Results The CV for tidal volume was significantly greater (p=0.001), and mutual information was significantly lower (p=0.041) in Group A as compared to Group B.
Conclusions Differences in two independent measures of breathing irregularity correlated with CPAP rejection in OSA patients without nasal symptoms or comorbidity. Prospective studies of adherence should examine traits of breathing stability.

Keywords Obstructive sleep apnea · CPAP adherence · Respiratory control · Nonlinear analysis

Introduction

Individuals breathe in different ways under strictly defined conditions during quiet wakefulness. There are also significant effects of different cognitive events such as thought, attention, and emotion on the basic breathing pattern, presumably through forebrain influences. Although forebrain activity is depressed during slow-wave sleep (non-REM), breathing individuality persists [1]. Moreover, identical twins breathe with a similar pattern [2, 3]. Thus, genetic background affects breathing pattern, and accounts for variation across individuals.

Breathing variability is measured not only through physiologic extractions of respiratory frequency and tidal volume but also using analyses of the breathing signal unrelated to the physiologic extractions. The latter includes methods such as sample entropy and mutual information that deconstruct the signal, and disclose features and patterns that reveal structural underpinnings and complexity. Such complexity occurs in expression of and differs among apnea types [4]. Previously, we reported a difference in an information theory-based metric of signal pattern variability (sample entropy) among patients with obstructive sleep apnea syndrome (OSAS) comparing those with many mixed apneas (>30 % of events being mixed apneas) to those with predominant obstructive apnea. Secondary observations in this data set suggested that breathing variability during wakefulness could be a predictor of acceptance of CPAP as a therapy [5]. While studies indicate that age, sex, severity of disease, symptoms of sleepiness, socioeconomic status, nasal symptoms, and psychological factors relate to CPAP adherence in OSAS [6–15], none have considered an individual's inherent features of respiratory control as quantified in terms of measures of variability.

Using a case–control design, we tested the hypothesis that the regularity of resting breathing during wakefulness might be a predictive feature of subsequent CPAP acceptance. Patients with nasal symptoms and comorbidity known to affect adherence were excluded, and our analysis focused on the breathing pattern during wakefulness prior to the diagnostic polysomnography (PSG). Ventilatory pattern variability was quantified using conventional (linear) statistical analysis (coefficient of variation (CV)) of breath-to-breath tidal volume and frequency from noninvasive measures, as well as an information-based analysis of the respiratory signal using mutual information, an approach that uses the raw respiratory waveform data that does not depend on either breath depth or frequency identification.

Methods

Subjects

There was an initial exclusion of patients with an apnea–hypopnea index (AHI) <20 who had medical history of arrhythmia, cerebral infarction, and psychosomatic/psychogenic diseases or who used opioid, hypnotic medications, or antidepressant; all of which might have an influence on breathing irregularity. Figure 1 shows the ascertainment profile of the study that resulted in the final comparison

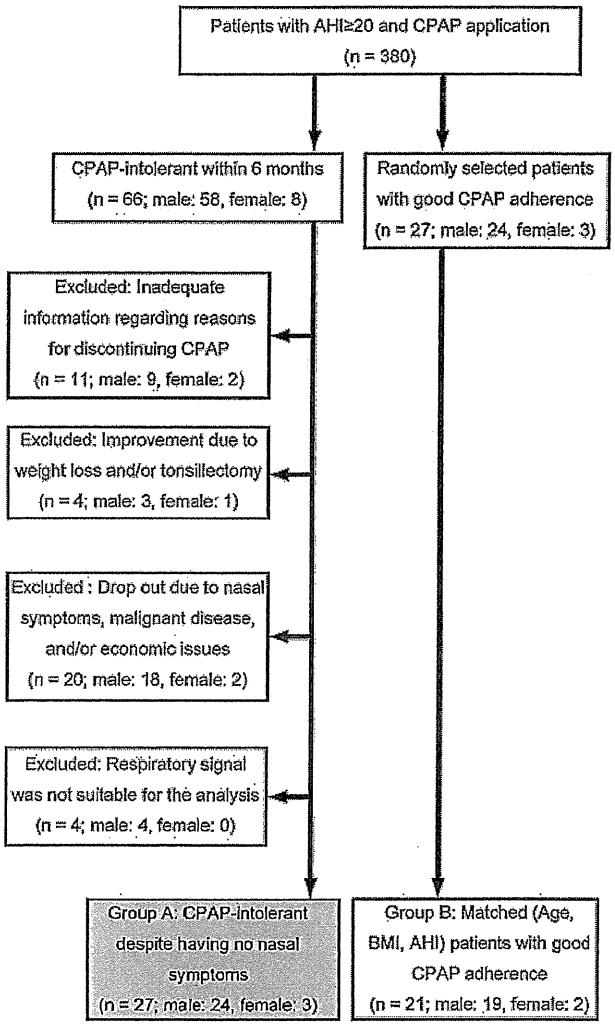

Fig. 1 Diagram for the comparison groups enrollment

groups. Among 380 patients with obstructive sleep apnea (OSA) who had a diagnostic PSG and then who were prescribed CPAP from 2007 to 2010, 66 patients quit CPAP treatment at 6 months. Among these 66 patients, 11 patients were excluded from further analysis due to loss of the information regarding reasons for CPAP dropout, 4 patients quit CPAP because sleep disordered breathing was improved by weight loss and/or tonsillectomy, 20 patients were CPAP-intolerant because of nasal symptoms, malignant diseases, and/or economic issues, and 4 patients were excluded as an adequate respiratory signal could not be obtained during wakefulness. Eventually, 27 patients were enrolled to this study analysis (Group A). We also randomly extracted 27 patients with good CPAP adherence from the same database. Fairly good adherence to CPAP was defined at a high threshold, i.e., more than 90 % of days with more than 5 h usage each night. A final group of 21 patients that were matched for age, body mass index (BMI), and AHI within the mean and standard deviation values for Group A were designated as Group B. Data were collected on the Epworth sleepiness scale (ESS) and current medications. Written informed consent was obtained from all patients, and the Human Subjects Ethics Committee of Nara Medical University approved the study.

Diagnostic PSG

Data acquisition started from 9 p.m. and continued until 6 a.m. on the following morning. Subjects were not informed that the respiratory signal before sleep onset was extracted and used for analysis. When sensors were applied and data acquisition could be initiated, subjects were instructed to close their eyes and the recording started.

The PSG was performed using a polygraph system (EEG7414; Nihon Kohden, Tokyo, Japan). electroencephalogram (EEG; C3-A2, C4-A1), bilateral EOG, submental electromyogram (EMG), ECG, and bilateral anterior tibial EMG were recorded. Airflow was monitored using an oronasal thermal sensor and/or nasal air pressure transducer. Thoracic and abdominal respiratory movements were monitored using respiratory inductance plethysmography (RIP) (Respitrace; Ambulatory Monitoring Inc., Ardsley, NY, USA). Oxyhemoglobin saturation and pulse rate were monitored using pulse oximetry with a finger probe (OLV-3100; Nihon Kohden, Tokyo, Japan). All the signals were digitized and stored on a personal computer. Apneas were defined as an episode of complete airflow cessation measured from the thermal sensor lasting more than 10 s. Hypopnea was defined by≥30 % reduction in amplitude of the RIP-sum signal lasting more than 10 s with≥3 % oxygen desaturation. AHI was calculated as the average number of apnea–hypopnea events per hour over the total sleep period.

CPAP

All patients were initiated on nasal CPAP (REMstar Auto; Respironics; Pittsburgh, PA, USA or GoodKnight 420E; Tyco Mallinckrodt Plaisir, France) with auto titrating mode. All patients under CPAP treatment visited our sleep laboratory every month, which is mandatory in the Japanese healthcare insurance system, and CPAP adherence was monitored every month using data extracted from the memory of the CPAP equipment. If necessary, CPAP settings including pressure range or CPAP mode (auto or fixed mode) were modified by an expert physician at the monthly visit to our laboratory. Eventually, most of the patients used CPAP with auto titrating mode during the follow up period.

Analysis of the respiratory signal

An investigator blinded to the groups chose approximately 5 min of artifact-free respiratory signal data before sleep onset, without a change in body position and scored as wakefulness, from the diagnostic polysomnography. Respiratory signals were generated by the sum of chest and abdominal signals using RIP. The sum was not calibrated to volume but adjusted to have a similar tidal displacement among subjects. The respiratory signal was identified, and the EMG (chin and limb) signal was used to detect body movements. When the amplitude of the EMG signal was high, that part of the respiratory signal was considered to be during movement and inappropriate for analysis. The part of respiratory signal in which eye movements without alpha rhythm in epochs not scored as sleep was also excluded from analysis. In the analytic phase of the study, investigators were also blinded to the group assignment, and each 5-min record of the respiratory signal during EEG-staged periods of wakefulness was analyzed for breath-to-breath inspiration time (T_i), expiration time (T_e), T_i+T_e (T_{tot}), and relative tidal volume. To avoid the fluctuation of breathing due to drowsiness, we extracted 5 min of respiratory signal if EEG were considered to be fully awake for each epoch (30 s) over a 5-min period. To assess breathing irregularity, the CV ([standard deviation / mean]×100) for each parameter was calculated.

To further quantify breathing pattern variability, the mutual information of the raw respiratory signal (RIP-sum signals) sampled at 10 Hz was quantified. Mutual information is a measure of statistical dependence in a data set [16, 17]. This information theory-based metric reflects the decrease in uncertainty associated with a time-shifted data point $x(t+\tau)$ that results from knowledge of the coordinate $x(t)$. Mutual information (measured in bits) was computed as described previously [18, 19], and additional details are provided in an appendix. Due to the periodic nature of the respiratory pattern, mutual information was calculated over

multiple time delays (τ's) from unity to one cycle length. Values were averaged across time lags excluding those with high linear correlations as defined by the first minimum of the mutual information function. Average mutual information (excluding small lags) was reported for each group. In practice, higher values of mutual information suggest increased statistical dependence (decreased variability and greater predictability) in the signal, while lower mutual information is associated with more variable (less predictable) patterns [20].

Statistical analysis

Comparison of continuous variables between the groups was done by the unpaired t test, and categorical variables were compared by the chi-squared test. Differences with $p<0.05$ were considered significant. All results were expressed as means±standard deviation (SD). Statistical analysis was done with IBM SPSS Statistics 19 for Windows software (SPSS Inc., Chicago, IL).

Results

Subject characteristics

Table 1 shows subject characteristics for each group. There were no significant differences in ESS and the use of medications for hypertension, hyperlipidemia, and diabetes mellitus between groups. In Group A, the main reasons for poor CPAP acceptance were an uncomfortable feeling with CPAP or a sensation of it being hard to breathe and fall asleep. Some reported removing CPAP without awareness during sleep. Also, those who refused or could not tolerate CPAP treatment generally felt no significant improvement in presenting symptoms such as excessive daytime sleepiness, morning headache, and sleep quality. Regarding the 39 patients with poor CPAP acceptance excluded from the analysis, the AHI, age, and ESS were similar to 27 patients that were analyzed in Group A (data not shown).

Table 1 Subject characteristics

	Group A (n=27)	Group B (n=21)	p value
Age, year	51.6±10.1	51.3±10.0	N.S.
Sex, (male/female)	24/3	19/2	N.S.
AHI, /h	46.4±18.3	53.6±23.7	N.S.
ESS	10.4±5.7	11.4±6.0	N.S.
BMI, kg/m^2	25.2±3.2	26.8±2.4	N.S.
Hypertension	6/27 (22.2 %)	8/21 (38.1 %)	N.S.
Dyslipidemia	4/27 (14.8 %)	4/21 (19.0 %)	N.S.
Diabetes mellitus	3/27 (11.1 %)	0/21 (0.0 %)	N.S.

