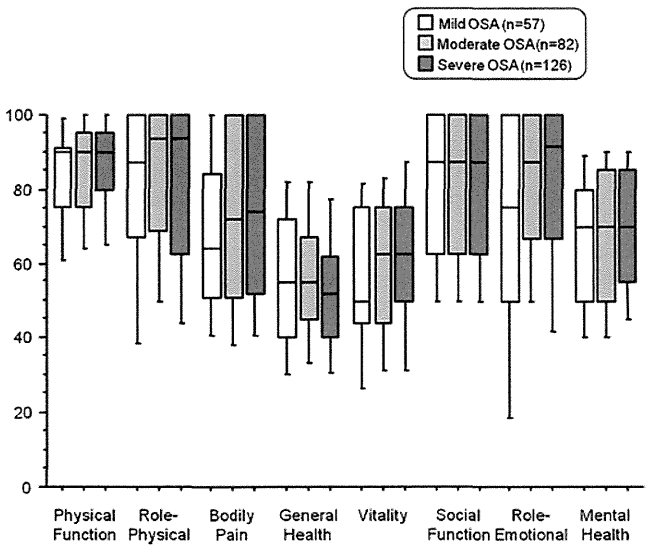

Fig. 2 *Box and whisker plots* representing the score distributions on the SF-36 between groups, based on the level of the AHI. The *boxes* show the first to third quartile, the *horizontal line* represents the median, and the *vertical bars* indicate the 10th to 90th percentiles

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.

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ORIGINAL ARTICLE

Analysis of systemic and airway inflammation in obstructive sleep apnea

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Abstract
Purpose The presence of both systemic and airway inflammation has been suggested in obstructive sleep apnea (OSA) by increased levels of inflammatory biomarkers in the circulation and respiratory specimens. We aimed to investigate the relationship between systemic and airway inflammation in OSA.
Methods This study was conducted by simultaneously measuring various biomarkers both in serum and induced sputum of 43 patients. We compared the relationships of these biomarker levels with polysomnographic data and obesity measurements and also investigated their interrelationships between systemic and local compartments. We also assessed the relation of inflammatory markers with proximal airway resistance measured by impulse oscillometry.
Results In multiple regression analyses, each measured serum biomarker [leptin, interleukin-6 (IL-6), IL-8, tumor necrosis factor-α (TNF-α), and vascular endothelial growth factor (VEGF)] significantly correlated with waist circumference or fat area determined by computed tomography. In contrast, regarding airway inflammation, sputum IL-6, IL-8, TNF-α, and VEGF significantly correlated with OSA severity as indicated by the respiratory disturbance index or oxygen desaturation indices. Sputum IL-6, IL-8, TNF-α, and VEGF were significantly related to sputum neutrophil number, and sputum IL-8 and TNF-α were related to proximal airway resistance independently of body mass index. There were no significant interrelationships between the same biomarkers in serum and induced sputum.
Conclusions Systemic and airway inflammation in OSA might be differently regulated by OSA itself and comorbid obesity, depending on the type of cytokine. Although we did not find apparent interrelationships between systemic and local compartments, further studies are needed to clarify this concept.

Keywords Airway inflammation · Airway resistance · Induced sputum · Obstructive sleep apnea · Systemic inflammation

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Introduction

Obstructive sleep apnea (OSA) is associated with systemic and airway inflammation [1–4]. The presence of systemic inflammation in OSA is demonstrated by increased levels of circulating inflammatory biomarkers such as C-reactive protein [5–7], leptin [8–10], interleukin-6 (IL-6) [6, 9], IL-8 [11, 12], tumor necrosis factor-α (TNF-α) [9, 12], and vascular endothelial growth factor (VEGF) [13, 14],

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particularly in relation to the future risk of cardiovascular diseases. Although the basic mechanisms underlying the inflammatory process in OSA remain unclear, recent studies suggest that not only repeated episodes of intermittent hypoxia but also increased fat tissue due to comorbid obesity seem to play significant roles [15, 16]. In particular, visceral adipose tissue accumulation may contribute to systemic inflammation by releasing numerous cytokines [17, 18].

As compared to systemic inflammation, less attention has been paid to airway inflammation in OSA. However, recent studies indicate that OSA causes respiratory symptoms such as cough [19] and increases proximal airway resistance [20], airway wall thickness and possibly airway hyperreactivity [21], or worsens comorbid airway diseases [22, 23], all of which might be related to airway inflammation. Airway inflammation in OSA seems to be directly and locally affected through mechanical stress [24], snoring-induced airway vibration [25, 26], or local oxidative stress [27].

