表2　トラック運転者における睡眠呼吸障害の重症度と眠気の自覚

エプワース眠気尺度(ESS)		睡眠呼吸障害(RDI：呼吸障害指数) 正常範囲(RDI 5 未満)	軽度(RDI 5－19.9)	中等度(RDI 20－39.9)	重度(RDI 40 以上)	計
弱	ESS 0～5	1457 (28%)	1391 (27%)	201 (3.8%)	46 (0.9%)	3095 (59%)
↑ 眠気の自覚 ↓	ESS 6～10	774 (15%)	725 (14%)	138 (2.6%)	52 (1.0%)	1689 (32%)
	ESS 11～15	142 (2.7%)	170 (3.2%)	34 (0.6%)	23 (0.4%)	369 (7%)
強	ESS 16 以上	37 (0.7%)	44 (0.8%)	5 (0.1%)	8 (0.2%)	94 (1.8%)
	計	2410 (46%)	2330 (44%)	378 (7.2%)	129 (2.5%)	5247 (100%)

谷川武ほか：眠気のない睡眠時無呼吸(NOSSA)が及ぼす社会影響への取り組み．日本医事新報，4513：51-55，2010 より

スの影響を及ぼし得る。

保健指導におけるアセスメント

睡眠障害による健康への影響は，適切な治療を行うことにより解消され得るため，保健指導による早期発見と介入を行い，必要に応じて医療機関への受診につなげることが重要である。

睡眠呼吸障害のスクリーニングに有用な症状としては，ベッドパートナーから指摘されるいびきや睡眠中の呼吸停止，日中の強い眠気，起床時の頭痛や口渇感，熟眠感不全や夜間頻尿などが挙げられる。

日本人は，顔面骨格の構造から，肥満でなくとも睡眠呼吸障害を発生することが多い。また，上述したように，重症の無呼吸であっても，自覚的な眠気を伴わないことも多い。睡眠呼吸障害のアセスメントをするときは，「肥満で眠そうな中年男性」というステレオタイプ像をいったん捨てなければならない。たしかにそのような典型的な患者は少なくないが，まったくそうした特徴が当てはまらない患者も多く，そのような睡眠呼吸障害を見逃した場合の健康への影響は大きいからである。

●文献

1）Tamakoshi A, Ohno Y：Self-reported sleep duration as a predictor of all-cause mortality：results from the JACC study, Japan. Sleep, 27(1)：51-54, 2004.

2）Doi Y, et al：Prevalence of sleep disturbance and hypnotic medication use in relation to sociodemographic factors in the general Japanese population, J Epidemiol, 10：79-86, 2000.

3）厚生労働省健康局総務課生活習慣病対策室健康情報管理係：健康づくりのための睡眠指針検討会報告書，2003. http://www.mhlw.go.jp/shingi/2003/03/s0331-3.html

4）Tanigawa T, et al：Sleep-disordered breathing and blood pressure levels among shift and day workers. Am J Hypertens, 19：346-351, 2006.

5）Muraki I, et al：Nocturnal intermittent hypoxia and development of type 2 diabetes：the Circulatory Risk in Communities Study(CIRCS). Diabetologia, 53：481-488, 2010.

6）平成18年度警察庁委託調査研究報告書「睡眠障害と安全運転に関する調査研究」，2007.

7）谷川武ほか：眠気のない睡眠時無呼吸(NOSSA)が及ぼす社会影響への取り組み．日本医事新報，4513：51-55，2010.

8）日本看護協会：平成17年度先駆的保健活動交流推進事業　睡眠に関する地域保健活動実践ガイドブック．2006.

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睡眠時無呼吸症候群(SAS)対策の現状

淡野 桜子　谷川 武

睡眠時無呼吸症候群(Sleep Apnea Syndrome：SAS)はありふれた症候群であるが，見過ごされていることが多い．SASが放置されると，単に本人の生活の質や将来の健康が脅かされるばかりではなく，交通事故や労働災害の増加により，社会活動全体にも悪影響が及ぶことが懸念される．公衆衛生の向上のためにも，われわれは，一人でも多くの患者が適切な治療を受けられるように働きかけていく必要がある．

SASとは

睡眠中の呼吸停止や低呼吸を繰り返す病態を，睡眠呼吸障害(Sleep Disordered Breathing：SDB)と言う．睡眠1時間あたり5回以上の睡眠呼吸障害に加えて，日中の過度な眠気などの自覚症状を伴うものがSASである．睡眠呼吸障害のほとんどは，睡眠中に軟口蓋や舌根が上気道を閉塞することによって起きる閉塞型の睡眠呼吸障害であり，閉塞型睡眠時無呼吸を主とするSASが閉塞型睡眠時無呼吸症候群(Obstructive Sleep Apnea Syndrome：OSAS)と呼ばれる．SAS患者全体に占める割合は，OSAS患者が圧倒的に多いため，以下，本稿における“SAS”は，OSASと同義として話を進める．