Data are shown as mean±SD or no. (%). Group A are the patients who dropped out of CPAP therapy; Group B are the patients with good CPAP adherence

AHI apnea–hypopnea index, *ESS* Epworth sleepiness scale, *BMI* body mass index, *N.S.* not significant

Breathing irregularity during rest before sleep onset

Figure 2 shows examples of RIP-sum signals during wakefulness for two subjects with poor CPAP acceptance (Group A) and two subjects with good CPAP adherence (Group B). These tracings highlight the more irregular breathing pattern, especially in amplitude rather than respiratory frequency, prior to sleep onset in Group A as compared to Group B. Although the CV values for T_i were significantly higher in Group A (22.6±10.2 vs. 15.9±7.8 %; $p<0.05$), the CV values for T_e and T_{tot} were similar between groups (T_e, 24.0±11.3 vs. 19.5±8.5 %; T_{tot}, 18.7±8.9 vs. 15.2±6.7 %, $p>0.05$). The CV values for tidal volume in Group A were significantly greater than in Group B (30.7±7.8 vs. 22.1±9.0 %; $p<0.01$) (Fig. 3). The independent analyses of the respiratory waveform also identified differences in breathing pattern. The mutual information was significantly lower in Group A as compared to Group B (0.94±0.16 vs. 1.16±0.52 bits, respectively, $p<0.05$) (Fig. 4). Mutual information is a measure of statistical dependence between points, so the lower value in Group A suggests a greater variability of the breathing pattern during wakefulness in subjects with poor CPAP acceptance. There were no correlations between severity of OSA (AHI) and parameters for breathing irregularity including CVs and the mutual information (data not shown).

Discussion

The present study supports the hypothesis of an association of breathing irregularity during wakefulness prior to the diagnostic sleep study, as quantified by two independent measures, to CPAP adherence. We observed that breathing irregularity is greater in the patients with OSA who could not tolerate CPAP therapy than in age-, AHI-, and BMI-matched patients with good CPAP adherence. While highly selected for the absence of nasal symptoms and confounding medical conditions, these findings suggest that during wakefulness, a pattern of individual resting breathing irregularity could be a predictive marker for CPAP acceptance.

Breathing irregularity during wakefulness is associated with genetic diseases such as RETT syndrome [21, 22], with certain environments such as high altitude [23, 24], with treatment with opioid medications [25, 26], and with medical conditions including heart failure [27–29] and cerebral infarction [30, 31]. These phenomena reflect particular features of the respiratory control system that involve respiratory rhythm generation and/or central and peripheral

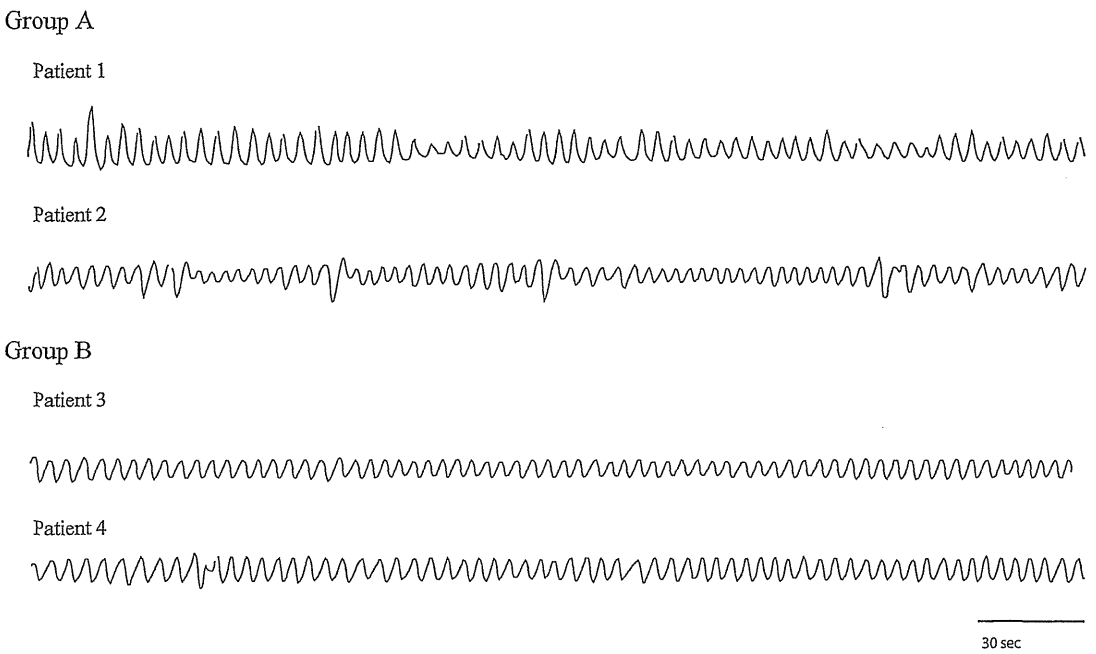

Fig. 2 Examples of RIP-sum tracings before sleep onset. Tracings of each two patients from Group A and B were presented, showing the breath-to-breath greater irregularity in tidal volume rather than respiratory frequency in Group A. *Group A* is composed of the patients who dropped out of CPAP therapy. *Group B* is composed of the patients with good CPAP adherence

chemoreception. Breathing "stability" or "instability" is operationally defined from the output of the respiratory controller. We previously reported that breathing behavior during wakefulness even in room air and in the phase of post acute hypoxic exposure as well were different between mouse strains [32–35], thus we think that the patterning of breaths over time (periodic, chaotic, etc.) around eupnea is an important feature to begin to define not only operationally but mechanistically. In a previous study, findings suggested that the central respiratory control system in mixed apnea dominant OSAS is different from obstructive apnea dominant OSAS and closer to patterning in central apnea syndrome [5]. These results taken together with the present study indicate that patients with OSA who cannot tolerate CPAP and showed irregular breathing may have somewhat of a different respiratory control system from patients with good adherence to CPAP.

An interaction of respiratory output with the upper airway and diaphragm may determine the expression of apnea types, such as central and obstructive [4]. The relative proportion of these components would depend on individual factors, which may be genetic or secondary to a medical condition. We speculate that patients with poor CPAP acceptance may have a relatively high central gain rather than peripheral chemoreceptor component as compared to patients with good adherence to CPAP, and this difference may be reflected by the breath-to-breath variability in tidal volume. Previously, we had compared mixed apnea predominant to obstructive apnea dominant, and in that comparison, the differences were in the variability in respiratory frequency and, to a lesser extent, tidal volume [5]. In the present study, we focused on obstructive apnea dominant patients; and, while variability was different in tidal volume, breath-by-breath variability in respiratory frequency was similar between groups. In both studies, however, analysis of the raw signal provided insight in the direction of difference, being lower in groups will less adherence.

Although the augmented breath, sigh, is considered an important component of normal breathing [36], Baldwin et al. concluded that sighs indicate maturity and functional integrity of the neurorespiratory feedback control and proposed sighs as being important for the regulation and resetting of the neurorespiratory controller [37]. Moreover, in general, sigh could occur both during stress and negative emotions, such as panic and pain, and during positive emotions, such as relaxation and relief [38–40]. In the current study, we did not exclude sighs from the 5-min segment of respiratory data. The number of sighs might affect the CV values for tidal volume. Thus, sigh was not discarded in the analysis, because it could contribute to greater tidal volume variability and poor CPAP acceptance. This is supported by previous reports that psychological factors may relate to adherence to CPAP [15]. Therefore, differences in the respiratory control system such as a high central component or an intrinsic psychological status can explain our results; however, exploring the exact mechanism for this variability

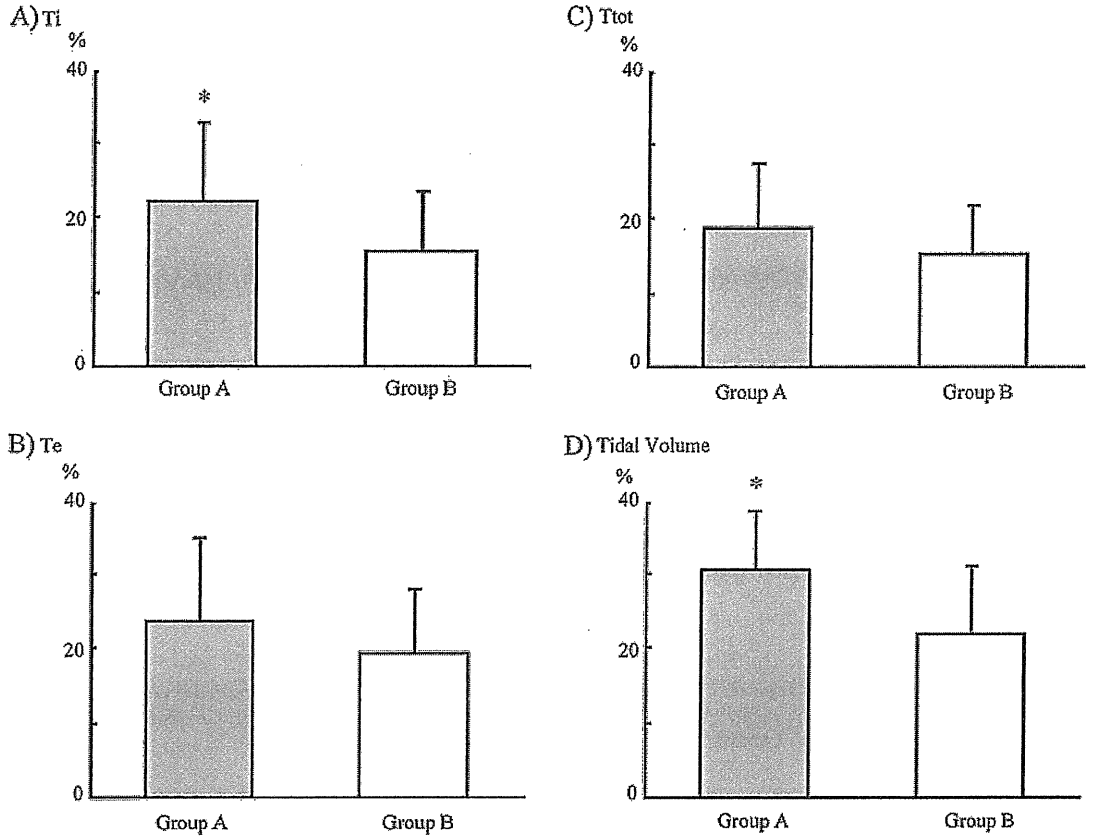

Fig. 3 Coefficients of variation for breath-to-breath respiratory variables during resting breathing before sleep onset. Values are mean±SD. **a** *Ti*, inspiration time; **b** *Te*, expiration time; **c** T_{tot}, T_i+T_e, **d** Tidal volume. *Group A* is composed of the patients who dropped out of CPAP therapy. *Group B* is composed of the patients with good CPAP adherence. The *asterisk* indicates significant difference between groups

is beyond the scope of this study. In addition, it has been recently demonstrated that arousability is one of the physiological traits that contribute to the pathogenesis of OSA [41]. Arousal due to positive airway pressure and/or CPAP discomfort may worsen CPAP adherence, thus the difference in individual arousal threshold may have contributed to our results, but further study would be needed to elucidate this issue.

