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Full title:

The relationship between spontaneous expiratory flow-volume curve configuration and airflow obstruction in elderly COPD patients

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Abstract

Background: Assessment of the degree of airflow obstruction is important for determining the treatment strategy in chronic obstructive pulmonary disease (COPD) patients. However, in some elderly COPD patients, measurement of a forced vital capacity (FVC) to assess the degree of airflow obstruction is often impossible because of cognitive dysfunction or severe dyspnea. In such circumstances, a simple test of airways obstruction requiring only a short run of tidal breathing would be useful. This study was designed to examine whether the spontaneous expiratory flow-volume (SEFV) curve configuration reflects the degree of airflow obstruction in elderly COPD patients.

Methods: Thirty-four elderly patients (mean ± SD age: 80 ± 7 y) with stable COPD (%FEV_1 39.0%±18.5% predicted) underwent measurements of flow-volume curves during quiet breathing and FVC. Twelve age-matched healthy subjects were also studied. The SEFV curve configuration (concavity/convexity), spirometry, breathing pattern, and demographic characteristics were examined. The SEFV curve concavity/convexity prediction accuracy was also examined by calculating the receiver operating characteristic (ROC) curves, cut-off values, area under the curve (AUC), sensitivity, and specificity of these indices.

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Results: Fourteen patients showed a concave SEFV curve, and all healthy subjects showed convex curves. The patients who showed concave curves often had very severe airway obstruction. The predicted value of %FEV1 (32.4%) was the most powerful SEFV curve concavity predictor, with an AUC of 0.92 (95% CI 0.83 - 1.00), with the highest sensitivity and specificity (0.93, 0.88, respectively) .

Conclusion: Concavity of the SEFV curve obtained during tidal breathing may be a useful test for determining the presence of very severe obstruction in elderly patients not able to perform a satisfactory FVC maneuver.

Key Words:

COPD, flow-volume curves, airflow obstruction, assessment, respiratory function test, configuration

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Introduction

Measurement of forced vital capacity (FVC) is a clinically useful test that is required to make diagnosis of airflow obstruction and to determine the severity of obstruction[1]. However, FVC often cannot be measured in elderly patients with problems such as cognitive dysfunction or severe dyspnea, because it depends on the subject's respiratory effort.

Recently, as a technique that can identify pathology, the oscillation method has been used for the measurement of resting breathing even in these patients.[2] However, the oscillation method is difficult to use widely in the clinical setting because the measurement equipment is too large and expensive. On the other hand, the assessment of the spontaneous expiratory flow-volume (SEFV) curve has been previously reported as a method to evaluate the severity of airway obstruction, which has the advantage that it can be implemented easily by measurement of quiet breathing using spirometry.[3-10] Shortening of the time to reach the peak expiratory flow rate[3] and the slope of the late SEFV curve[4], which can be obtained from the SEFV curve, have been reported to be related to airway obstruction. Moreover, a method to assess the configuration of the SEFV curve has been reported, and the concavity of the shape of the SEFV curve has been found to be related to expiratory flow limitation (EFL).[9,10] We considered that

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evaluation of SEFV curve shape could be used clinically if we could show an association between SEFV curve shape and the severity of airway obstruction, because SEFV curve shape can be easily evaluated during SEFV curve assessment.

The purpose of this study was to determine whether SEFV curve shape reflects the degree of airway obstruction in elderly chronic obstructive pulmonary disease (COPD) patients.

Methods

Subjects

A total of 34, clinically stable, elderly COPD patients (GOLD II (N=9), III (N=11), and IV (N=14)) who were receiving pulmonary rehabilitation at the Hyogo College of Medicine Sasayama Medical Center and who could perform spirometric testing according to the ATS/ERS Task Force Guidelines, participated.[1] Patients were clinically stable for ≥ 4 weeks. Exclusion criteria were: suspected asthma; other systemic conditions that could contribute to dyspnea or exercise limitation, such as heart failure or metabolic disorders; and neuromuscular comorbidity limiting all measurements (Table 1). Twelve age-matched healthy subjects were also studied. All subjects gave their written, informed consent in advance. All studies were approved by the Ethics

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Committee of Hyogo College of Medicine.

