Resting Breathing Instability During Wakefulness as a Predictor of Clinical Outcome in COPD

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BACKGROUND: Dyspnea is a common symptom in patients with COPD. It causes physical inactivity and impaired health-related quality of life. Although optimal breathing methods alleviate dyspnea, it is unclear whether breathing instability has a clinical impact on patients with COPD. This study aimed to investigate whether resting breathing instability during wakefulness was associated with dyspnea assessed by the modified Medical Research Council (mMRC) dsypnea scale and whether breathing instability can be a novel predictor of clinical outcomes. METHODS: Forty-four subjects with stable COPD were enrolled (mean age, 71.0 y). Resting breathing was monitored for 15 min by using respiratory inductance plethysmography. Breathing instability was evaluated with the coefficient of variation for breath-by-breath respiratory duration and tidal volume (V_T) by using an artifact-free respiratory signal for 5 min. Pulmonary function testing and blood gas analysis were performed (mean FEV_1 percent of predicted, 68.5%). Questionnaires with regard to dyspnea and health-related quality of life were also completed. Exacerbations were recorded prospectively for 1 year after the initial assessment. RESULTS: The coefficients of variation for V_T were significantly higher in the subjects with an mMRC dyspnea scale score $\geq$ 2 versus those with an mMRC dyspnea scale score < 2 (26.4 ± 7.4% vs 20.3 ± 6.4%, $P = .006$) . The coefficients of variation for respiratory duration and V_T were not associated with age, body mass index, and pulmonary function variables. In multivariate analysis, FEV_1 percent of predicted and coefficient of variation for V_T remained significant predictors for an mMRC dyspnea scale score $\geq$ 2 ($P = .004$ and $P = .01$, respectively). Coefficient of variation values were also correlated with several health-related quality of life domains. The exacerbation frequency was associated with the coefficient of variation for V_T. CONCLUSIONS: Resting breathing pattern during wakefulness is a novel assessment tool for severity of dyspnea, which can be one of the predictors for exacerbation in patients with COPD. *Key words: breathing instability; breathing pattern; COPD; Dyspnea; exacerbation; health-related quality of life*. [Respir Care 2021;66(9):1477–1484. © 2021 Daedalus Enterprises]

Introduction

COPD is characterized by persistent respiratory symptoms and air-flow limitation due to airway and/or alveolar abnormalities, usually caused by significant exposure to noxious particles or gases.[1] A diagnosis of COPD is based on air-flow limitation when FEV_1/FVC is < 0.7.[1] The severity of COPD is stratified by FEV_1 as a percent of the predictive value as follows: $FEV_1 \geq 80\%$ of predicted as mild (stage I), $50\% \leq FEV_1 < 80\%$ of predicted as moderate (stage II), $30\% \leq FEV_1 < 50\%$ of predicted as severe (stage III), $FEV_1 < 30\%$ predicted as very severe (stage IV).[1] Major symptoms of COPD include dyspnea, chronic cough, and sputum production. Among them, progressive

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dyspnea is known to cause physical inactivity[2] and impaired quality of life.[3] It has been reported that dyspnea is a better predictor of mortality[4] and is more closely related to health-related quality of life (HRQOL)[5] than air-flow limitation in patients with COPD. Although the modified British Medical Research Council (mMRC) dyspnea scale is widely used for the assessment of dyspnea in COPD, inconsistency between dyspnea and the degree of air-flow limitation is frequently observed in clinical settings.[6] In addition, the mMRC dyspnea scale has a poor ability to response to treatment, and the score cannot accurately predict response to treatment secondary to a limited number of categories.[7]