A strength of the study was an ability to select a sufficient number of patients to match highly successful CPAP users to an extremely intolerant group and in both excluding known factors (stroke, opioid use, etc.) that might confound the comparisons. There are limitations in the present work. First, we cannot exclude a possible effect of hypocapnia in the poor CPAP acceptance group; however, if this were the case, then the differences between the groups would be based on a respiratory control factor such as hypercapnic responsiveness and/or apneic threshold of carbon dioxide. Second, although the statistics reveal that the CV values for tidal volume in the patients with OSAS who can not tolerate CPAP were significantly higher than in patients with good adherence, the average difference in CV values between the groups was less than 10; however, the fact that the independent measure of mutual

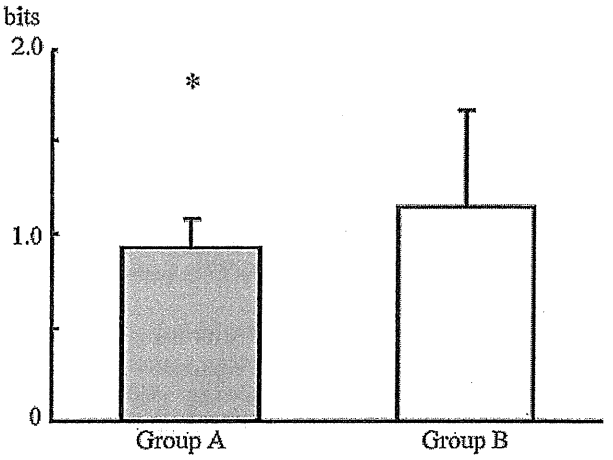

Fig. 4 The mutual information of the raw respiratory signal (RIP-sum signals). The mutual information was significantly lower in Group A as compared to Group B, suggesting a greater variability of the breathing pattern in Group A. *Group A* is composed of the patients who dropped out of CPAP therapy. *Group B* is composed of the patients with good CPAP adherence. The *asterisk* indicates significant difference between groups

information also showed such differences suggests that even small absolute differences could be important to consider. Third, although we successfully demonstrated a significant association between breathing irregularity during wakefulness and CPAP acceptance, this was a retrospective study. Thus, a prospective study will be needed to confirm that breathing irregularity predicts CPAP adherence. Lastly, the prescription of different commercial-based CPAP devices might be a confounding factor for CPAP adherence, but dropout rate was not different between these CPAP devises users.

In summary, we conclude that irregular breathing in terms of respiratory amplitude and temporal variability of the breathing signal during wakefulness may affect CPAP acceptance. This suggests that there are distinct features of respiratory control in patients who accept CPAP or cannot tolerate CPAP.

Acknowledgments The authors would like to thank Kaoru Senzaki, RPSGT, for her help with polysomnogram scoring. This study is partly supported by a Grant-in-Aid for Young Scientists (B) (21790781) from The Ministry of Education, Culture, Sports, Science and Technology, Japan. US investigators were supported in part by the NIH-NHLBI [R33HL087340-01], and the VA Research Service.

Conflicts of interest None of the authors have financial conflicts of interest to declare as it relates to the contents of this manuscript.

Appendix

Mutual Information: Mutual information (MI) is a measure of the statistical dependence between two time series, or two collections of points from a data set, that can arise from both linear and nonlinear sources [42]. The Mutual information between a given time series $x(t)$ and its time-shifted version $x(t+\tau)$ is computed from the joint probability distribution of $x(t)$ and $x(t+\tau)$, where τ represents a time lag. The joint probability distribution is defined as $P[x(t), x(t+\tau)]$, where $P[x(t)]$ and $P[x(t+\tau)]$ are the marginal distributions of the original and time-shifted time series, respectively. The MI can be computed as follows:

$$MI[x(t), x(t+\tau)] = \sum_i \sum_j P[x_i(t), x_j(t+\tau)] \log \left[\frac{P[x_i(t), x_j(t+\tau)]}{P[x_i(t)] \cdot P[x_j(t+\tau)]} \right]$$

Because the breathing pattern over long time periods is strongly periodic, we computed MI for τ values from one sample (adjacent points separated by 100 ms) to one cycle length. MI tends to decrease quickly as τ is increased from a lag of one and then becomes more uniform at higher time lags, and the average MI of a given epoch was quantified excluding small lags as defined by the first minimum of the MI function.

References

1. Shea SA, Guz A (1992) Personnalite ventilatoire—an overview. Respir Physiol 87(3):275–291
2. Shea SA, Benchetrit G, Pham Dinh T, Hamilton RD, Guz A (1989) The breathing patterns of identical twins. Respir Physiol 75 (2):211–223
3. Kawakami Y, Yamamoto H, Yoshikawa T, Shida A (1984) Chemical and behavioral control of breathing in adult twins. Am Rev Respir Dis 129(5):703–707
4. Cherniack NS (1981) Respiratory dysrhythmias during sleep. N Engl J Med 305(6):325–330
5. Yamauchi M, Tamaki S, Yoshikawa M, Ohnishi Y, Nakano H, Jacono FJ, Loparo KA, Strohl KP, Kimura H (2011) Differences in breathing patterning during wakefulness in patients with mixed apnea-dominant vs obstructive-dominant sleep apnea. Chest 140 (1):54–61
6. Basoglu OK, Midilli M, Midilli R, Bilgen C (2011) Adherence to continuous positive airway pressure therapy in obstructive sleep apnea syndrome: effect of visual education. Sleep Breath
7. Shapiro GK, Shapiro CM (2010) Factors that influence CPAP adherence: an overview. Sleep Breath 14(4):323–335
8. Yetkin O, Kunter E, Gunen H (2008) CPAP compliance in patients with obstructive sleep apnea syndrome. Sleep Breath 12(4):365–367
9. Gay P, Weaver T, Loube D, Iber C (2006) Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults. Sleep 29(3):381–401
10. Sin DD, Mayers I, Man GC, Pawluk L (2002) Long-term compliance rates to continuous positive airway pressure in obstructive sleep apnea: a population-based study. Chest 121(2):430–435
11. Budhiraja R, Parthasarathy S, Drake CL, Roth T, Sharief I, Budhiraja P, Saunders V, Hudgel DW (2007) Early CPAP use identifies subsequent adherence to CPAP therapy. Sleep 30(3):320–324
12. Weaver TE, Grunstein RR (2008) Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. Proc Am Thorac Soc 5(2):173–178
13. Simon-Tuval T, Reuveni H, Greenberg-Dotan S, Oksenberg A, Tal A, Tarasiuk A (2009) Low socioeconomic status is a risk factor for CPAP acceptance among adult OSAS patients requiring treatment. Sleep 32(4):545–552
14. Platt AB, Field SH, Asch DA, Chen Z, Patel NP, Gupta R, Roche DF, Gurubhagavatula I, Christie JD, Kuna ST (2009) Neighborhood of residence is associated with daily adherence to CPAP therapy. Sleep 32(6):799–806
15. Wild MR, Engleman HM, Douglas NJ, Espie CA (2004) Can psychological factors help us to determine adherence to CPAP? a prospective study. Eur Respir J 24(3):461–465
16. Shannon CE (1997) The mathematical theory of communication. 1963. MD Comput 14(4):306–317
17. Fraser AM, Swinney HL (1986) Independent coordinates for strange attractors from mutual information. Phys Rev A 33 (2):1134–1140
18. Koo BB, Strohl KP, Gillombardo CB, Jacono FJ (2010) Ventilatory patterning in a mouse model of stroke. Respir Physiol Neurobiol 172 (3):129–135
19. Dhingra RR, Jacono FJ, Fishman M, Loparo KA, Rybak IA, Dick TE (2011) Vagal-dependent nonlinear variability in the respiratory pattern of anesthetized, spontaneously breathing rats. J Appl Physiol 111(1):272–284
20. Jacono FJ, De Georgia MA, Wilson CG, Dick TE, Loparo KA (2010) Data acquisition and complex systems analysis in critical care: developing the intensive care unit of the future. J Healthc Eng 1(3):337–355
21. Kerr AM (1992) A review of the respiratory disorder in the Rett syndrome. Brain Dev 14(Suppl):S43–S45

22. Ogier M, Katz DM (2008) Breathing dysfunction in Rett syndrome: understanding epigenetic regulation of the respiratory network. Respir Physiol Neurobiol 164(1–2):55–63
23. Eckert DJ, Jordan AS, Merchia P, Malhotra A (2007) Central sleep apnea: pathophysiology and treatment. Chest 131(2):595–607
24. Netzer NC, Strohl KP (1999) Sleep and breathing in recreational climbers at an altitude of 4200 and 6400 meters: observational study of sleep and patterning of respiration during sleep in a group of recreational climbers. Sleep Breath 3(3):75–82
25. Pattinson KT (2008) Opioids and the control of respiration. Br J Anaesth 100(6):747–758
26. Teichtahl H, Wang D (2007) Sleep-disordered breathing with chronic opioid use. Expert Opin Drug Saf 6(6):641–649
27. Bradley TD, Floras JS (2003) Sleep apnea and heart failure: Part II: central sleep apnea. Circulation 107(13):1822–1826
28. Caples SM, Garcia-Touchard A, Somers VK (2007) Sleep-disordered breathing and cardiovascular risk. Sleep 30(3):291–303
29. Leung RS, Bradley TD (2001) Sleep apnea and cardiovascular disease. Am J Respir Crit Care Med 164(12):2147–2165
30. Cherniack NS, Longobardo G, Evangelista CJ (2005) Causes of Cheyne-Stokes respiration. Neurocrit Care 3(3):271–279
31. Hardavella G, Stefanache F, Ianovici N (2006) Cheyne stokes respiration in stroke patients. Rev Med Chir Soc Med Nat Iasi 110(1):82–87
32. Han F, Subramanian S, Dick TE, Dreshaj IA, Strohl KP (2001) Ventilatory behavior after hypoxia in C57BL/6J and A/J mice. J Appl Physiol 91(5):1962–1970
33. Han F, Subramanian S, Price ER, Nadeau J, Strohl KP (2002) Periodic breathing in the mouse. J Appl Physiol 92(3):1133–1140
34. Yamauchi M, Dostal J, Kimura H, Strohl KP (2008) Effects of buspirone on posthypoxic ventilatory behavior in the C57BL/6J and A/J mouse strains. J Appl Physiol 105(2):518–526
35. Yamauchi M, Ocak H, Dostal J, Jacono FJ, Loparo KA, Strohl KP (2008) Post-sigh breathing behavior and spontaneous pauses in the C57BL/6J (B6) mouse. Respir Physiol Neurobiol 162(2):117–125
36. Perez-Padilla R, West P, Kryger MH (1983) Sighs during sleep in adult humans. Sleep 6(3):234–243
37. Baldwin DN, Suki B, Pillow JJ, Roiha HL, Minocchieri S, Frey U (2004) Effect of sighs on breathing memory and dynamics in healthy infants. J Appl Physiol 97(5):1830–1839
38. Vlemincx E, Taelman J, De Peuter S, Van Diest I, Van den Bergh O (2011) Sigh rate and respiratory variability during mental load and sustained attention. Psychophysiology 48(1):117–120
39. Vlemincx E, Van Diest I, De Peuter S, Bresseleers J, Bogaerts K, Fannes S, Li W, Van Den Bergh O (2009) Why do you sigh? Sigh rate during induced stress and relief. Psychophysiology 46 (5):1005–1013
40. Wuyts R, Vlemincx E, Bogaerts K, Van Diest I, Van den Bergh O (2011) Sigh rate and respiratory variability during normal breathing and the role of negative affectivity. Int J Psychophysiol 82 (2):175–179
41. Wellman A, Eckert DJ, Jordan AS, Edwards BA, Passaglia CL, Jackson AC, Gautam S, Owens RL, Malhotra A, White DP (2011) A method for measuring and modeling the physiological traits causing obstructive sleep apnea. J Appl Physiol 110(6):1627–1637
42. Shannon CE, Weaver W (1949) The mathematical theory of communication. University of Illinois Press, Urbana

BMJ open accessible medical research

Cross-sectional and prospective study of the association between lung function and prediabetes

Takashi Yamane,[1,2] Akihito Yokoyama,[1] Yoshihiro Kitahara,[2] Shintaro Miyamoto,[1] Yoshinori Haruta,[2] Noboru Hattori,[2] Kiminori Yamane,[2,3] Hitoshi Hara,[3] Nobuoki Kohno[2]

To cite: Yamane T, Yokoyama A, Kitahara Y, *et al*. Cross-sectional and prospective study of the association between lung function and prediabetes. *BMJ Open* 2013;**3**:e002179. doi:10.1136/bmjopen-2012-002179

► Prepublication history for this paper are available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2012-002179).