SASの有病率について最もよく知られた研究は，Youngらによる Wisconsin Sleep Cohort Studyである．この研究では，30～60歳の米国の州政府職員1,490人より抽出した習慣性のいびきを有する626人を対象に終夜睡眠ポリグラフ(polysomnography：PSG)検査を実施し，無呼吸低呼吸指数(Apnea Hypopnea Index：AHI)≧5の有病率は男性で24%，女性で9%であったと報告した．また，AHI≧5に加えて日中の眠気まで伴う者の有病率は，成人男性の4%，成人女性の2%であると推定した[1]．Tanigawaらが，わが国の30～62歳の男性勤務者459人にパルスオキシメトリ検査を実施し，3%以上の動脈血酸素飽和度低下指数が1時間に15回以上をSDBと定義したときの有病率は7.6%[2]，40～69歳の男性地域住民1,424人の有病率を同様の方法で算出した場合は9.0%であった[3]．重症度の定義や調査方法によって，SDB/SASの有病率は異なってくるものの，概ね人口の数～十数%となる報告が多いようである．

SASは従来，太った中年男性の病気としてのみ捉えられる傾向があった．典型的な患者がそのような例であることは間違いないが，典型例のイメージに捉われていては，重症者の見落としにつながるおそれがある．SASは，性別を問わず，どの年齢層においても発生し得る．また，日本人では，欧米人と比較して非肥満者でもSDBを呈することが多い．咽頭のスペースに余裕がなく上気道が閉塞しやすい顔面頭蓋骨格の人が多いためである．患者が若年者でもやせ型でも女性でも，

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病歴などからSASの存在が疑われれば，客観的な検査を施行する必要がある．

SASによる事故リスクの上昇

SASの患者は深い睡眠をとれなくなる．睡眠中に生じる無呼吸・低呼吸イベントにより，睡眠が分断化されるためである．その結果として日中の過度の眠気および集中力の低下が生じ，運転事故や，業務中の事故の原因となる．Sassaniらは，1980～2003年までのSDB有病者による自動車事故発生に関する6本の関連論文を検討し，SDB患者が交通事故を起こすリスクは約2.5倍と述べている[4]．Ellenらによる27本の同様の論文の検討結果でも，SDB患者では自動車運転事故のリスクが2～3倍に上昇するとしている[5]．わが国の運転免許保有者3,235人を対象にしたアンケート調査においても，SASと診断されたことのある運転者の居眠り運転のリスクは，SASと診断されたことのない運転者と比較して3.2倍であった[6]．

2008年に愛知県で赤信号にもかかわらず交差点に入り歩行者をはねて死亡させた事故のトラック運転者や，2005年11月に名神高速道路で仮眠した10分後の居眠り運転で7人が死亡した多重衝突事故を起こしたトラック運転者のいずれもが，重症のSASであったと鑑定された．このようにSAS患者が自覚症状のないまま大事故の加害者となり，一般市民が被害者となる事例がある．したがって，運転業務やその他の危険作業に労働者を従事させる場合，使用者側は，労働者がSASに罹患していないかを確認する必要がある．SASに罹患しながら，医療機関で診断される機会がなかった労働者が，居眠りによる勤務中の事故を起こして第三者に損害を加えた場合，監督義務者や使用者が損害を賠償する責任を問われる可能性がある(民法第714条，715条)．

SASによる循環器疾患リスク

生活習慣病および循環器疾患発症にも，SASは深く関わっている．例えば，二次性高血圧の原因の一つとして，日本高血圧学会による「高血圧ガイドライン2009」にSASは挙げられている．糖尿病に関しても，SDBにより耐糖能障害やインスリン抵抗性が出現するという報告が集積しており，Murakiらも，地域住民においてSDBの重症度が，将来の糖尿病の発症とつながることを，前向きコホート研究で明らかにした[7]．近年，メタボリックシンドロームと睡眠呼吸障害の関連についても，疫学的な見地からの報告が多く出されている．わが国では，2006年にSasanabeらが，AHI≧30の重症のOSASの男性患者がメタボリックシンドロームを有するオッズ比は5.1であると報告している[8]．

一方，メタボリックシンドロームの患者におけるSDBのリスクについては，2010年にChinらが，メタボリックシンドロームに罹患している男性勤労者の6人に1人に重症の閉塞型睡眠時無呼吸が認められることを明らかにした[9]．これは，メタボリックシンドロームに罹患していない場合の40人に1人よりも有意に高い．循環器疾患のリスクに関しても，Marinらが健常人・単純いびき症患者・未治療OSAS患者・CPAP(Continuous Positive Airway Pressure；持続陽圧呼吸療法)治療中患者の約10年の追跡調査を行い，未治療OSAS患者の循環器疾患死亡，もしくは非致死的循環器疾患罹患に対するハザード比が，健常者に比べてそれぞれ2.9倍および3.2倍に上昇すると報告した[10]ものなど，多くの研究成果が出されている．

SASの治療

SASは，治療によって改善し得る疾患である．治療の第一選択は，CPAPで，これは，睡眠時に装着するマスクから陽圧をかけた空気を気道に送りこんで拡げるというものである．適切に使えればほぼ確実に効果があり，合併症の予防にもなり，副作用も少ないことが利点だが，対症療法であるため長期間使い続けなければならない．途中で治療を中断してしまう患者も残念ながら多く，効果的な治療を維持するためには，医療者からの