Procedures

All measurements were done with the patient seated. A hot wire spirometer (AE300-s; MINATO Medical Science, Osaka, Japan) connected to a mouthpiece was used to measure lung volume and flow during 1 min of quiet breathing and forced vital capacity (FVC). All subjects performed the IC maneuver at the start and at the end during quiet breathing to correct “drift” caused by mechanical error[11]. Mastery of the IC maneuver was ensured by having all patients practice it beforehand, however some patients often could not start IC measurement from functional residual capacity. We also measured “actual IC” volume at the start and at the end during quiet breathing. [12] To control measuring quality, all tests have obtained “actual IC” volume variation less than 10 % (Figure 2). The FVC measurements were done according to the guideline reported by the ATS/ERS Task Force Guidelines[1]. Lung volume and flow data were examined using an analyzing system (PowerLab, ADInstruments, Castle Hill, Australia). The last five breaths before IC were analyzed breath-by-breath, and mean values for each subject were obtained for Ti (inspiratory time), Te (expiratory time), Ttot (total breathing cycle time), Ti/Ttot (duty cycle), Vt (tidal volume), Vt/Ti (mean inspiratory flow), and Vt/Te

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(mean expiratory flow).

The SEFV curves were also drawn for the last five breaths before IC. Assessment of the shape of the SEFV curve was done according to the methods of Ma et al.[10] More specifically, two critical anchoring points were determined first: (A) maximum spontaneous expiratory flow ($\dot{V}max$), and (B) the point at which the expiratory flow takes a sharp decline, signaling the beginning of inspiration ($\dot{V}ee$). $\dot{V}ee$ was defined as the point associated with the greatest difference between the slopes of the SEFV curve during the last 0.25 sec. The area of the rectangle with the two points as vertices was calculated. Then, the area delimited by the SEFV curve in the rectangle was calculated, and the ratio of the delimited area to the rectangle area (rectangular area ratio; RAR) was calculated (Figure 1). The RARs were calculated for each breath, and a mean value for each subject was obtained (Figure 2). Mean values of RAR < 0.5 signify concavity, while values ≥ 0.5 signify convexity.

The reproducibility of RAR measurements was also evaluated by re-testing in 10 patients (GOLD II (N=2), III (N=3), and IV (N=5)) after the first measurement on the same day. Close correlations were found between the first and second RARs. The linear regression analyses between the two measurements (i.e. first and second) provided the following equation: $RAR_{1st} = 1.112\ RAR_{2nd} - 0.043$ ($r=0.96$, $p<0.0001$).

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Statistical Analysis

All results are shown as means ± SD. FEV1 and FVC are expressed as percentages of the values predicted for age, sex, and height established by the Japanese Respiratory Society.[13] The Mann-Whitney U-test was used to compare RARs between the healthy subjects and COPD patients. Group comparisons of demographic characteristics, lung function, breathing pattern, and RAR were performed using one-way ANOVA and post hoc comparisons (Bonferroni). The cut-off value to predict SEFV curve configuration (convexity/concavity) was determined for each variable that showed a significant difference in ANOVA (spirometric values included only predicted values) with the receiver operating characteristic (ROC) curve. The performance of the indices was evaluated by sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), likelihood ratio of a positive test (LR+), likelihood ratio of a negative test (LR-), and diagnostic accuracy (DA). The predictive performance of each index was also evaluated through the calculation of the area under the ROC curve (AUC). All tests were performed at a significance level of $P < .05$. Analyses were performed using SPSS version 18 (SPSS Japan Inc., Tokyo, Japan).