Received 12 October 2012
Revised 10 December 2012
Accepted 21 January 2013

[1]Department of Hematology and Respiratory Medicine, Kochi University, Kochi, Japan
[2]Department of Molecular and Internal Medicine, Hiroshima University, Hiroshima, Japan
[3]Nippon Telegraph and Telephone West Corporation Chugoku Health Administration Center, Hiroshima, Japan

Correspondence to Professor Akihito Yokoyama; ayokoyama@kochi-u.ac.jp

ABSTRACT

Objectives: A growing body of evidence suggests that there is a relationship between impaired lung function and the risk of developing diabetes mellitus (DM). However, it is not known if this reflects a causal effect of lung function on glucose metabolism. To clarify the relationship between lung function and the development of DM, we examined the incidence of newly diagnosed prediabetes (a precursor of DM) among subjects with normal glucose tolerance (NGT) at baseline.

Design: Primary analysis of an occupational cohort with both cross-sectional and longitudinal data (follow-up duration mean±SD: 28.4±6.1 months).

Setting and participants: Data were analysed from 1058 men in a cross-sectional study and from 560 men with NGT in a longitudinal study.

Outcomes and methods: Impaired lung function (per cent predicted value of forced vital capacity (%FVC) or per cent value of forced expiratory volume 1 s/FVC (FEV_1/FVC ratio)) in relation to the ratio of prediabetes or DM in a cross-sectional study and development of new prediabetes in a longitudinal study. NGT, prediabetes including impaired glucose tolerance (IGT) and increased fasting glucose (IFG) and DM were diagnosed according to 75 g oral glucose tolerance tests.

Measurements and main results: %FVC at baseline, but not FEV_1/FVC ratio at baseline, was significantly associated with the incidences of DM and prediabetes. Among prediabetes, IGT but not IFG was associated with %FVC. During follow-up, 102 subjects developed prediabetes among those with NGT. A low %FVC, but not FEV_1/FVC ratio, was predictive of an increased risk for development of IGT, but not of IFG.

Conclusions: Low lung volume is associated with an increased risk for the development of prediabetes, especially IGT, in Japanese men. Although there is published evidence for an association between chronic obstructive pulmonary disease and DM, prediabetes is not associated with the early stage of COPD.

ARTICLE SUMMARY

Article focus

- We hypothesised that lung function is associated with the development of impaired glucose metabolism. To investigate this, the data of an occupational cohort were analysed from 1058 men in a cross-sectional study and from 560 men with normal glucose tolerance (NGT) in a longitudinal study.

Key messages

- Low lung volume was significantly associated with the incidence of prediabetes or diabetes mellitus (DM) in both cross-sectional and longitudinal studies.
- Low lung volume is an independent risk factor for a particular type of prediabetes, impaired glucose tolerance rather than impaired fasting glucose. Our results suggested that prediabetes is not associated with the early stage of COPD, although there are published evidences for an association between COPD and DM.

Strengths and limitations of this study

- This is the first study that prospectively examined the incidence of newly diagnosed prediabetes among subjects with NGT at baseline. There are several limitations including that the subjects were limited to Japanese men and our occupational cohort may possibly be healthier than the general population.

INTRODUCTION

Accumulating evidence suggests that there is a close relationship between impaired lung function and diabetes mellitus (DM). Population-based studies have demonstrated associations between both obstructive and restrictive lung impairment and insulin resistance or DM.[1–9] A representative obstructive lung disease, chronic obstructive pulmonary disease (COPD), is now well known to be associated with a variety of comorbidities, including DM.[10–13] However, an accelerated decline of lung function has been observed in patients with DM.[14] The incidence rates of COPD, asthma, lung fibrosis and pneumonia

are greater in patients with DM than in those without DM.[15] The incidence of death from COPD is also increased in DM.[16]

The metabolic stage between normal glucose homeostasis and DM is called prediabetes, which the WHO divides into impaired glucose tolerance (IGT) and increased fasting glucose (IFG).[17] Both IFG and IGT are the established risk factors for DM.[18] The Diabetes Prevention Program Research Group[15] found that about 30% of subjects with prediabetes developed DM during 3–5 years of follow-up. IFG and IGT are also risk factors for cardiovascular disease (CVD), relationships that are not confounded by the development of DM.[19 20] Subjects with prediabetes also have higher incidence rates of microvascular complications, including neuropathy, retinopathy and nephropathy, than do those with normal glucose tolerance (NGT).[21 22]

We reported previously that smokers with airflow limitation had subclinical atherosclerosis as evidenced by carotid intima-media thickness (CIMT).[12] Although we excluded subjects with DM, the prediabetic state may influence the association, since prediabetes per se was accompanied by a modest but significant increase in the risk for developing CVD, as described above. However, there is no information regarding the association between lung function and prediabetes. Therefore, we explored the incidence of newly diagnosed prediabetes among selected subjects with NGT to further elucidate the nature of the relationship between lung function and the development of DM.

METHODS

Subjects

The subjects were recruited from 1218 men who attended the Nippon Telegraph and Telephone West Corporation Chugoku Health Administration Center for general health checkups between April 1999 and March 2006. One hundred and sixty subjects were excluded, because they did not meet the following inclusion criteria: (1) between 40 and 59 years of age at the first examination, and able to perform both a 75 g oral glucose tolerance test (OGTT) and adequate spirometric measurements (146 subjects excluded); (2) no known respiratory disease (14 excluded). Data from the remaining 1058 subjects were used for a baseline cross-sectional analysis. For the longitudinal study, subjects were restricted to those who had NGT (365 excluded), and could be followed up for more than 20 months (133 excluded). The remaining 560 subjects were included. Among these subjects, 77 were receiving medication for hypertension, 43 for dyslipidaemia and 11 for hyperuricaemia. The distributions of these subjects among the quartiles of percent predicted value of %FVC and percent value of 1 s/FVC (FEV_1/FVC ratio) were not significantly different.

The study was approved by the Ethical Committee of Kochi University.

75 g oral glucose tolerance test

DM and prediabetes were diagnosed according to the 2003 criteria of the WHO.[17] Subjects with prediabetes were classified into two categories: isolated IFG and IGT. Isolated IFG was defined as a fasting plasma glucose level of 6.1–6.9 mmol/l and a 2 h postload plasma glucose level of <7.8 mmol/l; and IGT was defined by a fasting plasma glucose level of <7.0 mmol/l and a 2 h postload plasma glucose level of 7.8–11.1 mmol/l. Blood samples were collected after a 10 h fast, and then 2 h after a 75 g oral glucose load.

Fasting insulin was measured by an enzyme immunoassay (Dainabot, Tokyo, Japan) with an intra-assay coefficient of variation of 3.1–4.4%. The homeostasis model assessment (HOMA) formula, (fasting insulin (mU/l)×fasting glucose (mmol/l))/22.5, was used to calculate the insulin resistance score.

Pulmonary function test

Pulmonary function was measured using a spirometer (Chest HI-801; Chest Co., Tokyo, Japan) by an experienced technician according to the recommendations of the American Thoracic Society.[23] The Japanese reference values were used.[24]

Statistical analysis

Statistical analysis was carried out using SPSS, V.18.0 (SPSS Japan Inc, Tokyo, Japan). Statistical comparisons of the baseline characteristics of each group were performed using either the χ-square test or one-way analysis of variance (ANOVA). Comparisons among the groups were performed by using post-hoc Tukey test. In the cross-sectional study, logistic regression models were used to estimate the relevant ORs. In the longitudinal study, the HR of each covariate for the risk of development of prediabetes with 95% CI was calculated using the Cox hazard model. Tests for a linear trend across increasing categories of spirometric indices were conducted by treating the categories as continuous variables in a model. In all analyses, $p<0.05$ was taken to indicate statistical significance.

RESULTS

Baseline analysis

At baseline, our study population (n=1058) consisted of 693 normal subjects, 93 with isolated IFG, 167 with IGT and 105 with DM. To examine the relationship between lung function parameters and impaired glucose metabolism, the subjects were divided into quartiles according to baseline %FVC and the FEV_1/FVC ratio. Some parameters, including age, body mass index (BMI), systolic blood pressure and total cholesterol, differed significantly among the quartiles (table 1). After adjustment for these parameters, impaired glucose metabolism was significantly associated with %FVC ($p<0.001$), but not with the FEV_1/FVC ratio ($p=0.80$). Specifically, IGT ($p=0.04$) and DM ($p=0.008$), but not isolated IFG ($p=0.28$), were associated with %FVC (table 2).

Table 1 Baseline characteristics of subjects with NGT, isolated IFG, IGT and DM in the cross-sectional study

	NGT	Isolated IFG	IGT	DM	p Value
Number of subjects	693	93	167	105	
Current smokers (%)	48	42	45	50	0.54
Age (years)	49.5±5.5	50.9±5.3*	51.1±5.3**	52.2±4.7***	<0.001
Height (cm)	169.9±5.7	168.8±5.8	169.1±6.0	168.4±5.0*	0.03
BMI (kg/m^2)	23.1±2.5	23.9±3.1**	24.6±2.8***	24.8±3.2***	<0.001
Systolic BP (mm Hg)	126.4±16.3	135.1±16.4***	135.9±18.2***	140.2±16.3***	<0.001
Pack-year smoking	30.5±15.6	38.0±22.6*	31.1±17.3	38.0±18.5**	0.002
FEV_1/FVC (%)	80.1±7.0	79.6±7.8	80.9±7.4	79.4±8.5	0.36
%FVC	97.9±14.2	96.5±12.9	92.0±13.3***	89.2±15.7***	<0.001
Fasting glucose (mmol/l)	5.3±0.4	6.3±0.2***	5.9±0.5***	8.1±1.6***	<0.001
120 min glucose (mmol/l)	5.7±1.0	6.5±0.8***	8.8±0.8***	12.4±4.0***	<0.001
HbA1c (%)	5.10±0.33	5.34±0.36***	5.37±0.41***	6.57±1.20***	<0.001
HOMA-R	1.08±0.56	1.91±2.23**	1.56±0.88***	2.33±1.41***	<0.001
C reactive protein (mg/l)	0.11±0.29	0.09±0.14	0.14±0.28	0.18±0.46	0.13
T-chol (mg/dl)	202.1±32.6	210.0±28.7*	209.5±36.3*	214.8±32.2***	<0.001

Values are numbers, percentages (%) or means ±SD.
*p<0.05.
**p<0.01.
***p<0.001 vs NGT.
BMI, body mass index; BP, blood pressure; CRP, C reactive protein; DM, diabetes mellitus; HbA1c, glycated haemoglobin; HOMA-R, homeostasis model assessment of insulin resistance; IFG, increased fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; T-chol, total cholesterol.

Frequencies of newly diagnosed prediabetes in subjects with NGT

After the observation period (mean±SD: 28.4 ±6.1 months), there were 44 subjects with isolated IFG and 58 with IGT among those previously categorised as NGT (n=560), but no subject developed DM. As shown in table 3, there were significant differences in several parameters at baseline, including height, BMI, systolic blood pressure and %FVC, but not in FEV_1/FVC ratio.