表　睡眠呼吸障害(SDB)の重症度と自覚的眠気

		睡眠呼吸障害				計
		正常範囲 (RDI 5未満)	軽度 (RDI 5～19.9)	中等度 (RDI 20～39.9)	重度 (RDI 40以上)	
弱↑眠気の自覚↓強	ESS 0～5	1,457 (28%)	1,391 (27%)	201 (3.8%)	46 (0.9%)	3,095 (59%)
	ESS 6～10	774 (15%)	725 (14%)	138 (2.6%)	52 (1.0%)	1,689 (32%)
	ESS 11～15	142 (2.7%)	170 (3.2%)	34 (0.6%)	23 (0.4%)	369 (7%)
	ESS 16 以上	37 (0.7%)	44 (0.8%)	5 (0.1%)	8 (0.2%)	94 (1.8%)
計		2,410 (46%)	2,330 (44%)	378 (7.2%)	129 (2.5%)	5,247 (100%)

出典：文献[11]より改変引用
注 1)　RDI：Respiratory Disturbance Index：呼吸障害指数
注 2)　ESS：Epworth Sleepiness Scale，エプワース眠気尺度(正常 0～10 点)

働きかけが重要である．他の治療法としては減量，睡眠中の口腔内装置の装着や，手術などがあるが，効果の出方に個人差が大きく，CPAP ほど合併症予防のエビデンスが確立していない．

眠気のない睡眠時無呼吸の問題

2003 年に，JR 西日本の新幹線運転士が居眠りしたまま新幹線を 26 km 走らせたという，一歩間違えれば大事故になりかねなかった事件があった．その運転士が重症の SAS に罹患していたことが明らかになり，一躍 SAS は世間の注目を集めた．このとき，スクリーニング法として企業などでよく用いられたものが，エプワース眠気尺度(Epworth Sleepiness Scale：ESS)である．これは，さまざまな状況における日中の主観的な眠気について点数をつけ，合計点から過度の眠気の有無を判断するというもので，簡便に出来ることが利点である．ただし実のところ，SAS の有無を ESS の点数によって判断することはできない．例えば，2003 年 10 月に名古屋で起きた列車衝突事故では，事故を起こした運転士は，事故前の ESS では病的な眠気はないと判断され，2 次検査の対象外とされていたが，事故直後の PSG 検査で重症の SAS と診断された．筆者(谷川)も，トラック運転手 5,287 人を対象に，フローセンサ法を用いて SDB の重症度と ESS の点数の関連を調べたところ，呼吸障害指数(Respiratory Disturbance Index：RDI)が 40 以上と重症の SDB が認められる群でも，自覚的眠気が正常範囲内(ESS 11 点未満)の者が 76% もいたことが判明した(表)[11]．

実際に自動車事故を起こした SAS 患者へのインタビューによると，「居眠りをして気がついたら前の車の後部に追突していた」「高速運転中，気がついたら出口で側壁に衝突していた」と，「気がつくと」「ふっと」という表現が散見され，自覚的な眠気を感じていない場合でも，SAS 患者は，予兆なく居眠りに陥っている場合があるのではないかと推測される[12]．実際には居眠りに落ちるほどの眠気があるにもかかわらず，眠気を自覚できない理由としては，SDB が慢性の経過をたどって徐々に重症化するために，眠気が加齢による慢性疲労症状と誤解されていることや，慢性の睡眠不足状態においてタバコやコーヒー，清涼飲料水が多量摂取され，ニコチンやカフェインの作用で眠気を自覚しにくくなっていることが考えられる．また，職域におけるスクリーニングとして眠気について尋ねた場合は，雇用上不利になることをおそれて，眠気を過少申告する者が多いであろうことも想像に難くない．眠気の訴えがないばかりに，潜在的な SAS 患者の多くが受診に至らず放置されているという現状があり，筆者は，自覚的眠気がない睡眠時無呼吸(Non Sleepy Sleep Apnea：NOSSA)という概念を提唱し，注意を喚起している．

業務中の居眠りが重大事故に直結するおそれがあり SAS を見逃してはならない集団，すなわち運転業務従事者などを対象とした SAS 健診においては，自覚的眠気を指標とした一次スクリーニングを行わずに，客観的な簡易検査を一次スクリーニングとして用いることが妥当と考えられる．

スクリーニングのための簡易検査としては，睡眠中の血中酸素飽和度の低下する頻度を測定するパルスオキシメトリ法が当初はよく用いられていたが，非肥満者においてSDBの際に血中酸素飽和度が低下しにくいことから，見逃しが多くなるという欠点があった．最近では，鼻と口の気流を検知するフローセンサ法が，非肥満者においてより感度の高いスクリーニング法として，全日本トラック協会および鉄道会社などにおいて施行されるようになってきた．

福島原発とSAS

筆者(谷川)は，20年来，東京電力福島原子力発電所の非常勤産業医を務めてきた．2011年3月11日の東日本大震災以来，現場と連絡を取り続け，4月16～19日に震災後初めて福島第二原子力発電所で健康支援活動に従事した．作業員の健康管理体制全般についての問題は他誌で取り上げられているので[13]，ここでは作業員がおかれていた睡眠環境についてのみ述べる．