The relationship between systemic and airway inflammation in OSA has not been investigated so far, but on the basis of differences in the speculated underlying mechanisms, we hypothesized that inflammatory processes in the two compartments would be differently related to OSA and comorbid obesity. Therefore, in the present study, by simultaneously measuring various biomarkers both in serum and induced sputum, we investigated their interrelationships between systemic and local compartments and also compared their relationships with polysomnographic data and obesity measurements.

Methods

Subjects

We recruited 43 consecutive patients who visited the Sleep Unit of Kyoto University Hospital. None had been previously diagnosed with or treated for OSA. Exclusion criteria included the following: (1) respiratory tract infection within the previous 4 weeks; (2) smoking history of more than 5 pack-years or during the past 6 months; (3) presence of other respiratory diseases such as asthma or chronic obstructive pulmonary disease (COPD) based on clinical history, chest radiograph, and spirometry; (4) treatments with corticosteroids or other immunosuppressive drugs; (5) comorbidities that may affect systemic inflammation such as collagen vascular disease or cancer; and (6) central sleep apnea. This study was approved by the Ethics Committee of Kyoto University (E558). Written informed consent was obtained from all patients.

Polysomnography

The diagnosis of OSA was confirmed by polysomnography (PSG) [28]. 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 SpO_2 of at least 3 % [29]. All apnea/hypopnea index (AHI) values were expressed as the number of episodes of apnea and hypopnea per hour over the total sleep time (TST). Respiratory effort-related arousal (RERA) was defined as a sequence of breaths lasting at least 10 s characterized by increasing respiratory effort or flattening of the nasal pressure waveform leading to an arousal from sleep but not meeting criteria for apnea or hypopnea. The respiratory disturbance index (RDI) includes the AHI and the number of episodes of RERA per hour of sleep. Nocturnal oxygen desaturation was assessed by the lowest SpO_2 during sleep and SpO_2<90 % time per TST (%TST<90 %).

Blood sample collection and sputum induction and processing

Following overnight PSG, peripheral venous blood samples were collected in the morning after an overnight fast. Sputum induction and processing were performed shortly after the blood collection, as previously described [30–32]. Briefly, after premedication with 200 μg of inhaled salbutamol, subjects inhaled hypertonic (3 %) saline solution delivered with an ultrasonic nebulizer for 15 min. Each collected sample was immediately separated from contaminating saliva by visual examination, then mixed with 0.1 % dithiothreitol (Suptasol; Oxoid Ltd., Hampshire, UK) and diluted with Dulbecco's phosphate-buffered saline. After centrifugation, cell differentiation was determined by counting at least 400 non-squamous cells stained using the Diff-Quik method. The supernatants were collected and stored at −80 °C.

Biomarkers

Leptin concentrations were measured using a radioimmunoassay kit (Human Leptin RIA kit; Linco Research, St. Charles, MO, USA). IL-6, IL-8, TNF-α, and VEGF concentrations were determined using the Bio-Plex Pro Human Cytokine Assay (Bio-Rad Laboratories, Hercules, CA, USA) according to the manufacturer's instructions [33]. Cytokine-specific antibody-coated beads were used for these experiments. Beads were read on the Bio-Plex 200 suspension array system, and cytokine concentrations were automatically calculated with Bio-Plex Manager Software by a standard curve derived from a recombinant cytokine standard. Albumin concentrations were measured by turbidimetric immunoassay (Superior-Microalbumin kit; Mitsubishi Chemical Medience, Tokyo, Japan), after which, we calculated the airway vascular permeability index (ratio of albumin concentrations in induced sputum and serum) [34]. It has been shown to be reliable and useful in assessing extravasation in airway diseases [34, 35].

Body fat distribution

Amounts of abdominal subcutaneous and visceral fat deposition were assessed by computed tomography (CT) [17]. The area of visceral fat was measured in a single cross-sectional scan at the level of the umbilicus. An image histogram was computed for the subcutaneous fat layers in order to determine the range of CT numbers for the fat tissue. The total fat area was then calculated by counting the pixels that had intensities within the selected range of CT numbers. The intraperitoneal space was defined by tracing its contour on the scan image. The total area with the same CT numbers was considered to represent the visceral fat area (VFA). Subtraction of the visceral fat area from the total fat area was defined as the subcutaneous fat area (SFA).