In our previous research,[7,8] we demonstrated that the breathing pattern contributed to the diversity of respiratory disease such as obstructive sleep apnea syndrome. For example, breathing instability could help distinguish the clinical phenotype of obstructive sleep apnea syndrome and affect the successful treatment rate of CPAP.[8,9] It is possible that COPD has several clinical phenotypes independent of pulmonary function because some patients do not perceive dyspnea commensurate with the severity of their disease and some exhibit repeated exacerbation regardless of the severity of air-flow limitation.[10,11] In general, people exhibit different breathing patterns, which implies that genetic factors may contribute to the individuality of the breathing pattern.[12] Irregular breathing has been observed in patients with anxiety, which has been shown to be associated with exacerbation and hospitalization[13] and which contributes to increased mortality in COPD.[14,15] Therefore our primary objective in this study was to determine whether resting breathing instability during wakefulness was associated with dyspnea evaluated by using the mMRC dyspnea scale in subjects with stable COPD. Secondary objectives were to assess the relationship between breathing instability and HRQOL, and to investigate whether breathing instability could be a predictor of exacerbation in subjects with COPD.

QUICK LOOK

Current knowledge

Breathing patterns are unique to each individual, and can be measured noninvasively with respiratory waveform analysis. The breathing pattern is influenced by genetic factors, and modified by psychological factors and medical comorbidities such as heart failure and respiratory diseases. An optimal breathing pattern can alleviate dyspnea, which causes physical inactivity and impairs health-related quality of life in patients with COPD.

What this paper contributes to our knowledge

We investigated breathing instability by using an objective and reliable method. We found that subjects with COPD and with irregular breathing were more likely to experience dyspnea, which impaired their quality of life; they also had more frequent exacerbations within 1 year. The resting breathing pattern during wakefulness was considered useful to assess pathophysiology of COPD.

Methods

Study Design and Subjects

Consecutive patients with COPD who had been making regular visits to Nara Medical University Hospital between September 2011 and March 2014 were eligible for this prospective observational study. A diagnosis of COPD was confirmed with $FEV_1/FVC < 0.7$ by spirometry according to the definition of the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[1] We excluded patients who had known heart disease, malignancy, interstitial pneumonia, cor pulmonale, or any other severe inflammatory or metabolic disease or psychological disorder. Patients receiving home oxygen therapy were also excluded. Eventually, 44 patients with stable COPD agreed to participate in this study. After enrollment into this study, all the subjects underwent pulmonary function testing. Vital capacity, FVC, FEV_1, residual volume, and total lung capacity were measured by using a pulmonary function instrument with computer processing (FUDAC 70, Fukuda Denshi, Tokyo, Japan) and FEV_1/FVC was calculated. Lung volumes were determined by using the helium gas dilution method, and the diffusing capacity for carbon monoxide was measured by the single-breath method. The obtained values were expressed as a percentage of the predicted values.[16] Arterial blood samples obtained with the subjects on room air were analyzed by using a standard blood gas analyzer (ABL800; Radiometer, Copenhagen, Denmark). In addition, the subjects were asked to complete an HRQOL questionnaire. Resting breathing during wakefulness at rest was monitored to analyze breathing instability. After the initial assessments, all the enrolled subjects were followed up for 1 year. This study was approved by the ethics advisory committee at Nara Medical University (389), and all the subjects provided written informed consent.

Assessment of Breathing Instability, Dyspnea, Quality of Life, and Exacerbation

Resting breathing during wakefulness was recorded with the subject in a sitting position in a quiet room for 15 min from the signal of thoracic and abdominal excursion by using uncalibrated double band respiratory inductance

plethysmography (Alice PDx, Philips Respironics, Tokyo, Japan). The respiratory signal sampling rate was 12.5 Hz. Data collection was performed in the same environment for all the subjects. The subjects sat on a chair in a quiet room and kept their eyes open. They were provided no instructions with regard to how to breathe or the procedures used for the analysis. Before we started to collect data, a synchronous signal of abdominal and thoracic movement was confirmed. Artifacts-free respiratory inductance plethysmography sum signals for 5 min were extracted for the evaluation of breathing instability. The most common causes of artifacts were body movement and contact failure of an electrode. Breathing instability was assessed by using the coefficient of variation (coefficient of variation percentage = [SD/mean] ×100) for breath-by-breath total duration of respiratory cycle (T_{tot}) and estimated tidal volume (V_T) with an arbitrary unit.