4月16日の作業員との面談時，他者のいびきにより1時間毎に目が覚めるという訴えがあった．第一原発の多くの従業員が主要な宿泊施設として使用していた第二原発の体育館の夜間巡視を行ったところ，体育館内で常時150～400人が就寝し，重症のSAS患者による強烈ないびきにより，多くの作業員の睡眠が妨げられている状況が判明した．SAS患者本人の循環器疾患のリスクなど健康上の問題に加えて，周囲の多くの作業員の安眠が妨げられることによって，結果として就寝する全員に日中の眠気が生じ，これらに起因するヒューマンエラーによる深刻な二次災害のおそれがあると推測された．

4月17日にフィリップス・レスピロニクス合同会社に支援を要請し，CPAP機器の提供を受け，震災前にCPAPを使用していた2名に装着した．この2名に翌日面談した結果，熟睡できて疲労も回復したとの感想を得た．さらにSASが強く疑われる大きないびきを発している方々の就床中に置き手紙をし，翌晩から，先の2名と併せて計11名にCPAP治療を実施した．6月末現在，約25人がCPAPを使用している．これによって，CPAPを装着できた本人の事故リスクおよび循環器疾患のリスクが避けられること，さらに他者の睡眠妨害が避けられることによって，発電所全体の事故予防および健康に資することを期待している．今後は，CPAP実施前後の睡眠状況の変化，日中の眠気などを評価する予定である．

文　献

1) Young T, et al : The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 328(17) : 1230-1235, 1993
2) Tanigawa T, et al : Sleep-disordered breathing and blood pressure levels among shift and day workers. Am J Hypertens 19(4) : 346-351, 2006
3) Tanigawa T, et al : Relationship between sleep-disordered breathing and blood pressure levels in community-based samples of Japanese men. Hypertens Res 27(7) : 479-484, 2004
4) Sassani A, et al : Reducing motor-vehicle collisions, costs, and fatalities by treating obstructive sleep apnea syndrome. Sleep 27(3) : 453-458, 2004
5) Ellen RL, et al : Systematic review of motor vehicle crash risk in persons with sleep apnea. J Clin Sleep Med 2(2) : 193-200, 2006
6) 平成18年度警察庁委託調査研究報告書「睡眠障害と安全運転に関する調査研究」, 2007
7) Muraki I, et al : Nocturnal intermittent hypoxia and the development of type 2 diabetes ; the circulatory risk in communities study (CIRCS). Diabetologia 53(3) : 481-488, 2010
8) Sasanabe R, et al : Metabolic syndrome in Japanese patients with obstructive sleep apnea syndrome. Hypertens Res 29(5) : 315-322, 2006
9) Chin K, et al : Associations between obstructive sleep apnea, metabolic syndrome, and sleep duration, as measured with an actigraph, in an urban male working population in Japan. Sleep 33(1) : 89-95, 2010
10) Marin JM, et al : Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure ; an observational study. Lancet 365(9464) : 1046-1053, 2005
11) 谷川武，他：眠気のない睡眠時無呼吸(NOSSA)が及ぼす社会影響への取り組み．日本医事新報 4513 : 51-55, 2010
12) 櫻井進，他：睡眠医療専門機関受診者における睡眠呼吸障害と交通事故との関連．厚生の指標 57(4) : 6-13, 2010
13) 谷川武：[Interview] 原発復旧作業員の健康管理．日本医事新報 4543 : 14-17, 2011

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特集 睡眠呼吸障害の最近の話題

睡眠呼吸障害と合併症
—特に糖尿病との関連での最近の話題—

淡野 桜子* 谷川 武*

はじめに

自覚症状の乏しい睡眠呼吸障害の患者が治療中断を希望する際に，合併症を防ぐ意義を説明することが治療継続に有用と考えられる．本稿では，睡眠呼吸障害の合併症，特に糖尿病に関する最近の研究成果を紹介する．

睡眠呼吸障害の合併症

睡眠呼吸障害の合併症は，「心血管疾患およびそのリスク因子」と「心血管疾患に関連しないもの」に二分される．

睡眠呼吸障害と高血圧の関連は，かつては疑問視されてきた．肥満が高血圧と睡眠呼吸障害の両方に大きな影響を及ぼすことや，睡眠呼吸障害の判定基準の妥当性の問題などからである．しかし，終夜睡眠ポリグラフ検査(polysomnography：PSG)を用いて，大規模な一般集団において睡眠呼吸障害と高血圧の関連を，年齢，肥満度，飲酒量などの交絡因子を多変量解析で調整した後に検討した結果が数多く出された．さらにPeppardらのWisconsin Sleep Cohort Studyでの追跡調査結果から，今日では睡眠呼吸障害は高血圧発症の一因であることが広く認識されている[1]．2003年のThe Seventh Report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure(JNC 7)においても，二次性高血圧の原因疾患の一つとして睡眠時無呼吸が挙げられている[2]．また，日本高血圧学会による高血圧治療ガイドライン(JSH2009)においても，閉塞性睡眠時無呼吸症候群(obstructive sleep apnea syndrome：OSAS)は「二次性高血圧の最も多い要因の一つ」で「これを適切に診断・治療することは，より効率的な高血圧治療を行う上でも極めて大きな意義がある」と記されている．