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Results

The RAR of all COPD patients was 0.507 ± 0.090; 14 showed concavity, while the others showed convexity. In healthy subjects, RAR was 0.664 ± 0.069; no healthy subjects showed concavity. As a result, RAR was smaller in the COPD patients than in the healthy subjects ($P < .0001$).

Table 2 shows the demographic characteristics, lung function, breathing pattern, and RAR according to SEFV shape in all subjects. There were significant differences in FEV1, %FEV1, FEV/FVC, FVC, %FVC, Ti, Ti/Ttot, and VT/Ti on ANOVA. Eleven patients in the concavity group had very severe airflow obstruction, the remaining three patients with concavity have sever obstruction (%FEV1; 30-50% (GOLD III)). On the other hand, age, height, body mass, BMI, and other breathing pattern indices were not significantly different.

Quality indicators of the 6 indices that showed significant differences on the ANOVA used to predict the SEFV curve configuration are shown in Table 3. Cut-off values (calculated from the ROC curves) for %FEV1, %FVC, Ti/Ttot, FEV/FVC, Ti, and Vt/Ti were 32.4%, 60.8%, 0.39, 46.7%, 1.06 sec, and 0.52 L/sec, respectively. %FEV1 showed the best DA (0.92), followed by %FVC (0.89), Ti/Ttot (0.81), FEV/FVC (0.80), Ti (0.77), and Vt/Ti (0.61) (Table 4). The predictive performance of a clinically useful

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value (%FEV1; 30% (GOLD IV: very severe airflow obstruction)) was also evaluated. The sensitivity, specificity, PPV, NPV, LR＋, LR-, and DA were 0.78, 0.91, 0.79, 0.91, 8.38, 0.24, and 0.87, respectively.

Discussion

The present results showed that the SEFV curve configuration changes in elderly COPD patients. In particular, concavity in the SEFV curve has been suggested as a useful index to predict very severe COPD in elderly patients.

Several studies have shown SEFV curve characteristics in COPD patients[4-10] from the study by Morris et al.[3] They reported that the characteristic SEFV curve in COPD reached maximal expiratory flow early from the beginning of the expiratory phase, and the time was correlated with the degree of air flow obstruction and airway resistance.[3] Moreover, the slope of the latter in the SEFV curve was correlated with air flow obstruction and airway resistance.[4] Baydur et al.[9] studied the visual assessment of SEFV curve configuration in patients with obstructive and restrictive disorders and reported the relationship between the configuration and EFL. Ma et al.[10] reported SEFV curve configuration using RAR during exercise, and they showed that COPD patients had a

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trend to concavity compared to normal subjects.

In the present study, it was clear that RAR decreased more in COPD patients than in normal subjects. Many COPD patients with more severe airflow obstruction tend to show expiratory flow limitation (EFL)[14], and EFL promotes dynamic hyperinflation, intrinsic positive end-expiratory pressure, or dyspnea[15]. It has also been reported that patients who show concave SEFV curves tend to have EFL[9]. Many of our COPD patients have very severe airflow obstruction (GOLD IV (N=14)), so it was shown that they had a more concave configuration. Moreover, the present RAR results showed significant differences between healthy subjects and COPD patients in the convexity group. The reason for these results is likely due to the presence of EFL in moderate or severe COPD patients. Baydur et al.[9] also reported that COPD patients with EFL often show convexity, so there must have been some EFL patients in the convexity group who tended to have decreased RAR more than patients without EFL**.** Indeed, expiratory flow in the convexity group tended to decrease linearly, despite many healthy subjects showing a sinusoidal configuration (Figure 3). However, the present study could not examine EFL because of the problem with measuring sensitivity[15]. EFL could have been examined by the method described by Hyatt et al[16], but it has a low accuracy to detect EFL[15].