Table 2 ORs*(95% CI) of prediabetes and DM according to the quartiles of %FVC† or FEV_1%‡ in the cross-sectional study

	I	II	III	IV	p for trend
IFG					
%FVC	1.0	4.60 (1.29 to 16.39)	2.03 (0.53 to 7.79)	2.57 (0.69 to 9.60)	0.06
FEV_1/FVC	1.0	1.00 (0.32 to 3.12)	1.39 (0.49 to 3.93)	1.81 (0.67 to 4.90)	0.53
IGT					
%FVC	1.0	1.35 (0.57 to 3.19)	2.18 (1.02 to 4.05)	2.59 (1.17 to 5.69)	0.04
FEV_1/FVC	1.0	0.60 (0.35 to 1.15)	0.62 (0.37 to 1.16)	0.50 (0.30 to 1.02)	0.12
IFG or IGT					
%FVC	1.0	2.18 (1.08 to 4.42)	2.09 (1.04 to 4.18)	2.55 (1.28 to 5.09)	<0.001
FEV_1/FVC	1.0	0.56 (0.31 to 1.07)	0.63 (0.35 to 1.14)	0.65 (0.36 to 1.17)	0.29
DM					
%FVC	1.0	3.77 (1.29 to 11.03)	1.28 (0.41 to 3.99)	2.50 (0.87 to 7.16)	0.02
FEV_1/FVC	1.0	2.08 (0.72 to 5.99)	3.05 (1.12 to 8.31)	2.13 (0.76 to 6.00)	0.18
IFG or IGT, or DM					
%FVC	1.0	3.32 (1.71 to 6.42)	2.04 (1.06 to 3.94)	3.33 (1.74 to 6.38)	<0.001
FEV_1/FVC	1.0	0.74 (0.40 to 1.35)	0.98 (0.56 to 1.75)	0.84 (0.48 to 1.49)	0.70

*OR was adjusted for age, BMI, pack-year smoking, systolic BP and T-chol.
†%FVC quartile; I (highest group) (≥104.2%), II (96.0%≤%FVC<104.2%), III (86.4%≤%FVC<96.0%), IV (lowest group) (%FVC<86.4%).
‡FEV_1/FVC quartile; I (highest group) (≥85.0), II (81.1%≤FEV_1/FVC<85.0%), III (76.5%≤FEV_1/FVC<81.1%), IV (lowest group) (FEV_1/FVC<76.5%).
BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; IFG, impaired fasting glucose; IFG, increased fasting glucose; IGT, impaired glucose tolerance; T-chol, total cholesterol.

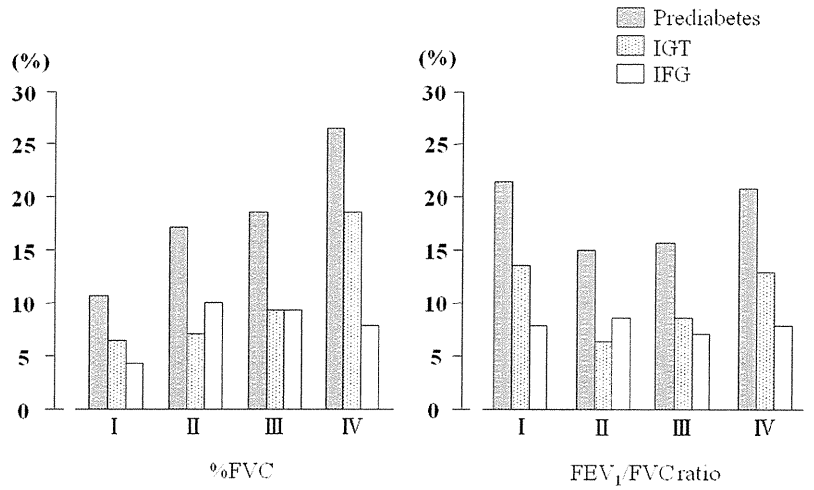

Figure 1 Incidences of newly diagnosed prediabetes, isolated IFG and impaired glucose tolerance (IGT) according to quartiles of % FVC and the FEV_1/FVC ratio. The incidence of prediabetes was significantly associated with %FVC, but not with the FEV_1/FVC ratio (p=0.01). Among subjects with prediabetes, lower %FVC was significantly associated with a higher incidence of IGT (p=0.04), but not of IFG (p=0.47).

Lung function parameters were divided into quartiles according to baseline %FVC and the FEV_1/FVC ratios. Among the quartiles the parameters, including age, BMI and systolic blood pressure, were significantly different (data not shown). Both in the crude model and following adjustment by age, BMI, pack-year smoking and systolic blood pressure, the development of prediabetes occurred significantly more frequently in the lowest quartile of % FVC, but not in that of the FEV_1/FVC ratio (table 4). Among prediabetes, IGT, but not isolated IFG, was significantly associated with %FVC, as in the baseline cross-sectional analysis (table 4; figure 1).

DISCUSSION

In the baseline cross-sectional study, we found that a low %FVC, but not a low FEV_1/FVC ratio, was significantly associated with increased prevalences of prediabetes and DM. As lung function might be impaired by DM, a causal effect of lung function on DM could not be established by these data. Therefore, we also explored prospectively the effect of lung function on the development of newly diagnosed prediabetes in the population with normal glucose metabolism, as evidenced by the results of an OGTT. We found that reduced lung volume (%FVC), but not airflow limitation (FEV_1/FVC ratio), was significantly associated with the future development of prediabetes.

This study demonstrated that IGT, but not IFG, was closely associated with lower lung volume in both cross-sectional and longitudinal settings. Our finding was supported by previous studies conducted in an Asian population with relatively low BMI but high smoking

Table 3 Baseline characteristics of subjects who remained NGT, developed isolated IFG and IGT in the longitudinal study.

	NGT	Isolated IFG	IGT	p Value
Number of subjects	458	44	58	
Current smokers (%)	48	30*	50	0.05
Age (years)	49.3±5.7	50.2±4.4	50.5±4.9	0.14
Height (cm)	169.9±5.6	170.2±4.9	167.1±6.7**	0.01
BMI (kg/m^2)	23.0±2.5	23.8±2.3*	23.7±3.0*	0.04
Systolic BP (mm Hg)	125.4±16.7	130.5±16.9*	129.3±14.5	0.048
Pack-year smoking	29.9±15.6	31.1±12.1	30.1±18.5	0.97
FEV_1/FVC (%)	80.1±7.1	79.7±6.3	79.9±7.9	0.95
%FVC (%)	97.5±14.2	93.0±14.7*	90.0±16.0***	<0.001
Fasting glucose (mmol/l)	5.3±0.4	5.6±0.2***	5.5±0.3**	<0.001
120 min glucose (mmol/l)	5.6±0.9	6.0±1.2	6.4±0.9***	<0.001
HbA1c (%)	5.07±0.33	5.31±0.37***	5.19±0.30*	<0.001
HOMA-R	1.04±0.53	1.19±0.61	1.31±0.64**	0.001
C reactive protein (mg/l)	0.10±0.23	0.18±0.42	0.16±0.30	0.26
T-chol (mg/dl)	201.4±34.5	205.3±27.1	212.5±28.6*	0.05
Duration (month)	28.6±6.2	28.5±5.1	27.6±5.6	0.13

Values are number, percentage (%) or mean±SD.
*p < 0.05.
**p<0.01.
***p<0.001 vs NGT.
BMI, body mass index; BP, blood pressure; CRP, C reactive protein; HOMA-R, homeostasis model assessment of insulin resistance; IFG, increased fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; T-chol, total cholesterol.

Table 4 HRs (95% CI) for development of isolated IFG or IGT according to the quartiles of %FVC*or FEV_1%†

	I	II	III	IV	p for trend
IFG					
%FVC					
Model 1	1.0	0.85 (0.38 to 1.92)	0.81 (0.36 to 1.79	1.96 (0.71 to 5.26)	0.31
Model 2	1.0	1.07 (0.48 to 2.39)	1.35 (0.60 to 3.03)	0.54 (0.20 to 1.49)	0.32
FEV_1/FVC					
Model 1	1.0	0.96 (0.42 to 2.17)	1.20 (0.51 to 2.86)	0.98 (0.43 to 2.27)	0.95
Model 2	1.0	0.99 (0.43 to 2.31)	0.84 (0.35 to 2.00)	1.04 (0.45 to 2.47)	0.96
IGT					
%FVC					
Model 1	1.0	1.96 (1.00 to 3.85)	2.63 (1.27 to 5.56)	3.03 (1.43 to 6.67)	0.006
Model 2	1.0	2.22 (1.02 to 3.88)	2.26 (1.07 to 4.78)	2.74 (1.26 to 5.98)	0.02
FEV_1/FVC					
Model 1	1.0	2.13 (0.96 to 4.76)	1.67 (0.81 to 3.45)	1.03 (0.54 to 1.96)	0.15
Model 2	1.0	2.09 (0.92 to 4.72)	1.69 (0.81 to 3.52)	1.11 (0.57 to 2.16)	0.10
IFG or IGT					
%FVC					
Model 1	1.0	2.13 (0.93 to 3.03)	1.85 (1.03 to 3.57)	2.63 (1.43 to 4.76)	0.01
Model 2	1.0	1.48 (0.89 to 2.44)	1.38 (0.82 to 2.34)	2.40 (1.30 to 4.44)	0.04
FEV_1/FVC					
Model 1	1.0	1.47 (0.84 to 2.56)	1.47 (0.85 to 2.56)	1.01 (0.61 to 1.69)	0.32
Model 2	1.0	1.47 (0.83 to 2.61)	1.47 (0.84 to 2.56)	1.09 (0.64 to 1.84)	0.21

*%FVC quartile; I (highest group) (≥106.0%), II (96.6%≤%FVC<106.0%) III (88.1%≤%FVC<96.6%), IV (lowest group) (%FVC<88.1%).
†FEV_1/FVC quartile; I (highest group) (≥85.0%), II (80.9%≤FEV_1/FVC<85.0%), III (76.0%≤FEV_1/FVC<80.9%), IV (lowest group) (FEV_1/FVC<76.0%).
IGT, impaired glucose tolerance; IFG, increased fasting glucose.
Model 1 denotes crude model and model 2, adjusted for age, BMI, pack-year smoking and systolic BP.

prevalence.[8 9] In addition, such association between lower lung function and impaired glucose metabolism was also demonstrated in Western populations with higher BMI but lower smoking prevalence, and the association had been shown to be independent of smoking or obesity (refs. [1–6], for review ref. [7]).

The mechanisms for the association are not clarified at present. It has been suggested that IGT is caused mainly by insulin resistance in the muscle, and IFG mainly by insulin resistance in the liver.[25] Reduced lung volume is associated with reduced maximum oxygen uptake, which may lead to poorer physical fitness and physical activity, and thus result in insulin resistance and DM.[26–28] This may explain why IGT is more closely associated with lung volume. Furthermore, poorer lung function in adulthood may be due to low birth weight or early-life malnutrition,[29 30] both of which have been reported to be associated with the development of diabetes.[31] Malnutrition as a neonate may be an important early cause of cardiac and metabolic disorders in adulthood as a consequence of fetal programming.[32 33]

This study had several limitations. The study population was limited to men, owing to the fact that sufficient female subjects were not available at the institute. The occupational cohort used in this study may not be representative of Japanese men in general. For example, the prevalence rates of hypertension and hyperlipidaemia in this cohort were 13% and 7%, respectively (data not shown). The National Health and Nutrition Examination Survey in Japan showed prevalence rate of these in general Japanese men aged 40–60 years, in general, were around 30% and 35%, respectively, suggesting that our occupational cohort may be healthier. Subjects taking medications, including simvastatin, which have been shown to lower the risk of impaired glucose metabolism were not excluded, although the distributions of %FVC and the FEV_1/FVC ratio in those taking drugs for hypertension, dyslipidaemia and hyperuricaemia were not significantly different from those of subjects not on such medication.

In conclusion, this study provides evidence for a prospective relationship between lung volume and the incidence of newly diagnosed prediabetes among subjects with normal glucose metabolism at baseline. Among subjects with prediabetes, the study also suggests that lung volume may be a risk factor for the development of IGT, which is mainly caused by insulin resistance in the

muscle, but not IFG, which is caused mainly by insulin resistance in the liver. Although there is published evidence for an association between COPD and DM, our results suggest that prediabetes is not associated with at least the early stage of COPD.

Acknowledgements The authors would like to thank the staff of Nippon Telegraph and Telephone West Corporation Chugoku Health Administration Center.