メタボリックシンドロームに関しては，2006年にSasanabeらが，無呼吸低呼吸指数(apnea hypopnea index：AHI)≧30の重症のOSASの男性患者がメタボリックシンドロームを有するオッズ比は5.1であると報告している[3]．

心血管疾患と睡眠呼吸障害に関しては，健常者・単純いびき症患者・未治療OSAS・CPAP治療中患者を対象とした約10年の追跡調査で，未治療OSAS患者の循環器疾患死亡，もしくは非致死的循環器疾患罹患に対するハザード比が，健常者に比べてそれぞれ2.9倍および3.2倍に上昇したと報告された[4]．Gottliebらは，4,422人の地域住民を約8年間追跡し，40歳から70歳の男性においてのみ，閉塞性睡眠時無呼吸(obstructive sleep apnea：OSA)が冠動脈疾患発症の予測因子となり，全年齢の男性においてOSAが心不全の予測因子となることを示した[5]．

脳卒中との関連については，PSG検査を実施した1,022人を対象とした前向きコホート研究において，脳卒中罹患もしくは死亡をエンドポイントとした場合，睡眠呼吸障害患者のハザード比は，非睡眠呼吸障害者と比較して，高血圧を含む循環器疾患と関連する危険因子の調整後も2.0倍であった[6]．Redlineらは，5,422人の地域住民を中央

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値8.7年間追跡して，OSAのある男性において，OSAと脳梗塞の新規発症との間に有意な正の関連を示した[7]．

心血管疾患以外にも，胃食道逆流，夜間頻尿，男性機能不全(ED)などが睡眠呼吸障害の合併症として指摘されている．これらの病態は致死的ではないものの，QOLの低下につながる．睡眠呼吸障害の治療によってこれらの病態が改善することにより，患者が治療を継続する動機付けとなり得る．さらに，睡眠呼吸障害はうつ病の危険因子との報告もあり，抑うつ状態の患者において睡眠呼吸障害の有無を確認することも重要である．

睡眠呼吸障害と糖尿病

糖尿病・耐糖能異常を合併する睡眠呼吸障害患者は多く，睡眠呼吸障害を合併する糖尿病患者も多い．地域住民を対象とした研究において，OSAS患者の30%が2型糖尿病を合併し，20%にimpaired glucose toleranceが認められた[8]．また，糖尿病患者の58%が何らかの睡眠呼吸障害を伴っていた[9]．International Diabetes Federationが2008年に出した勧告では，睡眠呼吸障害患者における耐糖能の評価および糖尿病患者における睡眠呼吸障害の評価を勧めている[10]．

肥満は，睡眠呼吸障害と糖尿病，両方の危険因子である．そのため，睡眠呼吸障害の患者に糖尿病が多く発症することは，肥満の影響であろうと長らく考えられてきた．近年になって，睡眠呼吸障害自体が，肥満とは独立して糖尿病・耐糖能異常の危険因子であることを示唆する報告が多く出ている．1999年にSpiegelらは，11人の若年男性の睡眠を6日間4時間に制限すると，十分に睡眠をとったときと比較して耐糖能は低下し，血中サイロトロピンおよび夕方の血中コルチゾールが上昇，交感神経活動が増大することを示し，睡眠負債が内分泌機能に悪影響を及ぼすことを初めて示した[11]．最近では，糖尿病に罹患していない118人にPSGおよび経静脈的ブドウ糖負荷試験を実施した結果，体脂肪率などを考慮に入れてもなお，睡眠呼吸障害の重症化に伴いインスリン感受性が低下し，中等症以上の睡眠呼吸障害患者ではインスリン分泌能も低下したという報告がある[12]．

睡眠呼吸障害が糖代謝に影響を及ぼすには，睡眠の断片化と間欠的低酸素の両方が関与しているとみられる．9人の若年健常者の徐波睡眠を聴覚刺激によって選択的に分断した研究では，徐波睡眠剥奪の程度とインスリン感受性の低下が強く関連していた[13]．11人の若年健常者の睡眠を，睡眠ステージに関わりなく分断した研究では，インスリン感受性およびグルコース感受性が，睡眠を分断していないときと比較していずれも有意に低下し，また，睡眠分断時に交感神経活動の活発化および朝のコルチゾールレベルの上昇が認められた[14]．一方，間欠的低酸素の影響に関しては，13人の健常者を覚醒時に間欠的低酸素の環境に置いた研究で，正常な酸素環境に置いた場合と比較してインスリン感受性およびグルコース感受性が有意に低下した[15]．これらの知見から，睡眠呼吸障害による間欠的低酸素によってhypoxia-inducible factor-1(HIF-1)が活性化し，インスリン感受性や交感神経活性化，脂質代謝，全身性の炎症など，動脈硬化に関わる種々の因子に影響を及ぼす可能性が指摘されている．