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The results of the present study showed decreased Ti and Ti/Ttot and increased Vt/Ti in patients showing concavity compared with healthy subjects. Morris et al.[3, 4] showed that deceleration in flow immediately preceding inspiration affected the SEFV curve configuration. The premature start of inspiration also supports other studies[17, 18] showing an increase in the time constant of the lung with increasing severity of obstructive airway disease. In order to increase ventilation in such COPD patients, expiration needs to be prolonged, since increased respiratory muscle activity is ineffective because of EFL. Shortening inspiration is one strategy for prolonging expiration and improving ventilation[17, 18]. Thus, the present patients with concavity showed these results.

%FEV1 was the most powerful SEFV curve concavity predictor, with an AUC of 0.92 (95% CI 0.83 - 1.00), and it had the highest sensitivity and specificity. In particular, the cut-off value was very low (%FEV1: 32.4%); it seems to be useful for detecting very severe airflow obstruction. Moreover, a cut-off value of %FEV1 of 30% was also useful, with high sensitivity and specificity. Morris et al. [3, 4] and Colasanti et al. [19] noted that the reason for the concavity of the SEFV curve was dynamic airway compression or gas compression by high pleural pressure during expiration. These changes appear to affect forced expiratory volume (FEV) curve configuration but not SEFV in moderate or

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severe COPD patients, but they affect SEFV curve configuration, not only FEV, in very severe COPD patients.

On the other hand, the present study showed no effects of age on SEFV curve configuration. This is important, because FEV curve configuration in elderly subjects normally shows some signs of scalloping because loss of lung elasticity occurs with aging[20]. Since the present study included no data about younger subjects, these effects could not be examined sufficiently, but SEFV curve configuration did not appear to change with aging in elderly COPD patients.

The present study had certain limitations. First, the sample size was too small to fully examine the relevant factors responsible for SEFV curve configuration. Second, the subjects were not consecutive patients. Third, there was variation in the distribution of severity among the subjects. Finally, in the present study, there were no subjects with mild airway obstruction (GOLD Ⅰ; $\%FEV_1 \geq 80\%$).

Conclusion

In the present study, the SEFV curve shape and lung function were studied in elderly COPD patients. It was demonstrated that the SEFV curve configuration was concave in patients with very severe airway obstruction. Therefore, elderly patients with very

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severe COPD could be evaluated by assessment of SEFV curve configuration, even those who cannot cooperate with measurements of FVC because of cognitive dysfunction or severe dyspnea.

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Figure legends

Figure 1. The method to calculate RAR

(A)

The maximum spontaneous expiratory flow ($\dot{V}$max) and the point at which the expiratory flow takes a sharp decline signaling the beginning of inspiration ($\dot{V}$ee) are first identified. Then, the area of the rectangle with the two points as vertices is calculated.

(B)

The area delimited by the SEFV curve in the rectangle is calculated, and then the SEFV curve area to rectangle area ratio is then calculated.

Figure 2. Lung Volume, Flow, and RAR Changes During Breathing.

The upper panel shows lung volume (A) and flow (B) during spontaneous breathing and inspiratory capacity. The lower panel shows each flow-volume curve and rectangular area ratio (RAR).

Figure 3. Representative SEFV curve and RAR.

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Table 1. Patients' Characteristics and Resting Pulmonary Function

	value (n=34)	range
Female (n)	7	—
age (mean ± SD y)	80±7	65 to 92
Weight (mean ± SD kg)	47±9	30 to 71
Height (mean ± SD cm)	158±7	143 to 172
BMI (mean ± SD kg/m2)	19±3	14 to 28
FEV1 (mean ± SD ℓ)	0.85±0.46	0.26 to 2.10
%FEV1 (mean ± SD % predicted)	39.0±18.5	18.2 to 79.7
FEV/FVC (mean ± SD %)	44.2±14.1	22.0 to 68.7
FVC (mean ± SD ℓ)	1.78±0.71	0.70 to 3.53
%FVC (mean ± SD % predicted)	62.7±19.9	27.2 to 106.3
Required domiciliary supplemental oxygen (n)	21	—

BMI = body mass index

FEV1 = forced expiratory volume in 1 second

%FEV1 = forced expiratory volume in 1 second % predicted

FVC = forced vital capacity

%FVC = forced vital capacity % predicted

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Table 2. Demographic Characteristics, Lung Function, Breathing Pattern and Rectangular Area Ratio of Patients and Healthy Subjects.