Spirometry and impulse oscillometry

Spirometry and impulse oscillometry (IOS) (Masterscreen IOS-J, Jaeger, Wurzburg, Germany) for measuring respiratory impedance were performed as previously reported [20, 36, 37]. As increased proximal airway resistance was reported as a clinical feature of OSA using IOS [20, 38, 39], we used respiratory resistance at 20 Hz (R20) in the supine position for the analyses.

Statistics

All statistical analyses were performed using StatView 5.0 (Abacus Concepts, Berkeley, CA, USA). Results are expressed as mean ± SD. Comparisons of variables between two groups were made by Fisher's exact tests or unpaired *t* tests. Relationships between two variables were analyzed by Pearson's correlation coefficient tests. Stepwise multiple regression analyses were performed to identify variables that could best explain inflammatory biomarker levels in serum and sputum using measurements that were significantly related to each biomarker level as explanatory variables. When assessing the relationships of proximal airway resistance with sputum biomarker levels, we adjusted for body mass index (BMI) by multiple regression analyses. A p value less than 0.05 was considered to indicate statistical significance.

Results

Clinical characteristics and polysomnographic data

Patient characteristics and polysomnographic data are shown in Table 1. Although the study included 43 patients at entry, samples from five patients could not be examined simultaneously due to scheduling considerations, and those patients were therefore excluded. Thereafter, the further analysis included the following 38 patients: 6 non-OSA (AHI<5), 9 mild OSA (5≤AHI<15), 13 moderate OSA (15≤AHI<30), and 10 severe OSA patients (AHI≥30). Sputum was successfully induced in 28 patients [sputum (+) group] but could not be induced in ten patients [sputum (−) group]. CT analysis of body fat distribution was not performed in 3 of the 38 patients. There were no significant differences in patients' background, smoking history, body fat distribution, and polysomnographic data between sputum (+) and sputum (−) groups (Table 1).

Table 1 Clinical characteristics and polysomnographic data

	Total (n=38)	Sputum (+) (n=28)	Sputum (−) (n=10)	p value[a]
Sex, male/female	21:17	15:13	6:4	0.99
Age, years	53.4±16.0	51.2±15.9	59.5±15.5	0.16
Smoking history, ex/never	5:33	4:24	1:9	0.99
Smoking, pack-years	0.4±1.3	0.5±1.5	0.02±0.05	0.28
Respiratory resistance at 20 Hz, kPa/l/s	0.34±0.14	0.34±0.14	0.32±0.15	0.68
BMI, kg/m^2	26.7±6.6	27.0±5.9	25.7±8.4	0.58
Waist circumference, cm	92.5±15.6	93.2±15.8	90.5±15.9	0.65
SFA, cm^2	182.7±147.2	185.7±131.3	173.8±198.0	0.85
VFA, cm^2	94.7±67.1	98.7±65.1	82.7±76.0	0.57
3 % ODI	24.0±25.7	21.4±22.0	31.3±34.4	0.30
4 % ODI	19.6±24.6	17.2±20.8	26.1±33.5	0.34
AHI, events/h	24.7±24.7	22.1±21.0	32.2±33.2	0.27
RDI, events/h	26.7±24.2	24.2±20.5	33.7±32.7	0.29
SpO_2<90 % time/TST, %	12.1±22.5	11.0±20.5	15.3±27.9	0.61
Lowest SpO_2, %	79.4±13.4	79.9±14.5	78.1±10.0	0.73

Data are presented as number or mean ± SD

BMI body mass index, *SFA* subcutaneous fat area, *VFA* visceral fat area, *ODI* oxygen desaturation index, *AHI* apnea/hypopnea index, *RDI* respiratory disturbance index, *TST* total sleep time

[a]Comparison between sputum (+) and sputum (−) groups

Table 2 Concentrations of albumin and biomarkers in serum and induced sputum

	Serum[a]		Induced sputum
	Sputum (+) (n=28)	Sputum (−) (n=10)	Sputum (+) (n=28)
Albumin, g/dl	4.2±0.3	4.1±0.3	0.03±0.03
Leptin, ng/ml	10.1±7.4	10.7±17.4	2.5±1.3
IL-6, pg/ml	0.9±0.6	1.2±0.7	42.8±53.1
IL-8, pg/ml	3.9±2.3	4.6±1.6	5,272.4±8,730.8
TNF-α, pg/ml	1.0±0.9	1.1±1.6	16.8±33.4
VEGF, pg/ml	61.8±60.8	40.2±39.0	978.0±967.2

Data are presented as mean ± SD

IL-6 interleukin-6, *IL-8* interleukin-8, *TNF-α* tumor necrosis factor-α, *VEGF* vascular endothelial growth factor

[a] Significant differences were not found in biomarker levels between sputum (+) and sputum (−) groups

Concentrations of albumin and biomarkers in serum and induced sputum

Concentrations of albumin and biomarker levels in serum and induced sputum samples are shown in Table 2. Significant differences were not found in serum biomarker levels between sputum (+) and sputum (−) groups (p=0.17 to 0.88).