睡眠呼吸障害と糖尿病の関連に関する疫学研究(表1)は，これまでは横断研究が多かった．Punjabiらは，米国のSleep Heart Health Study(SHHS)からPSGと75g経口ブドウ糖負荷試験(oral glucose tolerance test：OGTT)を実施した2,656人の男女のデータを解析し，呼吸障害指数(respiratory disturbance index：RDI)15回/hr以上の群では性，年齢，BMI，腹囲を含めた多変量を調整後も空腹時血糖と血糖の2時間値が有意に上昇し〔オッズ比はそれぞれ1.46(95%信頼区間1.09-1.97)と1.44(95%信頼区間1.11-1.87)〕，睡眠呼吸障害の重症度と耐糖能異常の有病率との間に正の関連があることを示した．また同様に，睡眠中の血中酸素飽和度の平均値と空腹時血糖の間に負の関連があること，睡眠中の血中酸素飽和度が90%未満に低下している時間と空腹時血糖・血糖の2時間値の間に負の関連があることを示した．しかし，覚醒指数と血糖値の間には有意な関連は認められなかった[16]．

Seiceanらは同じくSHHSから2,588人のデータを解析し，RDI 10回/hr以上を睡眠呼吸障害群としたときに，性，年齢，BMI，腹囲を調整後にOGTTによる境界型に対するオッズ比が非睡眠呼

表1　睡眠呼吸障害と糖尿病・耐糖能異常についての最近の疫学研究

発表者（発表年）	解析対象	睡眠呼吸障害の評価法	耐糖能の評価法	結果の概要
Punjabi et al (2004)[16]	2,656人の米国の地域住民の男女.	PSG	OGTT	RDI 15の群で，空腹時血糖と血糖の2時間値が上昇した(横断研究).
Seicean et al (2008)[17]	2,588人の米国の地域住民の男女.	PSG	OGTT	RDI 10以上の群で，OGTTによる境界型・糖尿病型の有病率が上昇した(横断研究).
Reichmuth et al (2005)[18]	1,387人の米国の州職員の男女.	PSG	空腹時血糖，糖尿病罹患の自己申告	AHI 15以上の群で糖尿病の有病率が上昇(横断研究)，4年間追跡時にはベースラインのAHIと追跡期間中の糖尿病発症との間に有意な関連は認められなかった(縦断研究).
Marshall et al (2009)[20]	295人のオーストラリアの地域住民の男女.	簡易PSG	空腹時血糖，糖尿病罹患の自己申告	RDI 15以上の群で，追跡期間中の糖尿病発症率が増大した(縦断研究).
Shin et al (2005)[21]	2,719人の韓国地域住民の男性.	いびきの自己申告	OGTT	いびきの習慣がある群は，OGTTにおける血糖の1時間値，2時間値が上昇していた(横断研究).
Muraki et al (2009)[22]	3,864人の日本の地域住民の男女.	オキシメトリー	空腹時血糖，随時血糖，糖尿病罹患の自己申告	3%ODI 15以上の群で追跡期間中の糖尿病発症率が増大した(縦断研究).

吸障害群に比して1.4(95%信頼区間1.1-2.7)，同様に糖尿病型に対するオッズ比が1.7(95%信頼区間1.1-2.7)であると報告した．ただし，この研究ではBMI 25kg/m²を境に層別化したとき，BMI 25 kg/m²未満の群では睡眠呼吸障害と耐糖能異常の関連は弱まり，交絡因子を調整後は空腹時血糖が高値となるオッズ比のみ1.6(95%信頼区間1.0-2.5)と有意に上昇していた[17]．

Wisconsin Sleep Cohort Studyでは，1,387人の男女を対象として，PSGおよび空腹時採血，病歴聴取を行い，AHI 15回/hr以上の群においての糖尿病罹患のオッズ比は，性，年齢，体形の調整後も，AHI 5回/hr未満の群に比して2.30(95%信頼区間1.28-4.11)と有意に大きいことを示した．この研究では，同じ被験者を対象とした縦断研究の結果も報告している．4年間追跡したときの糖尿病発症率をAHI 15回/hr以上の群とAHI 5回/hr未満の群で比較すると，性，年齢，体形で調整後には発症率の有意な差は認められず，睡眠呼吸障害と糖尿病の間の因果関係は確認できなかった[18]．

他の縦断研究としては，米国の睡眠センターへ紹介されてきた544人の非糖尿病患者をPSG後平均2.7年間追跡したものがある．この研究では，BMIおよび体重変化を含む多変量で解析した後も睡眠時無呼吸と糖尿病発症(空腹時血糖および医師の診断)との間に独立した関連が認められた(ハザード比1.43，95%信頼区間1.10-1.86)[19]．

ほかにも，オーストラリアの地域住民295人を簡易PSG後4年間追跡した研究では，RDI 15以上の睡眠呼吸障害において，空腹時血糖により判定した糖尿病発症のオッズ比が，RDI 5未満の群と比して，性，年齢，腹囲調整後に13.45(95%信頼区間1.59-114.11)であった[20]．

ただし，人種によるインスリン分泌や感受性の違い，肥満度の違いを考慮すると，上記の研究結果をそのまま日本人にあてはめることはできない．被験者の平均BMIが多くの研究で30kg/m²に近く，肥満の影響を排除しきれていないおそれもある．