	Healthy (n=12)	Convexity (n=20)	concavity (n=14)	ANOVA
Female (n)	4	3	4	—
Age (mean ± SD y)	77±5	80±7	79±8	0.381
Weight (mean ± SD kg)	55±12	48±10	46±6	0.058
Height (mean ± SD cm)	161±9	158±7	158±8	0.626
BMI (mean ± SD kg/m2)	21±4	19±4	18±3	0.116
FEV1 (mean ± SD ℓ)	2.06±0.43	1.06±0.49**	0.55±0.16**††	<.0001
%FEV1 (mean ± SD % predicted)	90.4±11.7	48.2±18.9**	25.8±5.6**††	<.0001
FEV/FVC (mean ± SD %)	76.1±5.2	47.8±13.3**	39.1±14.1**	<.0001
FVC (mean ± SD ℓ)	2.76±0.60	2.07±0.73*	1.36±0.42**††	<.0001
%FVC (mean ± SD % predicted)	95.3±11.7	71.8±17.5**	49.8±15.8**††	<.0001
Ti (mean ± SD sec)	1.56±0.33	1.26±0.49	1.00±0.44**	0.01
Te (mean ± SD sec)	1.96±0.54	2.03±1.04	1.83±0.74	0.798
Ttot (mean ± SD sec)	3.43±0.90	3.31±1.37	2.84±1.16	0.395
Ti/Ttot (mean ± SD)	0.45±0.03	0.39±0.08*	0.35±0.03**	0.001
Vt (mean ± SD ℓ)	0.58±0.19	0.65±0.16	0.52±0.18	0.132
Vt/Ti (mean ± SD ℓ/sec)	0.38±0.11	0.56±0.20**	0.55±0.19*	0.013
Vt/Te (mean ± SD ℓ/sec)	0.31±0.11	0.36±0.12	0.30±0.09	0.282
RAR (mean ± SD)	0.664±0.069	0.570±0.045**	0.456±0.08**††	<.0001

* = P < .05. ** = P < .01 vs. healthy   † = P < .05. †† = P < .01 vs. convexity

BMI = body mass index   FEV1 = forced expiratory volume in 1 second

%FEV1 = forced expiratory volume in 1 second % predicted   FVC = forced vital capacity

%FVC = forced vital capacity % predicted RAR = rectangular area ratio

Ti = inspiratory time   Te = expiratory time   Ttot = total breathing cycle time   Ti/Ttot = duty cycle

Vt = tidal volume   Vt/Ti = mean inspiratory flow   Vt/Te = mean expiratory flow

RAR = rectangular area ratio

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Table 3. Quality Indicators of the Indexes Used to Predict the airflow obstruction

	cut off	sensitivity	specificity	PPV	NPV	LR+	LR-	DA
%FEV1	32.4	0.93	0.88	0.76	0.97	7.43	0.08	0.89
%FVC	60.8	0.79	0.88	0.73	0.90	6.29	0.24	0.85
Ti/Ttot	0.39	0.86	0.78	0.63	0.93	3.92	0.18	0.80
FEV/FVC	46.7	0.79	0.69	0.52	0.88	2.51	0.31	0.72
Ti	1.06	0.79	0.75	0.58	0.89	3.14	0.29	0.76
TV/Ti	0.52	0.64	0.63	0.43	0.80	1.71	0.57	0.63

PPV = positive predictive value, NPV = negative predictive value, LR+ = likelihood ratio of positive test,