Relationships of systemic inflammation markers with obesity measurements and polysomnographic data

Table E1 shows the relationships of serum biomarker levels with obesity measurements and polysomnographic data. Obesity measurements according to BMI, waist circumference, SFA, and VFA were significantly related to serum leptin, IL-6, IL-8, TNF-α, and VEGF [$|r$ (correlation coefficients)$|$=0.37 to 0.78, $p<0.05$]; nonsignificant relationships were shown between BMI and IL-8, SFA and IL-8, and SFA and VEGF. PSG measurements of ODI, AHI, and RDI were positively significantly related to serum leptin, IL-6, and TNF-α ($|r|$=0.34 to 0.63, $p<0.05$). In contrast, serum IL-8 and VEGF were related to none of the PSG measurements. %TST<90 % was significantly related to serum levels of leptin and IL-6, and the lowest SpO_2 was significantly related only to serum leptin levels.

Next, using the indices significantly related to each serum biomarker, we performed stepwise multiple regression analyses (Table 3). Regarding serum leptin, SFA most significantly explained it [r^2 (coefficient of determination)=0.59] followed by the lowest SpO_2 (r^2=0.10). Serum IL-6 and VEGF were significantly related to VFA (r^2=0.43 and 0.21, respectively), and IL-8 and TNF-α were significantly related to waist circumference (r^2=0.16 and 0.43, respectively).

Relationships of airway inflammation markers with obesity measurements and polysomnographic data and with sputum neutrophil number

Table E2 shows the relationships of sputum biomarker levels with obesity measurements and polysomnographic data. With regard to obesity measurements, significant relationships were only found between SFA and leptin, BMI and IL-6, and VFA and IL-8. Sputum IL-8 and TNF-α were significantly related to all PSG measurements ($|r|$=0.49 to 0.69, $p<0.05$), except for nonsignificant relationships between IL-8 and the lowest SpO_2. Sputum IL-6 and VEGF were significantly related to

Table 3 Stepwise multiple regression analyses to predict serum biomarker levels

	Leptin (ng/ml)	IL-6 (pg/ml)	IL-8 (pg/ml)	TNF-α (pg/ml)	VEGF (pg/ml)
Obesity measurements					
BMI, kg/m^2	–	–		–	–
Waist circumference, cm	–	–	r^2=0.16 p=0.01	r^2=0.41 $p<0.001$	–
SFA, cm^2	r^2=0.59 $p<0.001$	–		–	
VFA, cm^2	–	r^2=0.43 $p<0.001$	–	–	r^2=0.21 p=0.009
Polysomnographic data					
3 % ODI	–	–		–	
4 % ODI	–	–		–	
AHI, events/h	–	–		–	
RDI, events/h	–	–		–	
SpO_2<90 % time/TST, %	–	–			
Lowest SpO_2, %	r^2=0.10 p=0.02		–		

– data did not show statistical significance, *IL-6* interleukin-6, *IL-8* interleukin-8, *TNF-α* tumor necrosis factor-α, *VEGF* vascular endothelial growth factor, *BMI* body mass index, *SFA* subcutaneous fat area, *VFA* visceral fat area, *ODI* oxygen desaturation index, *AHI* apnea/hypopnea index, *RDI* respiratory disturbance index, *TST* total sleep time

the lowest SpO_2 and RDI, respectively. Sputum leptin was related to none of the PSG measurements.

We also performed stepwise multiple regression analyses with respect to sputum biomarkers (Table 4). Sputum leptin was significantly related to SFA (r^2=0.22). Regarding sputum IL-6, the lowest SpO_2 significantly explained it (r^2=0.33). Sputum IL-8 and TNF-α were significantly related to %TST<90 % (r^2=0.48 and 0.43, respectively), and sputum VEGF was related to RDI (r^2=0.16).