Dyspnea was assessed by using the mMRC dyspnea scale.[17] The mMRC dyspnea scale scores range from 0 to 4. The intensity of symptoms was classified as an mMRC dyspnea scale score of 0–1 and an mMRC dyspnea scale score of ≥2 in ABCD assessment of the GOLD.[1] HRQOL was assessed by the St George Respiratory Questionnaire.[18] The St George Respiratory Questionnaire is a 76-item questionnaire with 3 domains: symptoms, activity, and impacts. It is scored on a 100-point scale with lower scores indicating better quality of life. The COPD assessment test is one of the tools recommended by the GOLD Strategy for assessing symptoms in patients with COPD.[19] The COPD assessment test consists of 8 items scored from 0 to 5 (0, best; 5, worst) that include coughing, mucus production, chest tightness, capacity for exercise and activities, confidence, sleep quality, and energy levels. The COPD assessment test scores range from 0 to 40. After the initial assessments, the subjects regularly visited our hospital and exacerbations were recorded prospectively for 1 year. Exacerbation was defined as an acute event characterized by worsening of the subject's respiratory symptoms beyond normal day-to-day variations that require a change in medication.[1]

Statistical Analysis

Continuous variables were presented as means ± SDs. Statistical significance was set at $P < .05$ (2-sided). Associations between breathing instability and objective parameters were explored by using the Spearman correlation analysis. The Mann-Whitney U test was used for comparison of non-parametric continuous variables. Logistic regression analysis was used to assess the correlation between the objective parameters and the degree of dyspnea assessed by using the mMRC dyspnea scale (mMRC score of 0–1 or mMRC score of ≥2) and exacerbation. Factors that tended to be associated in the univariate analysis were included in the multivariate analysis. Statistical analysis was performed by using IBM SPSS Statistics version 20 for Windows (IBM, Armonk, New York).

Table 1. Subject Characteristics

Characteristic	Results
Men/women, *n*	41/3
Age, y	71.0 ± 8.3
BMI, kg/m^2	21.5 ± 3.5
Smoking habit, pack-years	67.5 ± 30.1
FEV_1, L	1.54 ± 0.60
FEV_1, %	68.5 ± 23.5
GOLD stage I/II/III/IV, *n*	14/23/6/1
VC, %	104.6 ± 19.5
RV, %	124.9 ± 33.5
D_{LCO}, %	54.9 ± 22.5
P_{aO_2}, mm Hg	73.6 ± 9.6
P_{aCO_2}, mm Hg	41.0 ± 4.6
mMRC dyspnea scale score 0/1/2/3/4, *n*	7/19/17/1/0
Breathing frequency	19.3 ± 4.7
Coefficient of variation for T_{tot}, %	15.4 ± 7.4
Coefficient of variation for V_T, %	22.8 ± 7.4

Data are presented as mean ± SD (range) unless otherwise indicated.
BMI = body mass index
GOLD = Global Initiative for Chronic Obstructive Lung Disease
mMRC = Modified British Medical Research Council
T_{tot} = respiratory duration
V_T = tidal volume
VC = vital capacity
RV = residual volume
D_{LCO} = diffusing capacity for carbon monoxide

Results

Subject characteristics are summarized in Table 1. The mean ± SD age and body mass index were 71.0 ± 8.3 y and 21.5 ± 3.5 kg/m^2, respectively. Among all included subjects, 41 (93.2%) were men. Thirty-seven subjects (84.1%) had mild-to-moderate air-flow limitation and 7 (15.9%) had severe or very severe air-flow limitation.

Breathing Instability, Dyspnea, and Quality of Life

As for breathing instability parameters, the mean ± SD coefficients of variation for T_{tot} and for V_T were 15.4 ± 7.4% and 22.8 ± 7.4%, respectively (Table 1). The coefficients of variation for T_{tot} and for V_T were not significantly correlated with age, body mass index, pulmonary function variables (VC, RV) and P_{aO_2}. Eighteen subjects had an mMRC dyspnea scale score ≥ 2. The mean ± SD coefficient of variation values for V_T were significantly higher in the subjects with an mMRC dyspnea scale score ≥ 2 than in those with an mMRC dyspnea scale score < 2 (26.4 ± 7.4% vs 20.3 ± 6.4%, respectively; $P = .006$). As shown in Figure 1, this significance did not come from the data of subjects classified with GOLD stage III and IV. Univariate analysis