Contributors TY contributed to the collection of data, analysis and interpretation of data, and writing of the draft. AY contributed to the study design, analysis and interpretation of data, editing of the draft and acquisition of funding. YK and SM contributed to the collection of data and analysis, YH, NH and KY contributed to the collection and interpretation of data, and editing the draft. NK contributed to the analysis and interpretation of data, and editing of the draft. All authors read and approved the final manuscript.

Funding This work was supported in part by a grant-in-aid for scientific research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (No. 23390222 and 24659405), and a grant to the Respiratory Failure Research Group from the Ministry of Health, Labor and Welfare, Japan.

Competing interests None.

Patient consent Obtained.

Ethics approval The Ethical Committee of Kochi University.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

REFERENCES

1. Engström G, Janzon L. Risk of developing diabetes is inversely related to lung function: a population-based cohort study. *Diabet Med* 2002;19:167–70.
2. Ford ES, Mannino DM; National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. Prospective association between lung function and the incidence of diabetes: findings from the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. *Diabetes Care* 2004;27:2966–70.
3. Lawlor DA, Ebrahim S, Smith GD. Associations of measures of lung function with insulin resistance and type 2 diabetes: findings from the British Women's Heart and Health Study. *Diabetologia* 2004;47:195–203.
4. Yeh HC, Punjabi NM, Wang NY, *et al.* Cross-sectional and prospective study of lung function in adults with type 2 diabetes: the atherosclerosis risk in communities (ARIC) study. *Diabetes Care* 2008;31:741–6.
5. Lee HM, Le H, Lee BT, *et al.* Forced vital capacity paired with Framingham Risk Score for prediction of all-cause mortality. *Eur Respir J* 2010;36:1002–6.
6. Hickson DA, Burchfiel CM, Liu J, *et al.* Diabetes, impaired glucose tolerance, and metabolic biomarkers in individuals with normal glucose tolerance are inversely associated with lung function: the Jackson Heart Study. *Lung* 2011;189:311–21.
7. Klein OL, Krishnan JA, Glick S, *et al.* Systematic review of the association between lung function and type 2 diabetes mellitus. *Diabet Med* 2010;27:977–87.
8. Heianza Y, Arase Y, Tsuji H, *et al.* Low lung function and risk of type 2 diabetes in Japanese men: the Toranomon Hospital Health Management Center Study 9 (TOPICS 9). *Mayo Clin Proc* 2012;87:853–61.
9. Kwon CH, Rhee EJ, Song JU, *et al.* Reduced lung function is independently associated with increased risk of type 2 diabetes in Korean men. *Cardiovasc Diabetol* 2012;11:38.
10. Sinden NJ, Stockley RA. Systemic inflammation and comorbidity in COPD: a result of 'overspill' of inflammatory mediators from the lungs? Review of the evidence. *Thorax* 2010;65:930–6.
11. Mannino DM, Thorn D, Swensen A, *et al.* Prevalence and outcome of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J* 2008;32:962–9.
12. Iwamoto H, Yokoyama A, Kitahara Y, *et al.* Airflow limitation in smokers is associated with subclinical atherosclerosis. *Am J Respir Crit Care Med* 2009;179:35–40.
13. Feary JR, Rodrigues LC, Smith CJ, *et al.* Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: a comprehensive analysis using data from primary care. *Thorax* 2010;65:956–62.
14. Davis WA, Knuiman M, Kendall P, *et al.* Glycemic exposure is associated with reduced pulmonary function in type 2 diabetes: the Fremantle Diabetes Study. *Diabetes Care* 2004;27:752–7.
15. Ehrlich SF, Quesenberry CP Jr, Van Den Eeden SK, *et al.* Patients diagnosed with diabetes are at increased risk for asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and pneumonia but not lung cancer. *Diabetes Care* 2010;33:55–60.
16. Seshasai SR, Kaptoge S, Thompson A, *et al.* Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med* 2011;364:829–41.
17. World Health Organization. *Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation.* Geneva: World Health Organization, 2006.
18. Knowler WC, Barrett-Connor E, Fowler SE, *et al.* Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393–402.
19. Unwin N, Shaw J, Zimmet P, *et al.* Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. *Diabetes Med* 2002;19:708–23.
20. Qiao Q, Jousilahti P, Eriksson J, *et al.* Predictive properties of impaired glucose tolerance for cardiovascular risk are not explained by the development of overt diabetes during follow-up. *Diabetes Care* 2003;26:2910–14.
21. Gabir MM, Hanson RL, Dabelea D, *et al.* Plasma glucose and prediction of microvascular disease and mortality: evaluation of 1997 American Diabetes Association and 1999 World Health Organization criteria for diagnosis of diabetes. *Diabetes Care* 2000; 23:1113–18.
22. Singleton JR, Smith AG, Bromberg MB. Increased prevalence of impaired glucose tolerance in patients with painful sensory neuropathy. *Diabetes Care* 2001;24:1448–53.
23. American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995;152:1107–36.
24. Committee report of pulmonary physiology in Japan Respiratory Society. Reference values for spirogram and arterial blood gas analysis in Japanese. (In Japanese.) *Nihon Kokyuki Gakkai Zasshi* 2001;39:1S–17S.
25. Abdul-Ghani MA, Jenkinson CP, Richardson DK, *et al.* Insulin secretion and action in subjects with impaired fasting glucose and impaired glucose tolerance: results from the Veterans Administration Genetic Epidemiology Study. *Diabetes* 2006;55:1430–5.
26. Eriksson KF, Lindgärde F. Poor physical fitness, and impaired early insulin response but late hyperinsulinaemia, as predicts of NIDDM in middle-aged Swedish men. *Diabetologia* 1996;39:573–9.
27. Burney PG, Hooper R. Forced vital capacity, airway obstruction and survival in a general population sample from the USA. *Thorax* 2011;66:49–54.
28. Guerra S, Sherrill DL, Venker C, *et al.* Morbidity and mortality associated with the restrictive spirometric pattern: a longitudinal study. *Thorax* 2011;65:499–504.
29. Orfei L, Strachan DP, Rudnicka AR, *et al.* Early influences on adult lung function in two national British cohorts. *Arch Dis Child* 2008;93:570–4.
30. Sebert S, Sharkey D, Budge H, *et al.* The early programming of metabolic health: is epigenetic setting the missing link? *Am J Clin Nutr* 2011;94:1953S–8S.
31. Whincup PH, Kaye SJ, Owen CG, *et al.* Birth weight and risk of type 2 diabetes: a systematic review. *JAMA* 2008;300:2886–97.
32. Osmond C, Barker DJ. Fetal, infant, and childhood growth are predictors of coronary heart disease, diabetes, and hypertension in adult men and women. *Environ Health Perspect* 2000;108:545S–53S.
33. Barker DJ. The developmental origins of adult disease. *J Am Coll Nutr* 2004;23:588S–95S.

BMJ Open

Cross-sectional and prospective study of the association between lung function and prediabetes

Takashi Yamane, Akihito Yokoyama, Yoshihiro Kitahara, et al.

BMJ Open 2013 3:
doi: 10.1136/bmjopen-2012-002179

Sekiduka-Kumano et al. BMC Psychiatry 2013, 13:159
http://www.biomedcentral.com/1471-244X/13/159

BMC Psychiatry

RESEARCH ARTICLE Open Access

Positive association between the plasma levels of 5-hydroxyindoleacetic acid and the severity of depression in patients with chronic obstructive pulmonary disease

Tomomi Sekiduka-Kumano[1], Tomotaka Kawayama[1*], Kosuke Ito[1], Yoshihisa Shoji[2], Kazuko Matsunaga[1], Masaki Okamoto[1], Nobutaka Edakuni[1], Haruki Imaoka[1], Naohisa Uchimura[2] and Tomoaki Hoshino[1]

Abstract

Background: The role of plasma monoamines in patients with chronic obstructive pulmonary disease (COPD) with depression is unclear. To investigate monoamines in 20 depressed patients with COPD, the plasma concentrations of serotonin, 5-hydroxyindoleacetic acid (5-HIAA), homovanillic acid, and 3-methoxy-4-hydroxyphenylglycol (MHPG) were measured and compared with those in 50 non-depressed COPD patients, and also with 23 age- and gender-matched non-smokers and 13 smokers as non-depressed healthy controls.

Methods: Diagnosis of depression was assessed using the Centre for Epidemiologic Studies Depression Scale. Plasma concentrations of monoamines were measured by high-performance liquid chromatography.

Results: None of the depressed COPD patients had suicidal ideation. The plasma 5-HIAA level [median, (25% and 75% quartiles)] in depressed COPD patients [6.8 ng/mL, (4.9 and 13.1)] was significantly higher than in non-depressed COPD patients [5.4, (4.2 and 7.5)] ($p=0.022$) and non-smokers [5.1 (3.8 and 7.2)] ($p=0.041$), but not smokers [4.7, (4.0 and 6.7)] ($p>0.05$). The plasma 5-HIAA level ($r=0.24$, $p=0.049$) was significantly associated with the severity of depression in patients with COPD. The plasma MHPG level was significantly higher in depressed COPD patients ($p=0.043$) than in smokers, but was not higher than that in non-depressed COPD patients or non-smokers, although the level of MHPG was not associated with the severity of depression.

Conclusion: The plasma 5-HIAA level is increased in depressed COPD patients. Plasma monoamines may be a good biomarker for detection of depression in patients with COPD.

Keywords: COPD, Monoamine, Depression

Background

Chronic obstructive pulmonary disease (COPD) is characterized by a chronic airflow limitation, and is recognized as a major health problem responsible for chronic morbidity and mortality worldwide [1]. Symptomatic COPD patients who have suffered previous repeated exacerbations have poor disease control and prognosis [2]. Improvement of symptoms and prevention of exacerbations may contribute to an improvement of health-related quality of life (HRQOL) and lower mortality for patients with COPD.

COPD patients often have psychological disorders, including depression, and such patients tend to have more frequent exacerbations and a poor prognosis [3-7]. Recently, we demonstrated that depressed COPD patients had a lower HRQOL and more frequent exacerbations and hospitalizations those non-depressed COPD patients [3]. The severity of depression in COPD is closely associated with suicidal ideation [8,9].

* Correspondence: kawayama_tomotaka@med.kurume-u.ac.jp
[1]Division of Respirology, Neurology, and Rheumatology, Department of Medicine 1, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830-0011, Japan
Full list of author information is available at the end of the article

It is well known that depressive symptoms are associated with dysfunction of brain monoaminergic neurons, and that the levels of serotonin (5-hydroxytryptamine [5-HT]) released in the brain are linked to a decrease in responsiveness to anti-depressants [10,11]. It is also well known that the functions of monoamine and monoamine oxidase are associated with smoking-related diseases [12,13]. However, the relationship between levels of plasma monoamines and their metabolites in patients with COPD-associated depression is still unclear.

In the present study, we analyzed serotonin metabolites to investigate possible biomarkers of depressed COPD patients. Plasma homovanillic acid (HVA), 3-methoxy-4-hydroxyphenylglycol (MHPG), 5-HT, and 5-hydroxyindoleacetic acid (5-HIAA) were measured in COPD patients who were depressed (depressed COPD) and COPD patients who were not depressed (non-depressed COPD), and also in age- and gender-matched non-depressed nonsmokers and smokers as controls.

Methods

Participants

The subjects of this study were outpatients or healthy volunteers. We randomly enrolled 70 patients with COPD, and recruited 36 age- and gender-matched healthy controls between September 1st 2009 and August 31st 2011 at the Chest Disease Center of Kurume University Hospital, Japan (Table 1). All of the patients analyzed had had stable COPD for at least 4 weeks prior to blood tests. None had received oral or injective corticosteroids or antibiotics for 4 weeks prior to the blood tests. Individuals with asthma, bronchiectasis, interstitial pneumonia, tuberculosis, pneumoconiosis, ischemic heart disease, chronic heart disease, renal or liver failure, active malignancies of any organs, sleep apnea syndrome, and a presence and history of psychological diseases such as major depression, bipolar disorder, or schizophrenia were excluded. Also excluded were patients who had been taking anti-depressants, and patients who had a history of lung volume reduction surgery, lung transplantation, or pneumonectomy. Patients with central nervous system disorders and cerebrovascular diseases were excluded on the basis of brain computed tomography (CT) or magnetic resonance imaging (MRI) examinations. Patients with COPD who were undertaking respiratory rehabilitation, or receiving long-term oxygen therapy and non-invasive positive pressure ventilation were excluded, because these treatments are thought to affect psychological status. We carefully excluded any subjects with renal function disorders (serum creatinine levels >1.2 mg/dL).