We then further investigated whether sputum biomarker levels were related to the degree of infiltration of neutrophils. The sputum neutrophil number significantly correlated with sputum levels of IL-6, IL-8, TNF-α, and VEGF (Fig. 1), but not with sputum levels of leptin (r=0.07, p=0.74).

Extravasation in the airways and interrelationships between systemic and airway inflammation markers

The airway vascular permeability index was significantly related to PSG measurements ($|r|$=0.41 to 0.60, p<0.05) (Table 5). Then, to investigate the possible relationships between systemic and airway inflammation, we analyzed the relationships between the same biomarkers in serum and sputum. However, there were no significant relationships with regard to leptin, IL-6, IL-8, TNF-α, and VEGF (Table E3).

Relationships between airway inflammation and proximal airway resistance

To assess the impact of airway inflammation on proximal airway resistance in OSA, we investigated the relationships of proximal airway resistance with sputum biomarker levels (Table 6). R20 determined by IOS had significant positive correlations with sputum levels of IL-6, IL-8, and TNF-α ($|r|$=0.43 to 0.62, p<0.05), but not with sputum leptin and VEGF. Even after adjustment for BMI, which was significantly associated with R20 (r=0.52, p<0.001), the correlation of R20 with sputum IL-8 and TNF-α remained statistically significant (β coefficient=0.47, p=0.003 and β coefficient=0.46, p=0.004, respectively).

Discussion

This study focused on the relationships between systemic inflammation, airway inflammation, and OSA. We found that (1) regarding systemic inflammation, multiple regression analyses indicated that all measured serum markers were significantly related to obesity measurements, and serum leptin was also significantly related to OSA severity (lowest SpO_2); (2) regarding airway inflammation, multiple regression analyses showed that sputum IL-6, IL-8, TNF-α, and VEGF were significantly related to OSA severity, whereas sputum leptin was related to an obesity measurement (SFA); (3) sputum IL-6, IL-8, TNF-α, and VEGF were significantly related to sputum neutrophil number; (4) the airway vascular permeability index was significantly related to OSA severity but there were no significant direct interrelationships between the same biomarkers in serum and induced sputum; and (5) sputum IL-8 and TNF-α were significantly related to proximal airway resistance independently of BMI.

We simultaneously investigated multiple biomarkers both in serum and induced sputum of patients with OSA.

Table 4 Stepwise multiple regression analyses to predict sputum biomarker levels

	Leptin (ng/ml)	IL-6 (pg/ml)	IL-8 (pg/ml)	TNF-α (pg/ml)	VEGF (pg/ml)
Obesity measurements					
BMI, kg/m^2		–			
Waist circumference, cm					
SFA, cm^2	r^2=0.22 p=0.03				
VFA, cm^2			–		
Polysomnographic data					
3 % ODI			–	–	
4 % ODI			–	–	
AHI, events/h			–	–	
RDI, events/h			–	–	r^2=0.16 p=0.04
SpO_2<90 % time/TST, %			r^2=0.48 p<0.001	r^2=0.43 p=0.001	
Lowest SpO_2, %		r^2=0.37 p<0.001		–	

– data did not show statistical significance, *IL-6* interleukin-6, *IL-8* interleukin-8, *TNF-α* tumor necrosis factor-α, *VEGF* vascular endothelial growth factor, *BMI* body mass index, *SFA* subcutaneous fat area, *VFA* visceral fat area, *ODI* oxygen desaturation index, *AHI* apnea/hypopnea index, *RDI* respiratory disturbance index, *TST* total sleep time