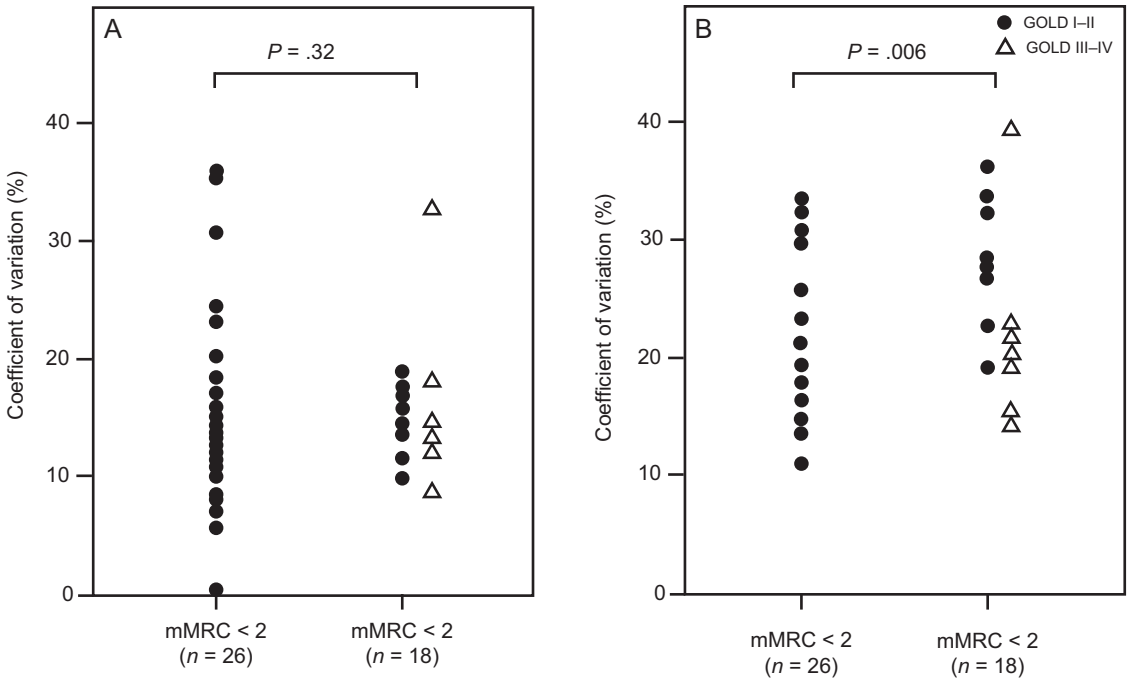

Fig. 1. The relationship between breathing instability and dyspnea. Coefficient of variation for A: respiratory duration and B: tidal volume. Coefficient of variation values for tidal volume were significantly higher in the subjects with a modified Medical Research Council (mMRC) dyspnea scale score ≥ 2 than in those with an mMRC dyspnea scale score < 2 ($P = .006$).

(Table 2) revealed that the FEV_1 percent of predicted and the coefficient of variation for V_T were significantly associated with an mMRC dyspnea scale score ≥ 2, and a RV showed a tendency to be correlated with an mMRC dyspnea scale score ≥ 2. In the multivariate analysis, FEV_1 percent of predicted and coefficient of variation for V_T remained significant predictors for an mMRC dyspnea scale score ≥ 2 (odds ratio [OR] 0.91, 95% CI 0.86–0.97 [$P = .004$]; and OR 1.19, 95% CI 1.03–1.38 [$P = .02$], respectively).