As reported previously [14,15], the sample sizes for the patients with COPD and healthy controls were >70 and >35, respectively, in plasma levels of monoamines, when the sample ratio was 1:2 (power = 80%; alpha error = 5%; and beta error = 80%).

Study protocol

After the patients had provided written informed consent, information on age, gender, smoking status (current-, ex- or non-smoker), cumulative smoking history (pack-yrs), body mass index (BMI; weight/height^2), comorbidities, and history of pharmacological treatments was obtained. Each subject underwent blood tests, spirometry, electrocardiography, chest radiography, chest high-resolution CT (HRCT), and brain CT or MRI. Spirometry and bronchodilator response tests were performed using an electronic spirometer (Chestgraph Jr HI-101, CHEST Ltd., Tokyo, Japan) in accordance with the American Thoracic Society (ATS) recommendations [16]. A metered-dose salbutamol (400 mcg/subject, GSK, Japan) inhaler was used as a bronchodilator, and bronchodilator response tests were performed before and 30 min after salbutamol inhalation. Predicted values of spirometry parameters were calculated according to the prediction equations of the Japanese Respiratory Society, as we have reported previously [17]. HRQOL was assessed using the validated Japanese St. George's Respiratory Questionnaire (SGRQ) [18,19]. The SGRQ contains three subscales (symptoms, activity, and impact), and the total score varies from 0 to 100 with a higher score indicating a worse health status [19]. Dyspnea was evaluated using the 5-grade (0 to 4) modified Medical Research Council (mMRC) dyspnea scale [20]. Arterial blood gas analysis was performed with each subject supine breathing room air. After assessing the SGRQ, the mMRC dyspnea scale, and the Centre for Epidemiologic Studies depression (CES-D) scale (Purchased from Saccess Bell Co., Ltd, Japan) for depression, all blood samples were taken between 9:00 and 10:00 AM following 10 minutes with the subjects supine. Samples were kept at -80°C until analysis.

The study protocols (Approval No. 08091, May 29th, 2009) were approved by the research ethics board of Kurume University and written informed consent was obtained from the internal review board and all participants.

Diagnosis and severity of COPD

Diagnosis and staging of COPD were in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [2], and included a post-bronchodilator forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio of <70%, and <200 mL and <12% reversibility of FEV_1 before and after bronchodilator administration. Patients with COPD who had a smoking history of 10 pack-yrs and over and also had emphysematous changes in the lungs were selected to carefully remove asthmatics. The emphysematous

Table 1 Profiles of the four participant groups

Parameter	Control subjects		COPD patients	
	Nonsmokers	Smokers	Non-depressed	Depressed
Number of subjects	23	13	50	20
Age (yr)	66.7 ± 9.0	66.5 ± 11.6	68.5 ± 7.2	68.2 ± 7.8
Gender[a] (no. of males; %)	15 (65.2)	12 (92.3)	47 (94.0)	14 (70.0)
Body mass index (kg/m^2)	22.1 ± 2.4	23.0 ± 2.8	21.9 ± 3.1	19.8 ± 3.8†
Smoking status[a]				
Non / Ex / Cu (no.)	23 / 0 / 0	0 / 4 / 9	0 / 33 / 17	0 / 14 / 6
Smoke index (pack-yrs)	0	40.0 ± 18.2***	59.3 ± 30.3***	52.2 ± 27.0***
Comorbidities[a]				
Hypertension (no; %)	7 (30.4)	4 (30.8)	13 (26.0)	4 (20.0)
Diabetes (no; %)	5 (21.7)	1 (7.7)	11 (22.0)	6 (30.0)
Duration of COPD (yr)	N/A	N/A	5.3 ± 3.9	5.5 ± 4.4
GOLD stage[a]				
I / II / III / IV (no.)	N/A	N/A	7 / 22 / 17 / 4	2 / 4 / 8 / 6
Lung function parameters				
Before bronchodilator				
FVC (L)	3.5 ± 0.9	3.6 ± 0.7	3.4 ± 0.8	2.7 ± 0.9*†‡
%FVC	108.5 ± 17.0	105.6 ± 19.3	98.8 ± 18.3	86.4 ± 22.2**†
FEV_1 (L)	2.6 ± 0.6	2.6 ± 0.5	1.5 ± 0.6***†††	1.1 ± 0.7***†††
%FEV_1	100.8 ± 14.3	94.9 ± 20.1	54.9 ± 20.8***†††	44.8 ± 24.9***†††
FEV_1/FVC (%)	77.2 ± 6.9	73.8 ± 5.2	44.4 ± 12.7***†††	41.0 ± 16.2***†††
After bronchodilator				
FVC (L)	3.4 ± 0.9	3.5 ± 0.7	3.4 ± 0.8	2.6 ± 1.0*†‡
%FVC	108.0 ± 17.4	104.3 ± 18.0	99.3 ± 18.5	84.9 ± 23.5**†‡
FEV_1 (L)	2.7 ± 0.6	2.7 ± 0.4	1.6 ± 0.6***†††	1.2 ± 0.7***†††
%FEV_1	103.0 ± 15.5	96.5 ± 19.9	56.4 ± 20.8***†††	45.3 ± 25.0***†††
FEV_1 / FVC (%)	79.2 ± 6.5	76.0 ± 5.9	45.6 ± 13.4***†††	42.3 ± 15.9***†††
Reversibility of FEV_1 (%)	2.2 ± 4.5	1.8 ± 3.8	3.3 ± 5.3	1.0 ± 5.2
Arterial blood gases				
PaO_2 (Torr)	90.3 ± 7.5	92.9 ± 5.9	76.6 ± 9.5***†††	71.9 ± 13.9***†††
$PaCO_2$ (Torr)	41.4 ± 3.2	41.7 ± 3.5	40.0 ± 4.0	44.6 ± 7.1‡
mMRC dyspnea scale	0.0 ± 0.0	0.2 ± 0.6	1.0 ± 1.1***†††	2.1 ± 1.6***†††§
SGRQ				
Total score (units)	8.4 ± 8.3	15.7 ± 12.0	32.6 ± 15.9***††	57.8 ± 20.8***†††¶
Symptom score (units)	19.6 ± 13.4	30.9 ± 18.9	40.8 ± 21.3***††	66.2 ± 16.7***†††¶
Activity score (units)	6.0 ± 7.1	20.9 ± 17.2	42.9 ± 24.1***†††	68.2 ± 29.7***†††§
Impact score (units)	6.2 ± 10.0	8.0 ± 9.9	21.3 ± 13.9**††	52.0 ± 23.2***†††¶
CES-D scale	1.7 ± 2.9	2.5 ± 3.1	8.5 ± 5.2***†††	24.5 ± 6.0***†††¶
Treatments for COPD[b]				
LAMA (no; %)	0	0	33 (66.0)	16 (80.0)

Table 1 Profiles of the four participant groups *(Continued)*

LABA (no; %)	0	0	21 (42.0)	10 (50.0)
ICS (no; %)	0	0	15 (30.0)	11 (55.5)
SRT (no; %)	0	0	7 (14.0)	4 (20.0)

All data were expressed as mean ± SD and compared by one-way ANOVA and Tukey-Kramer test for multiple comparisons among the four groups.
[a] Data were compared among groups by chi-squared test for trend.
[b] Data were compared between depressed and non-depressed COPD patients by Fisher's exact test. Numbers of non-depressive and depressive COPD patients who used salmeterol and fluticasone devices in combination were 13 and 10, respectively. Some patients were taking multiple medications.
* $p<0.05$, ** $p<0.01$, and *** $p<0.001$ vs. nonsmokers.
† $p<0.05$, †† $p<0.01$, and ††† $p<0.001$ vs. smokers.
‡ $p<0.05$, § $p<0.01$, and ¶ $p<0.001$ vs. non-depressed COPD patients.
Non, non-smokers; Ex, ex-smokers; Cu, current smokers; GOLD, Global Initiative for Chronic Obstructive Lung Disease; FVC, forced expiratory capacity; FEV_1, forced expiratory volume in 1 second; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; mMRC, modified Medical Research Council; SGRQ, St George's respiratory questionnaire; CES-D, Center for Epidemiological Studies depression scale; LAMA, long-acting muscarinic receptor antagonist; LABA, long-acting β_2 agonist; ICS, inhaled corticosteroid; SRT, slow-release theophylline; N/A, not available.

changes were visually recognized as low-attenuation areas by chest HRCT [21].

Diagnosis of depression

Diagnosis of depression was assessed using the validated Japanese CES-D scale. The cut-off point for depression was CES-D >16 [22,23] and a CES-D score was assessed for each subject. The results of the CES-D score were not opened until this study was completed. Therefore, physicians did not know the psychological conditions of each subject. In this study, patients with a CES-D score of > 16 were a subgroup of "depressed" COPD patients. For the purpose of this study, "depression" means possible "depression" as determined by the CES-D score.

Measurement of plasma monoamine levels

Plasma levels of 5-HT, 5-HIAA, HVA, and MHPG were measured by high-performance liquid chromatography (SRL Inc., Tokyo, Japan), as previously reported [15,24-26]. The lowest detection limits for 5-HT, 5-HIAA, HVA, and MHPG were 0.01 μg/mL, 1.8 ng/mL, 4.4 ng/mL, and 3.2 ng/mL, respectively, and for statistical analysis one half of the lowest value was assigned if the value was below the detection limit.

Statistical analyses

Data analyses were performed using JMP version 7 (SAS Institute, Inc., Cary, NC). Data for the subjects were expressed as the mean ± standard deviation (SD), and data for plasma monoamine levels were expressed as the median, and 25% and 75% quartiles. Statistical analyses were performed using parametric Student's *t* test for comparison between two groups, or one-way analysis of variance (ANOVA) and Tukey-Kramer test for multiple comparisons among four groups. Correlations were analyzed by parametric or non-parametric Spearman's tests. Differences between groups were evaluated using the chi-squared test for trend and Fisher's exact test. The level of significance was set at $P < 0.05$.

Results

Subject characteristics

A total of 106 subjects participated in the study and the characteristics of the four groups, namely the 23 non-smokers and 13 smokers (as age- and gender-matched non-depressed healthy controls), and 50 non-depressed and 20 depressed COPD patients, are compared in Table 1. The depressed subjects without COPD were not enrolled in the study. None of participants, including the depressed COPD patients, had any history of attempted suicide.

The control subjects were 23 non-, 4 Ex-, and 9 current smokers, whereas the number of non-, Ex-, and current smokers were zero, 57, and 23 in patients with COPD ($p<0.001$). There was no significant difference in the smoke index among smokers, and non-depressed, and depressed COPD patients. There were no significant difference in the populations of subjects with hypertension and diabetes among nonsmokers, smokers, and, non-depressed, and depressed COPD patients ($p>0.05$). All the subjects with hypertension had been taking anti-hypertensive medications whereas the numbers of non-smokers, smokers, non-depressed, and depressed COPD patients taking anti-diabetes medications were 5, 1, 7 and 4, respectively.

In COPD, there was no significantly difference in duration of COPD between non-depressed and depressed COPD patients ($p>0.05$). The depressed COPD patients trended to have more progressive GOLD stages than the non-depressed patients but there was no significant difference in the populations of GOLD stage I (14% vs 10%), II (44% vs 20%), III (34% vs 40%), and IV (8% vs 30%) between two groups ($p>0.05$ by Chi-square test for trend).