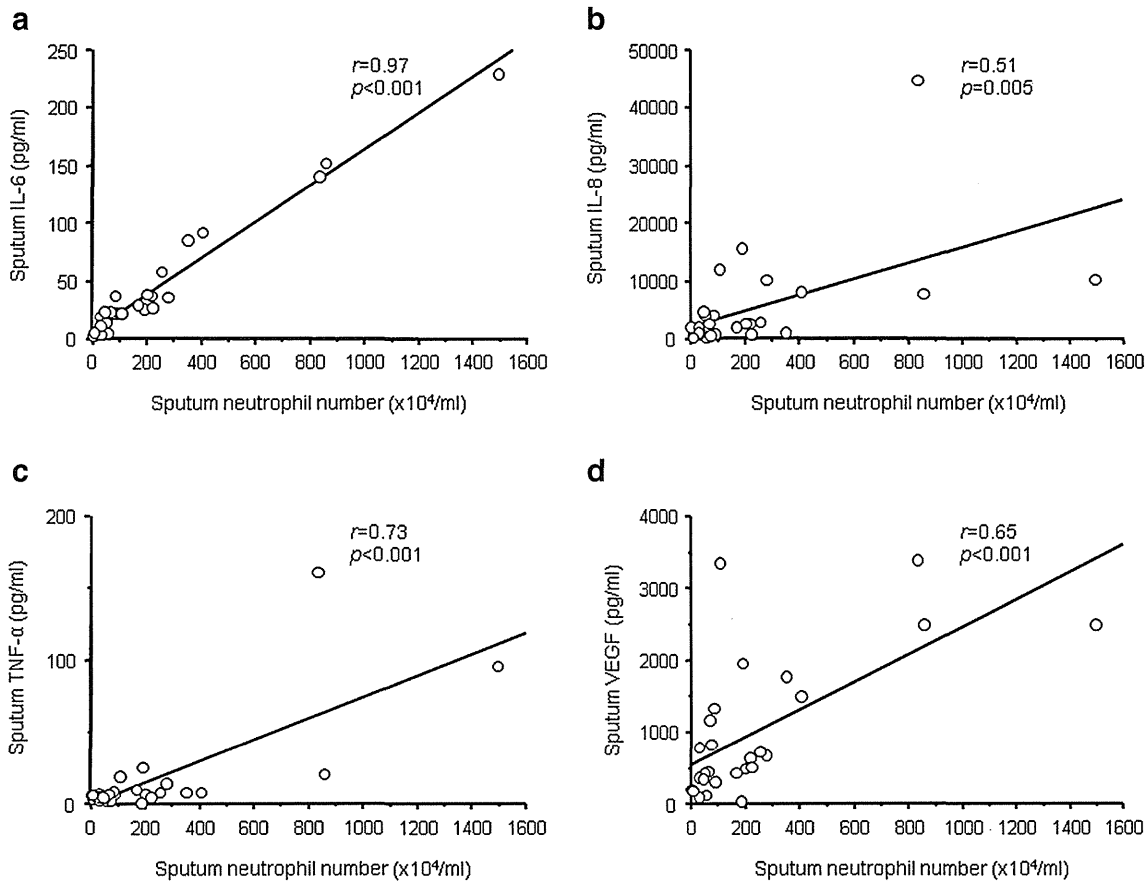

Fig. 1 Scatter diagrams showing the correlation of sputum neutrophil number with sputum levels of IL-6 (**a**), IL-8 (**b**), TNF-α (**c**), and VEGF (**d**). The *r* value indicates a correlation coefficient. *Lines* indicate regression lines

Comparative analyses of relationships of systemic and airway inflammation markers with obesity and OSA severity suggest that inflammatory processes in these two compartments are not similarly regulated in OSA. Systemic inflammation markers were predominantly related to obesity, especially fat accumulation around the abdomen, rather than the severity of OSA. Many previous reports pointed out increased levels of circulating inflammatory markers in OSA [5–14], whereas recent studies suggest that obesity is also an important determinant of systemic inflammation [15, 16]. Because obesity is associated with OSA, the relative contributions of obesity and of OSA itself to systemic inflammatory responses are difficult to clearly distinguish. However, obesity and OSA, both of which are associated

Table 5 Relationships of airway vascular permeability index with polysomnographic data

	Permeability index[a]	
	r value	*p* value
3 % ODI	0.41	0.03
4 % ODI	0.42	0.03
AHI, events/h	0.44	0.02
RDI, events/h	0.44	0.02
SpO_2<90 % time/TST, %	0.41	0.03
Lowest SpO_2, %	−0.60	<0.001

[a] Permeability index indicates albumin concentration in induced sputum/serum

ODI oxygen desaturation index, *AHI* apnea/hypopnea index, *RDI* respiratory disturbance index, *TST* total sleep time

Table 6 Relationships of proximal airway resistance with sputum biomarker levels

	Unadjusted		Adjusted[a]	
	β coefficient	*p* value	β coefficient	*p* value
Leptin, ng/ml	0.18	0.40		
IL-6, pg/ml	0.43	0.02	0.23	0.18
IL-8, pg/ml	0.62	<0.001	0.47	0.003
TNF-α, pg/ml	0.60	<0.001	0.46	0.004
VEGF, pg/ml	0.34	0.07		

IL-6 interleukin-6, *IL-8* interleukin-8, *TNF-α* tumor necrosis factor-α, *VEGF* vascular endothelial growth factor

[a] Adjusted for body mass index