The relationship between breathing instability and questionnaires on HRQOL is shown in Table 3. The coefficient of variation for V_T was significantly correlated with the

Table 2. Logistic Regression Analysis for a Modified British Medical Research Council Dyspnea Scale Score ≥ 2

Variable	Univariate		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	0.96 (0.89–1.04)	.32	NA	NA
Body mass index	0.93 (0.78–1.11)	.42	NA	NA
FEV_1, %	0.94 (0.89–0.98)	.003	0.91 (0.86–0.97)	.004
VC, %	0.98 (0.95–1.01)	.23	NA	NA
RV, %	1.02 (0.998–1.05)	.08	0.98 (0.94–1.02)	.34
D_{LCO}, %	0.97 (0.94–1.01)	.11	NA	NA
Breathing frequency	1.02 (0.89–1.16)	.78		
P_{aO_2}	0.98 (0.91–1.04)	.49	NA	NA
Coefficient of variation for T_{tot}	1.01 (0.93–1.09)	.91	NA	NA
Coefficient of variation for V_T	1.13 (1.03–1.25)	.01	1.19 (1.03–1.38)	.02

OR = odds ratio
NA = not applicable
T_{tot} = respiratory duration
V_T = tidal volume
VC = vital capacity
RV = residual volume
D_{LCO} = diffusing capacity for carbon monoxide

Table 3. Relationship Between Breathing Irregularity and Questionnaires on Health-Related Quality of Life

Questionnaire	Coefficient of Variation for T_{tot}		Coefficient of Variation for V_T	
	r	*P*	r	*P*
Chronic COPD assessment test	0.30	.051	0.35	.02
St George Respiratory Questionnaire				
Symptom domain	0.21	.17	0.24	.12
Activity	0.40	.008	0.44	.003
Impacts	0.18	.25	0.23	.13
Total score	0.35	.02	0.37	.01

T_{tot} = respiratory duration
V_T = tidal volume

COPD assessment test ($P = .02$; $r = 0.35$), whereas the correlation between the coefficient of variation for T_{tot} and the COPD assessment test did not reached statistical significance ($P = .051$; $r = 0.30$). Coefficients of variation for T_{tot} and for V_T were significantly correlated with the total St George Respiratory Questionnaire score ($P = .01$, $r = 0.37$; and $P = .02$, $r = 0.36$, respectively) and the activity domains of the St George Respiratory Questionnaire score ($P < .001$, $r = 0.41$; and $P = .004$, $r = 0.42$, respectively) but showed no correlation with the symptoms and the impacts domain.

Exacerbation

Fourteen subjects showed exacerbation during the 1-year follow-up period after the initial assessment. The mean ± SD coefficients of variation values for V_T were significantly higher in the subjects with exacerbation for 1 year versus those without exacerbation (25.9 ± 5.9% vs 21.3 ± 7.6%; $P = .030$) (shown in Fig. 2). The variables associated with exacerbation are shown in Table 4. Univariate analysis revealed that P_{aO_2} was a significant predictor of the incidence of exacerbation ($P = .030$), and the coefficient of variation for V_T was a tendency to predict the incidence of exacerbation ($P = .06$). However, in a univariate analysis, body mass index, pulmonary function variables, mMRC dyspnea scale score, and the coefficient of variation for T_{tot} were not significant predictors for exacerbation. In a multivariate analysis, exacerbation frequency was associated with P_{aO_2} and the coefficient of variation for V_T (OR 0.88, 95% CI 0.79–0.99 [$P = .031$]; and OR 1.13, 95% CI 1.01–1.27 [$P = .035$], respectively).