Lung function tests showed that he depressed COPD patients had significantly lower FVC and %FVC than the non-depressed patients both before and after bronchodilator use, although both depressed and non-depressed COPD patients had significantly lower FEV_1, $\%FEV_1$ and FEV_1/FVC both before and after bronchodilator use than non-smokers and smokers, respectively (all $p<0.001$).

However, there was no difference in the reversibility of FEV_1 after bronchodilator use among the four groups.

Arterial blood gas analysis showed that the depressed COPD patients ($p<0.05$) had significantly more severe hypercapnia than the non-depressed patients, whereas both depressed (both, $p<0.001$) and non-depressed COPD patients (both, $p<0.001$) had significantly more severe hypoxia than the non-smokers and smokers, respectively.

Depressed COPD patients had significantly higher mMRC dyspnea scales ($p<0.05$) and lower HRQOL scores ($p<0.05$) than the non-depressed patients, although both the depressed (both, $p<0.001$) and non-depressed COPD patients (both, $p<0.001$) had significantly higher MRC dyspnea scales and lower HRQOL scores than the non-smokers and smokers, respectively.

In managements for COPD, all patients with COPD were receiving vaccinations for seasonal and H1N1 influenza virus and the numbers of depressed and non-depressed COPD patients who had been receiving pneumococcal vaccination within 5 yrs before recruitment were 13 and 8, respectively. There was no significant difference in the ratio of regular use of ICS, LAMA, LABA, and SRT between non-depressed and depressed COPD patients ($p=0.061$, $p=0.387$, $p=0.601$, and $p=0.717$, respectively. The effects of ICS on psychological and mood status could not be directly determined, as the study was not designed to include a period for wash-out of each controller for COPD.

Plasma monoamine levels

Plasma 5-HIAA levels [median, (25% and 75% quartiles)] in the depressed COPD patients [6.8 ng/mL, (4.9 and 13.1)] were significantly higher than in the non-depressed patients [5.4, (4.2 and 7.5)] ($p=0.022$) and non-smokers [5.1 (3.8 and 7.2)] ($p=0.041$), respectively, but were not significantly higher than in the smokers [4.7, (4.0 and 6.7)] (Figure 1).

Median (25% and 75% quartiles) plasma 5-HT levels in the non-smokers, smokers, and non-depressed and depressed COPD patients were 0.06 μg/mL (0.04 and 0.09), 0.05 (0.04 and 0.08), 0.06 (0.03 and 0.08), and 0.06 (0.02 and 0.09), respectively. The differences among the four groups were not significant (Figure 1).

Median (25% and 75% quartiles) plasma HVA levels in the non-smokers, smokers, and non-depressed and depressed COPD patients were 12.8 ng/mL (11.0 and 14.8), 11.8 (10.3 and 21.3), 14.8 (11.1 and 20.9), and 15.7 (9.9 and 22.2), respectively. The differences among the four groups were not significant (Figure 1).

Plasma MHPG level [median, (25% and 75% quartiles)] in the depressed COPD patients [6.8 ng/mL, (5.2 and 8.7)] ($p=0.043$) was significantly higher than in the smokers [4.6, (4.3 and 5.5)]. There was no significant difference in plasma MHPG level between the depressed COPD patients and either non-smokers [5.7 (4.7 and 7.2)] or non-depressed COPD patients [6.7, (4.1 and 8.2)] ($p>0.05$), respectively (Figure 1).

To investigate seasonal effects in plasma 5-HIAA levels, plasma obtained in four seasons, spring (March-May), summer (June-August), fall (September-November), and winter (December-February), were measured. Number of all subjects and COPD patients in four seasons were 17 and 10, 34 and 27, 25 and 16, and 30 and 17, respectively. There was no significant difference in median plasma 5-HIAA [6.7 ng/mL (5.1 and 7.6) in spring, 5.3 ng/mL (4.3 and 7.4) in summer, 5.9 ng/mL (3.9 and 10.6) in fall, and 5.4 ng/mL (3.7 and 8.2) in winter, respectively, $p>0.05$].

The plasma levels of 5-HT, 5-HIAA, HVA, and MHPG were not associated with age and there was no significant difference in those plasma levels between male and female.

Correlation between plasma 5-HIAA level and total CES-D scales in patients with COPD

Plasma level of 5-HIAA ($r=0.24$, $p=0.049$), but not that of 5-HT ($r=-0.06$, $p>0.05$), HVA ($r=0.19$, $p>0.05$), or MHPG ($r=0.14$, $p>0.05$), was significantly associated with total CES-D scales in patients with COPD (Figure 2).

Correlation between plasma 5-HIAA level and BMI, lung function, arterial blood gas parameters, and total SGRQ score in patients with COPD

There was a significant correlation between BMI and plasma MHPG ($r=-0.24$, $p=0.041$), but not 5-HIAA ($r=-0.21$, $p>0.05$), 5-HT ($r=0.07$, $p>0.05$), HVA ($r=-0.09$, $p>0.05$), and MHPG ($r=-0.24$, $p=0.041$) level in COPD patients.

Plasma 5-HIAA and MHPG level showed significant negative associations with %FVC, $\%FEV_1$, and partial pressure of arterial oxygen (PaO_2), and positively associations with partial pressure of arterial carbon dioxide ($PaCO_2$) and total SGRQ scores. There was no significant correlation between the plasma 5-HT level and lung function, arterial blood gas parameters, or total SGRQ scores. Plasma HVA level showed a significant negative association with $\%FEV_1$ and PaO_2, and a positive association with $PaCO_2$ and total SGRQ scores (Table 2).

Correlation between lung function, total SGRQ scores and total CES-D scales in patients with COPD

The $\%FEV_1$ showed a significant negative association with total SGRQ scores ($r=-0.69$, $p<0.0001$) and total CES-D scales ($r=-0.27$, $p=0.025$) in patients with COPD. The PaO_2 ($r=-0.53$, $p<0.0001$) and $PaCO_2$ ($r=0.44$, $p=0.0002$) showed a significant association with total SGRQ scores. Interestingly, there was no correlation between PaO_2 ($r=-0.21$, $p>0.05$) and $PaCO_2$ ($r=0.22$, $p>0.05$) and total CES-D scales in COPD patients.

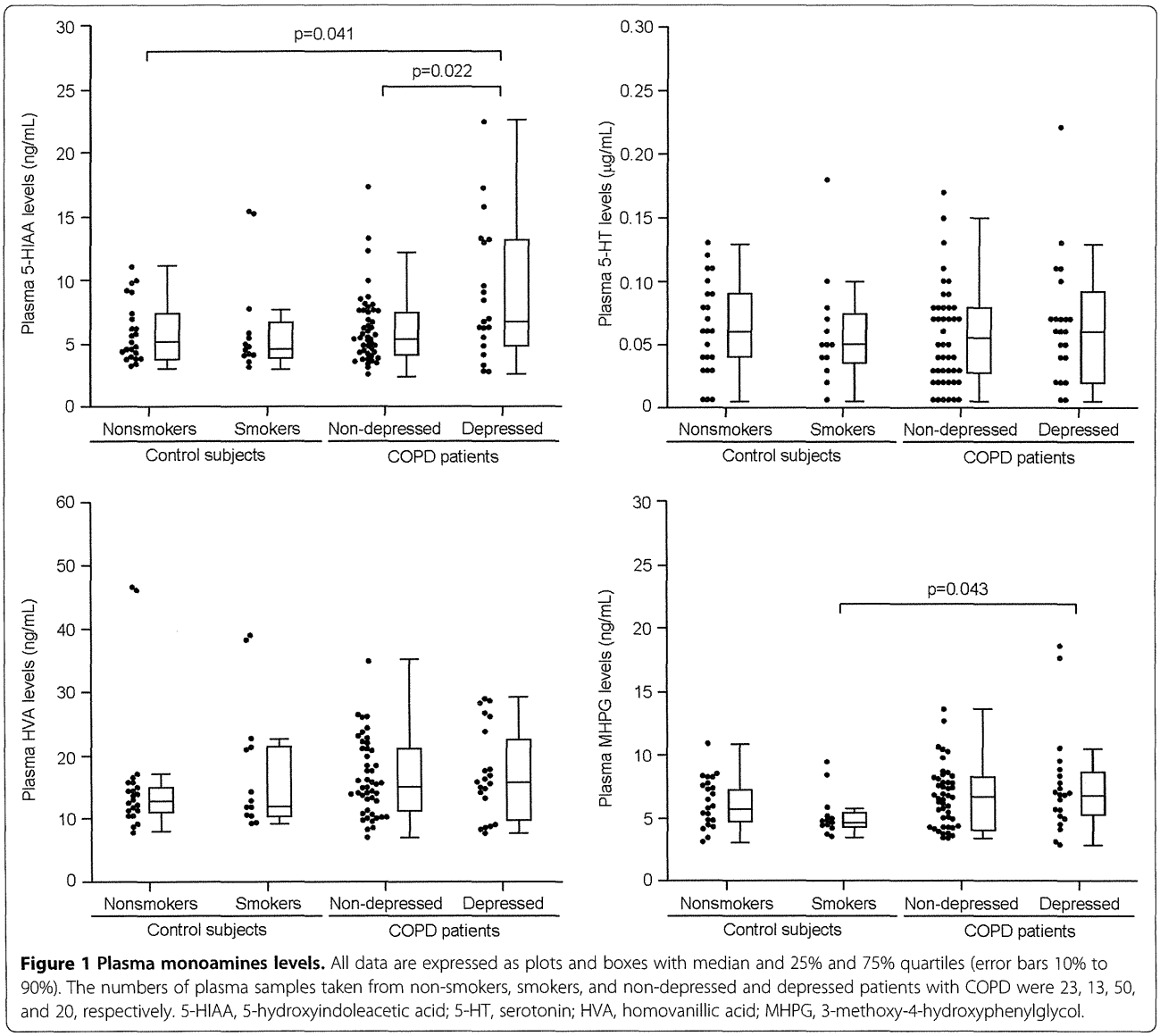

Figure 1 Plasma monoamines levels. All data are expressed as plots and boxes with median and 25% and 75% quartiles (error bars 10% to 90%). The numbers of plasma samples taken from non-smokers, smokers, and non-depressed and depressed patients with COPD were 23, 13, 50, and 20, respectively. 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, serotonin; HVA, homovanillic acid; MHPG, 3-methoxy-4-hydroxyphenylglycol.

Discussion

To our knowledge, this is the first study to have measured the plasma levels of monoamines and their metabolites in depressed patients with COPD. Our present results demonstrated that depressed patients with COPD had significantly higher plasma 5-HIAA levels than non-depressed COPD patients and non-smokers. The plasma 5-HIAA levels also showed a significant positive correlation with the severity of depression in the patients with COPD. Our present results support those of a previous study demonstrating that the plasma 5-HIAA levels were significantly increased in patients with depression relative to control subjects, and that the plasma 5-HIAA levels were positively related to the severity of depression [14]. Previous studies have shown that the level of 5-HIAA in cerebrospinal fluid (CSF) was positively associated with the severity of depression in abstinent alcoholics, and that treatment with the antidepressant fluoxetine decreased both the CSF 5-HIAA levels and the mean Hamilton depression rating scale score [27,28]. Other studies have demonstrated that decreased CSF 5-HIAA levels were associated with attempted suicide in patients with depression, and that non-impulsive suicide attempters had higher plasma 5-HIAA levels than impulsive suicide attempters [15,29,30]. In the COPD patients we analyzed, increased plasma 5-HIAA levels were also associated with poor lung function, hypoxia and hypercapnia. Poor lung function is closely correlated with a poor HRQOL, and may result in depression. In COPD patients it has been shown that hypoxia and/or hypercapnia induces oxidative stress and results in an increase of reactive oxygen species (ROS) throughout the whole body including the lungs, brain, and muscles [1-5]. Therefore, it is possible that ROS may have a direct or