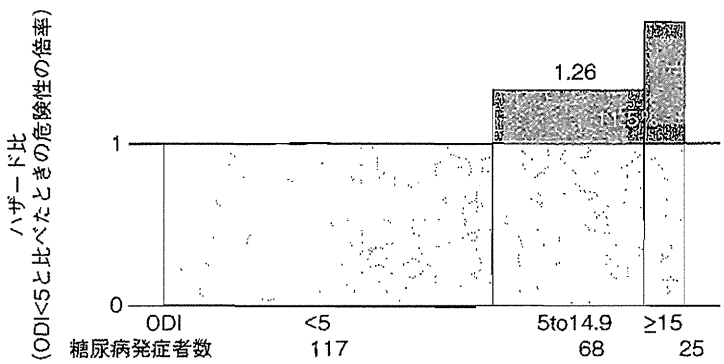

図1　Murakiらの報告[22]における糖尿病発症の寄与危険割合
年齢，性別，body mass index，喫煙状況，現在飲酒量，閉経状況，境界型糖尿病，睡眠時間，調査地域を調整．

Shinらは，韓国人の男女2,719人〔糖尿病，重症高血圧，肥満者(BMI 27.5以上)を除外したもの〕を対象としていびき習慣の有無と75gOGTTの結果の関連を調べた．いびきの習慣がある群は，いびきの習慣のない群と比較して，BMI調整後も，75gOGTTにおける血糖の1時間値および2時間値が上昇するオッズ比がそれぞれ1.33(95%信頼区間1.05-1.71)，1.32(95%信頼区間1.03-1.68)であった[21]．

日本の地域住民を対象とした大規模な縦断研究として，Murakiらは，地域住民の男女3,864人をパルスオキシメトリ検査後，約3年間追跡し，3%酸素飽和度低下指数(oxygen desaturation index：ODI)15以上の睡眠呼吸障害がベースラインにあった者が追跡期間中に糖尿病を発症したオッズ比が1.69(95%信頼区間1.04-2.76)であったことを示した．このとき，3%ODIが5-14.9のときと15以上のときの糖尿病発症の寄与危険割合を合計すると11.5%となった(図1)．すなわち，わが国の糖尿病の約10%は，睡眠呼吸障害を早期発見・早期治療(3%ODI 5未満まで)することにより予防できる可能性が示された[22]．

まとめ

睡眠呼吸障害と糖尿病に関するこれまでの研究成果として，軽症の睡眠呼吸障害と糖尿病の有意な関連を示す報告はこれまでのところ乏しいが，中等症以上の睡眠呼吸障害に関しては糖尿病・耐糖能異常と関連しているとする報告が多い．ただし，非肥満者のみの解析では有意な結果が出ていないことから肥満が交絡している可能性は否定できず，また縦断研究によって因果関係が立証された知見は少ない．SHHSなどの大規模疫学研究による縦断研究の報告が待たれる．

肥満度を調整しない解析においては睡眠呼吸障害の重症度と糖尿病・耐糖能異常との間にほぼ例外なく正の関連が認められており，二者間に独立した関連があるか否かは議論の余地があるにしても，睡眠呼吸障害患者が糖尿病を合併しやすいこと自体は間違いない．したがって，睡眠呼吸障害患者の診断時およびその後の治療中に適宜耐糖能の評価，糖尿病の管理が重要と考えられる．

文　献

1) Peppard PE et al：Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000；342；1378-1384.
2) National Heart Lung and Blood Institute：The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure-complete report. http://www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.htm
3) Sasanabe R et al：Metabolic syndrome in Japanese patients with obstructive sleep apnea syndrome. Hypertens Res 2006；29：315-322.
4) Marin JM et al：Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure：an observational study. Lancet 2005；365：1046-1053.
5) Gottlieb DJ et al：Prospective study of obstruc-

tive sleep apnea and incident coronary heart disease and heart failure : The Sleep Heart Health Study. Circulation 2010 ; 122 : 352-360.
6) Yaggi HK et al : Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med 2005 ; 353 : 2034-2041.
7) Redline S et al : Obstructive sleep apnea-hypopnea and incident stroke : The Sleep Heart Health Study. Am J Respir Crit Care Med 2010 ; 182 : 269-277.
8) Meslier N et al : Impaired glucose-insulin metabolism in males with obstructive sleep apnea syndrome. Eur Respir J 2003 ; 22 : 156-160.
9) Resnick HE et al : Diabetes and sleep disturbances : findings from the Sleep Heart Health Study. Diabetes Care 2003 ; 26 : 702-709.
10) Shaw JE et al : Sleep-disordered breathing and type 2 diabetes : A report from the International Diabetes Federation Taskforce on Epidemiology and Prevention. Diabetes Res Clin Pract 2008 ; 81 : 2-12.
11) Spiegel K et al : Impact of sleep debt on metabolic and endocrine function. Lancet 1999 ; 354 : 1435-1439.
12) Punjabi NM and Beamer BA : Alterations in glucose disposal in sleep-disordered breathing. Am J Respir Crit Care Med 2009 ; 179 : 235-240.
13) Tasali E et al : Slow-wave sleep and the risk of type 2 diabetes in humans. PNAS 2008 ; 105 : 1044-1049.
14) Stamatakis KA and Punjabi NM : Effects of sleep fragmentation on glucose metabolism in normal subjects. Chest 2010 ; 137 : 95-101.
15) Louis M and Punjabi NM : Effects of acute intermittent hypoxia on glucose metabolism in awake healthy volunteers. J Appl Physiol 2009 ; 106 : 1538-1544.
16) Punjabi NM et al : Sleep-disordered breathing, glucose intolerance, and insulin resistance : The Sleep Heart Health Study. Am J Epidemiol 2004 ; 160 : 521-530.
17) Seicean S et al : Sleep-disordered breathing and impaired glucose metabolism in normal-weight and overweight/obese individuals : the Sleep Heart Health Study. Diabetes Care 2008 ; 31 : 1001-1006.
18) Reichmuth KJ et al : Association of sleep apnea and type II diabetes : a population-based study. Am J Respir Care Med 2005 ; 172 : 1590-1595.
19) Botros N et al : Obstructive sleep apnea as a risk factor for type 2 diabetes. Am J Med 2009 ; 122 : 1122-1127.
20) Marshall NS et al : Is sleep apnea an independent risk factor for prevalent and incident diabetes in the Busselton Health Study? J Clin Sleep Med 2009 ; 5 : 15-20.
21) Shin C et al : Association of habitual snoring with glucose and insulin metabolism in nonobese Korean adult men. Am J Respir Crit Care Med 2005 ; 171 : 287-291.
22) Muraki I et al : Nocturnal intermittent hypoxia and the development of type 2 diabetes : the Circulatory Risk in Communities Study(CIRCS). Diabetologia 2010 ; 53 : 481-488.