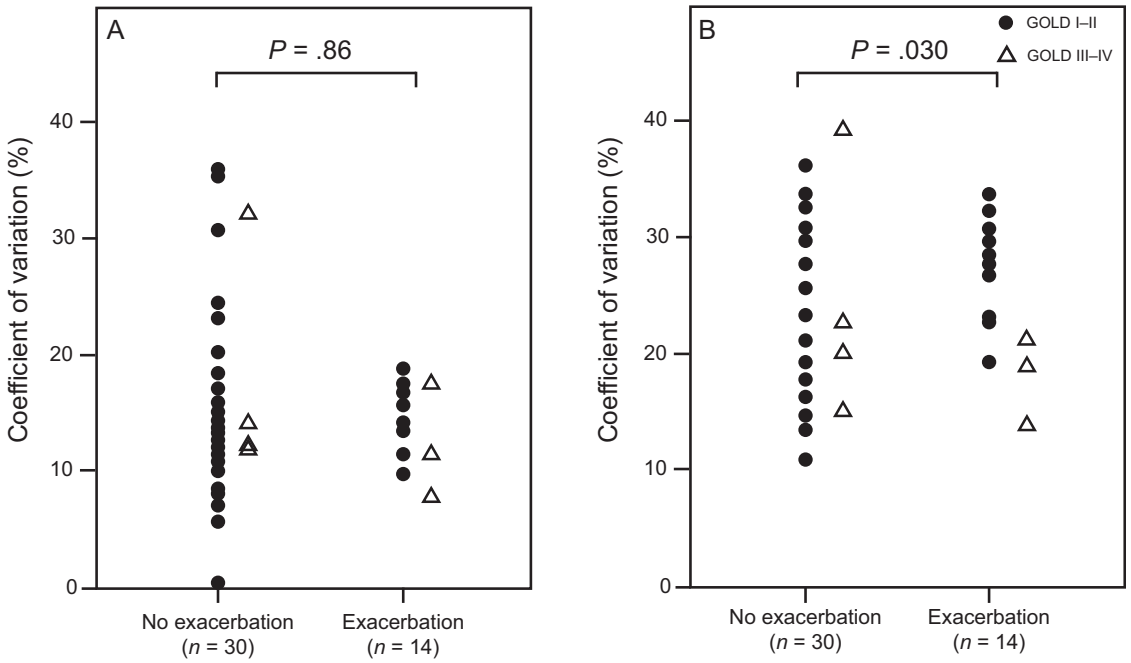

Fig. 2. Relationship between breathing instability and exacerbation. Coefficient of variation for A: respiratory duration and B: tidal volume. Coefficient of variation values for tidal volume were significantly higher in the subjects with exacerbation for 1 year than in those without exacerbation ($P = .030$).

Table 4. Logistic Regression Analysis for Exacerbation

Variable	Univariate		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	1.02 (0.94–1.10)	.65	NA	NA
Body mass index	1.09 (0.90–1.32)	.36	NA	NA
FEV_1, %	0.98 (0.95–1.01)	.17	NA	NA
VC, %	0.99 (0.96–1.03)	.70	NA	NA
RV, %	1.003 (0.98–1.02)	.74	NA	NA
D_{LCO}, %	1.01 (0.98–1.04)	.38	NA	NA
P_{aO_2}	0.89 (0.80–0.99)	.030	0.88 (0.79–0.99)	.031
P_{aCO_2}	1.07 (0.91–1.25)	.40	NA	NA
Breathing frequency	1.001 (0.87–1.15)	.99	NA	NA
mMRC dyspnea scale	1.87 (0.75–4.64)	.18	1.05 (0.34–3.13)	.95
Coefficient of variation for T_{tot}	1.002 (0.92–1.09)	.97	NA	NA
Coefficient of variation for V_T	1.09 (0.995–1.20)	.062	1.13 (1.01–1.27)	.035

OR = odds ratio
NA = not applicable
mMRC = Modified British Medical Research Council
T_{tot} = respiratory duration,
V_T = tidal volume
VC = vital capacity
RV = residual volume
D_{LCO} = diffusing capacity for carbon monoxide

Discussion

The main findings of the present study are as follows: (1) breathing instability was independently associated with dyspnea and HRQOL in the subjects with stable COPD, (2) breathing instability could be a significant predictor of exacerbation in patients with stable COPD. In the present study, we focused on the individuality of the pattern of breathing in the subjects with COPD. The breathing pattern represents the output of the respiratory control system and a complex combination of behavioral factors. Because breathing patterns of identical twins are similar,[20,21] genetic factors may have an impact on breathing pattern. In addition, the breathing pattern can be modified by psychological factors and medical comorbidities such as heart failure and respiratory diseases. Reportedly, patients with panic disorders show irregular breathing[20,22,23] and patients with chronic heart failure often develop breathing abnormalities, such as various forms of oscillatory breathing patterns characterized by rises and falls in the ventilation.[24] Patients with interstitial lung diseases and COPD have more rapid and shallow breathing when compared with control subjects.[25,26]