LR－ = likelihood ratio of negative test , DA = diagnostic accuracy

%FEV1 = forced expiratory volume in 1 second % predicted

%FVC = forced vital capacity % predicted RAR = rectangular area ratio

Ti/Ttot = duty cycle Ti = inspiratory time Vt/Ti = mean inspiratory flow

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Table 4. Values of the Area Under the Receiver Operating Characteristic Curve for Each Variables

	AUC	95% CI
%FEV1	0.92	0.83 to 1.00
%FVC	0.89	0.80 to 0.99
Ti/Ttot	0.81	0.68 to 0.94
FEV/FVC	0.80	0.67 to 0.93
Ti	0.77	0.61 to 0.93
TV/Ti	0.61	0.43 to 0.80

AUC = area under curve CI = confidence interval

%FEV1 = forced expiratory volume in 1 second % predicted

%FVC = forced vital capacity % predicted RAR = rectangular area ratio

Ti/Ttot = duty cycle Ti = inspiratory time Vt/Ti = mean inspiratory flow

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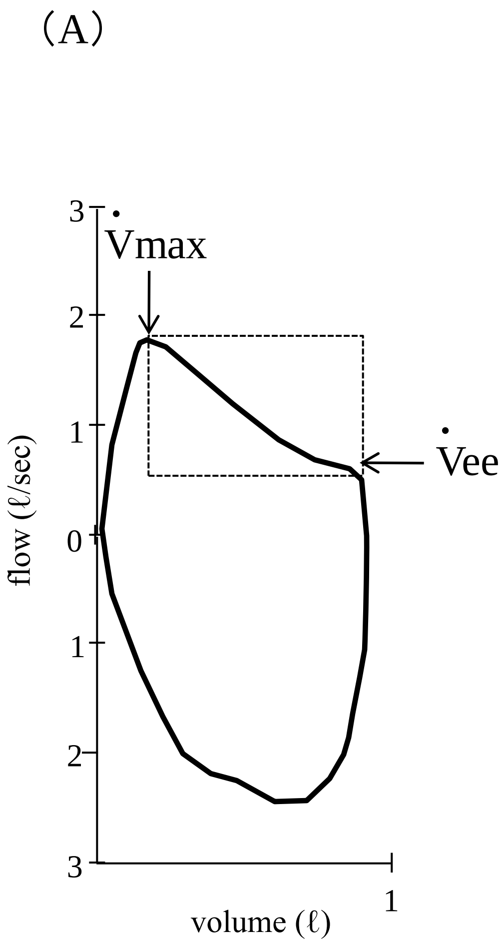