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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

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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

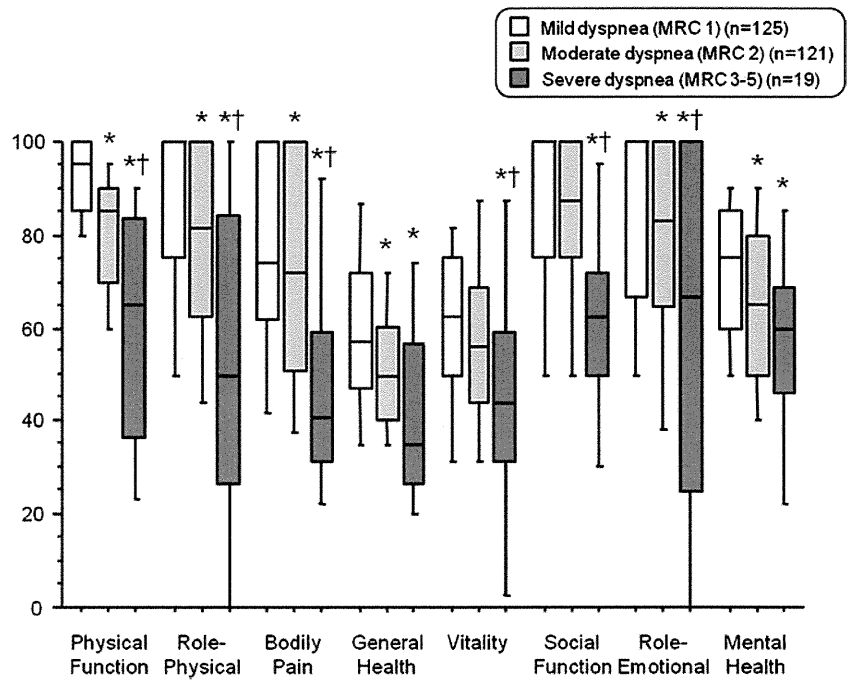

Fig. 1 *Box and whisker plots* representing the score distributions on the SF-36 between groups, based on the MRC dyspnea scale. The *boxes* show the first to third quartile, the *horizontal line* represents the median, and the *vertical bars* indicate the 10th to 90th percentiles. *Asterisk*, significant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

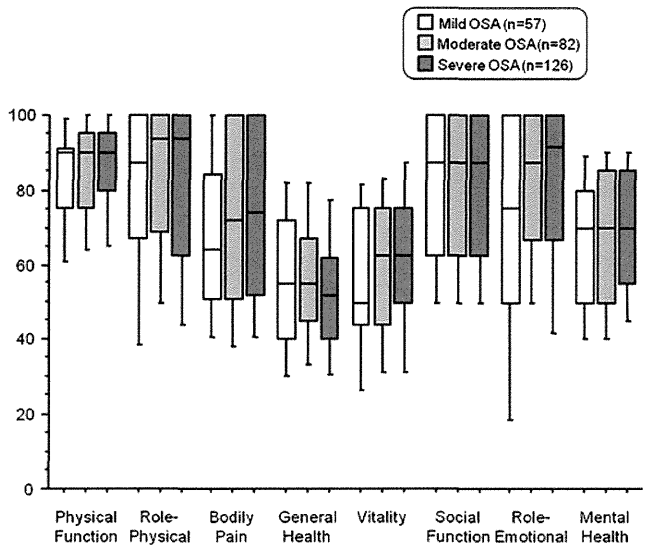

Fig. 2 *Box and whisker plots* representing the score distributions on the SF-36 between groups, based on the level of the AHI. The *boxes* show the first to third quartile, the *horizontal line* represents the median, and the *vertical bars* indicate the 10th to 90th percentiles

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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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

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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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