The rapid shallow breathing index, which is the ratio of respiratory frequency to V_T, is one of the most commonly used predictors of weaning from mechanical ventilation.[27] Although some investigators have measured respiratory frequency and V_T in patients with respiratory diseases, few studies have evaluated resting breathing patterns. In this study, breathing instability was useful to discriminate the presence of dyspnea, whereas the breathing frequency showed no correlation with dyspnea. Although most of the subjects were classified with GOLD stage I or II, the average breathing frequency seemed to be fast. We speculated that they might have been nervous because their breathing was monitored by using a thoracic and abdominal band. The subjects had various air-flow limitations, ranging from mild to very severe, but breathing instability was not related to air-flow limitation. Therefore, we considered that respiratory instability could be influenced by factors other than air-flow limitation. To the best of our knowledge, this was the first study to focus on breathing instability during wakefulness as a clinical indicator of dyspnea and exacerbation in the subjects with COPD.

Air-flow limitation and air trapping in patients with COPD result in hyperinflation and reduce inspiratory capacity. Particularly, dynamic hyperinflation during exertion is known to be the main cause of dyspnea on exertion. Although residual volume was not associated with dyspnea in the multivariate analysis, we successfully demonstrated that breathing instability, especially the coefficient of variation for V_T, contributed to dyspnea in the subjects with COPD. This finding was supported by the established knowledge that certain breathing techniques have been shown to alleviate dyspnea.[28] We speculate that dynamic hyperinflation may be associated with breathing instability. A physiologic explanation of the association between dyspnea and variability of breath-to-breath V_T could be that patients with COPD and with dyspnea who particularly complain of air hunger want to inhale more air. Excessive inhalation may follow the next normal depth of breath and this cycle may be repeated.

Another interesting finding in the present study was that breathing instability could be a predictor of exacerbation in the subjects with COPD. However, its precise mechanism was unclear. Physical inactivity caused by dyspnea characterized by breathing instability may affect the development of exacerbation and/or mortality. Although we did not evaluate the association between breathing instability and anxiety or depression, anxiety and/or depression has been reported to be associated with an increased risk for exacerbation in patients with COPD.[13,29] One may think that a pneumotachograph is preferable to assess quantitative breathing behavior. Although the pneumotachograph is the established reference standard to measure the absolute value of breathing analysis, it is uncomfortable and stressful.

We did not consider the pneumotachograph preferable for obtaining the resting breathing pattern; therefore, we decided instead to adopt respiratory inductance plethysmography. Several studies demonstrated the accuracy of respiratory inductance plethysmography in healthy subjects and subjects with pulmonary diseases.[30,31] Respiratory inductance plethysmography has also been considered as an alternative and quantitative measurement method of pneumotachograph.[32,33] In this study, the respiratory inductance plethysmography sum signal was not calibrated, so the absolute value of the V_T could not be measured. However, it would be acceptable to use the estimated V_T obtained from an uncalibrated respiratory inductance plethysmography sum signal for assessing the variability of breath-by-breath V_T within one individual.

The present study had some potential limitations. First, we did not compare the differences in breathing patterns between control subjects and the subjects with COPD. Thus, we did not clarify whether development of COPD affected breathing patterns. A causal relationship between breathing instability and dyspnea in subjects with COPD was not elucidated in the present study. Further interventional studies are required to determine whether stabilization of the breathing pattern can improve dyspnea. Second, most of the subjects in this study were men. However, most of the large clinical trials of COPD in Japanese subjects consisted mostly of men such as those in the present study.[34,35] This implies that there exists male predominancy in the clinical setting, which is different from epidemiologic studies in the general population. Third, all the subjects were assessed for breathing instability during the day, from 10:00 AM to 2:00 PM but not at the same time. They also did not receive any instructions regarding sleep time during the night before the assessment. Thus, the effect of diurnal variation on the breathing pattern cannot be rejected.

Conclusions

Assessment of resting breathing patterns during wakefulness is a powerful objective tool for dyspnea in COPD. Moreover, breathing instability could be a predictive marker for future exacerbation in patients with COPD.

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