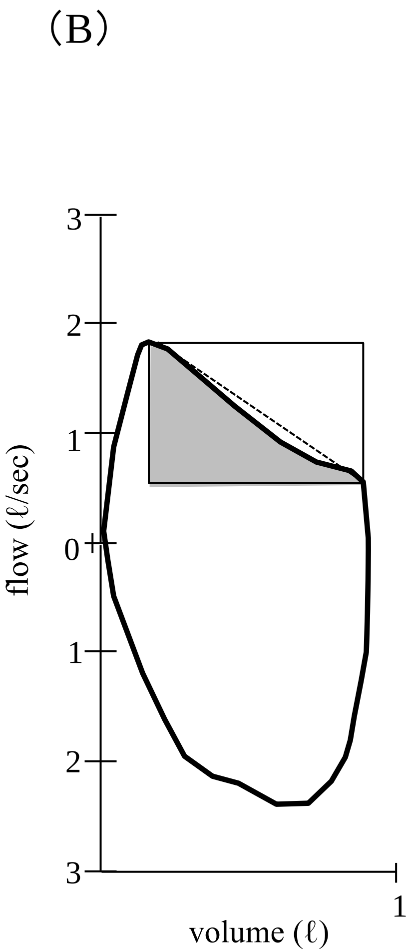

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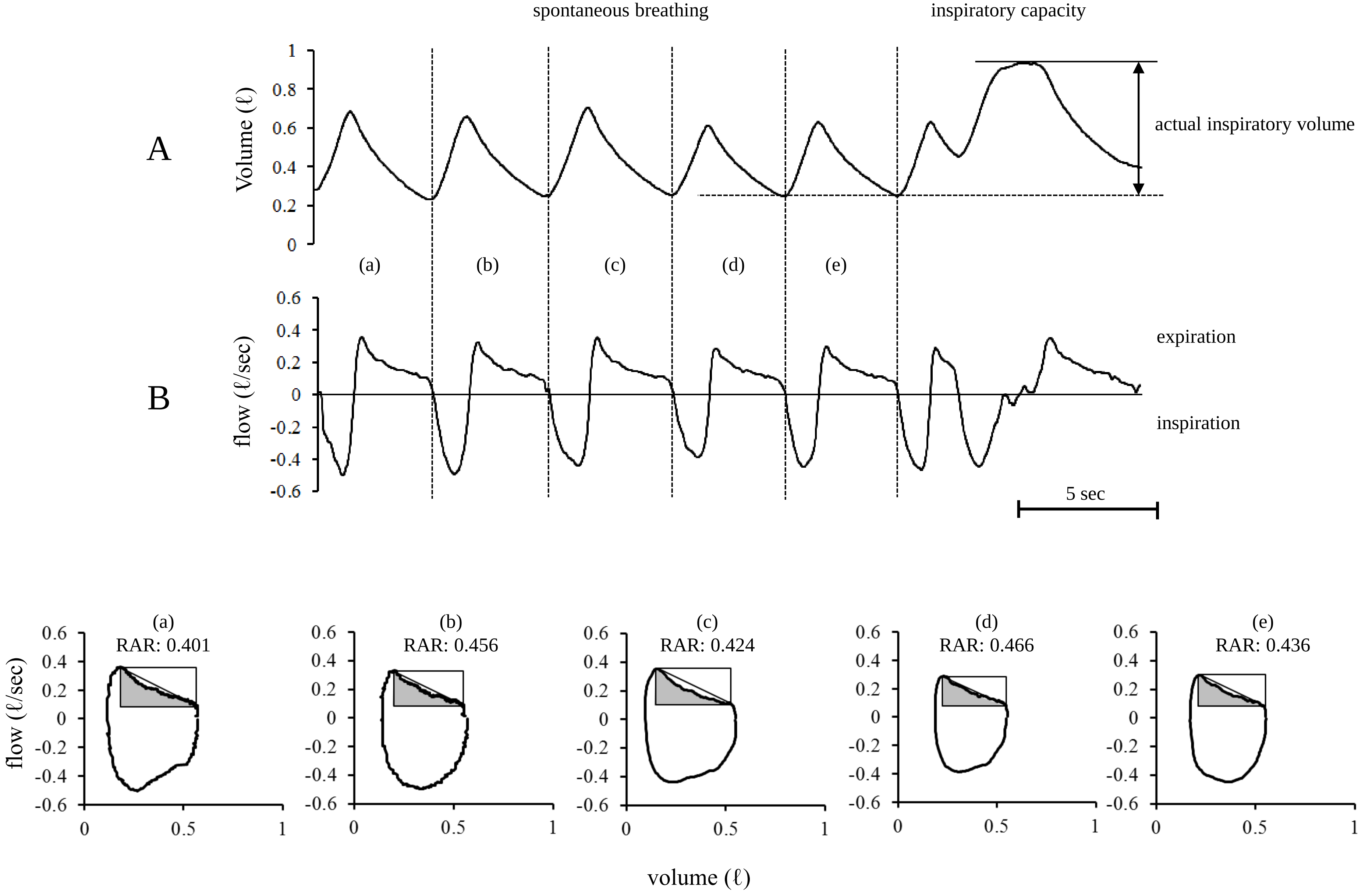

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