SCIENTIFIC REPORTS

OPEN

Developing a New Marker of Dynamic Hyperinflation in Patients with Obstructive Airway Disease - an observational study

Ming-Lung Chuang[1,2], Meng-Jer Hsieh [ID][3,4], Tzu-Chin Wu[1,2] & I-Feng Lin[5]

Tidal volume at peak exercise and vital capacity ratio (V_{Tpeak}/VC) and V_{Tpeak}/inspiratory capacity (IC) were used to differentiate lung expansion in subjects with normal health and chronic obstructive pulmonary disease (COPD) from that in subjects with restrictive ventilation. However, VC and IC variably change due to pseudorestriction of lung volumes. Thus, these variables are currently not recommended. In contrast, total lung capacity (TLC) does little change during exercise. The aims of the study investigated whether V_{Tpeak}/TLC is more significantly correlated with static air trapping and lung hyperinflation in patients with COPD than V_{Tpeak}/IC, V_{Tpeak}/FVC, and V_{Tpeak}/SVC (study 1), and developed a marker to replace dynamic IC maneuvers by evaluation of the relationship between end-expiratory lung volume (EELV) and V_{Tpeak}/TLC and identification of a cutoff value for V_{Tpeak}/TLC (study 2). One hundred adults with COPD (study 1) and 23 with COPD and 19 controls (study 2) were analyzed. Spirometry, lung volume, diffusing capacity, incremental cardiopulmonary exercise tests with dynamic IC maneuvers were compared between groups. An ROC curve was generated to identify a cut off value for V_{Tpeak}/TLC. In study 1, V_{Tpeak}/TLC was more significantly associated with airflow obstruction, static air trapping and hyperinflation. In study 2, V_{Tpeak}/TLC was highly correlated with EELV in the patients ($r = -0.83$), and V_{Tpeak}/TLC ≥ 0.27 predicted that 18% of the patients with static air trapping and hyperinflation can expand their V_T equivalent to the controls. In conclusions, V_{Tpeak}/TLC was superior to other V_{Tpeak}/capacities. V_{Tpeak}/TLC may be a marker of dynamic hyperinflation in subjects with COPD, thereby avoiding the need for dynamic IC maneuvers. V_{Tpeak}/TLC < 0.27 identified approximately 82% of subjects with COPD who could not adequately expand their tidal volume. As most of our participants were male, further studies are required to elucidate whether the results of this study can be applied to female patients with COPD.

In normal healthy subjects, tidal volume (V_T) rapidly expands at the start of rapid incremental exercise and gradually reaches a plateau after reaching approximately 55% of vital capacity (VC)[1]. V_T/VC and V_T and inspiratory capacity ratio (V_T/IC) have been reported to range from 0.55 ± 0.09 to 0.63 ± 0.19 and from $\leq 0.7 \pm 0.11$ to 0.79 ± 0.04[1–6], respectively. V_T/IC values in subjects with restrictive ventilatory impairment usually reach 1, up to the limit of IC[1].

Reduced dynamic inspiratory reserve volume (IRV) or O'Donnell's threshold[7] combined with elevated end-expiratory lung volume (EELV) can substantially constrain expansion of operating V_T in patients with chronic obstructive pulmonary disease (COPD). Furthermore, V_T/VC tends to be more variable because of variations in SVC and FVC in subjects with COPD due to pseudorestriction (i.e., low FVC%pred but normal total lung capacity, TLC). In this context, variations in operating V_T at peak exercise and the "false" restriction of FVC

[1]Division of Pulmonary Medicine and Department of Internal Medicine, Chung Shan Medical University Hospital, Taichung, 40201, ROC, Taiwan. [2]School of Medicine, Chung Shan Medical University, Taichung, 40201, ROC, Taiwan. [3]Department of Pulmonary and Critical Care Medicine, Chiayi Chang-Gung Memorial Hospital, Chang-Gung Medical Foundation, Chiayi, ROC, Taiwan. [4]Department of Respiratory Therapy, Chang Gung University, Taoyuan, ROC, Taiwan. [5]Institute of Public Health, National Yang Ming University, Taipei, ROC, Taiwan. Correspondence and requests for materials should be addressed to M.-L.C. (email: yuan1007@ms36.hinet.net)

1
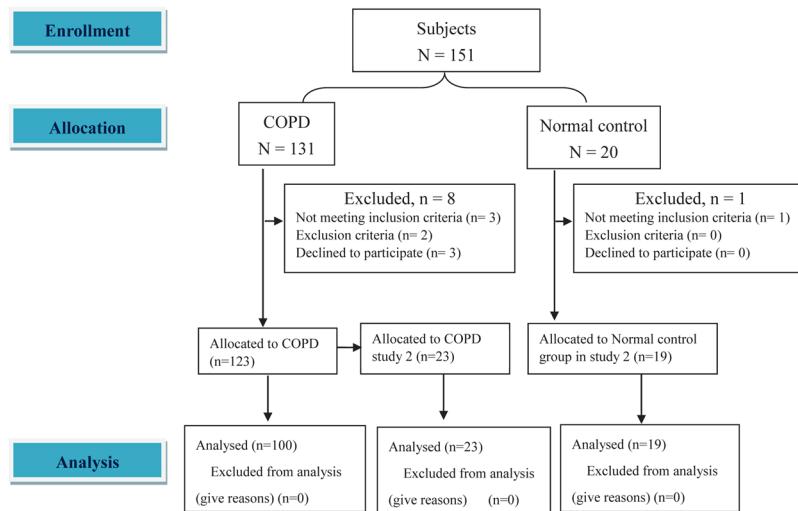
Figure 1. Flow diagram. A total of 131 subjects with chronic obstructive pulmonary disease were screened along with 20 normal healthy controls. After excluding eight subjects with COPD, the remaining 123 were allocated to study 1 (n = 100) and study 2 (n = 23). After excluding one subject, the remaining 19 normal subjects were allocated to study 2.

(or SVC or IC) lead to inconsistent values of V_T/FVC, V_T/SVC, and V_T/IC. Therefore, these variables are not recommended to differentiate obstructive from restrictive ventilatory limitations[8].

Dynamic IC measurements have been reported to be a good way to identify dynamic hyperinflation[2–5,7]. However, IC maneuvers have to be standardized and the study subjects have to become familiarized with the maneuvers, and IC measurements and analysis also have to be standardized by researchers[9]. Nevertheless, dynamic IC measurements are not recommended for ramp-pattern protocols in which V_T cannot steadily proceed to perform IC maneuvers[9]. However, the ramp-pattern protocol is a widely used protocol to test incremental exercise.

TLC does not change or only changes a little during exercise in normal subjects and subjects with lung diseases[10–12]. We hypothesized that V_T/TLC at peak exercise (V_{Tpeak}/TLC) would be lower in subjects with COPD compared to normal subjects, and that it would be less variable than V_{Tpeak}/FVC, /SVC and /IC. As TLC and V_{Tpeak} are routinely measured during lung function tests and cardiopulmonary exercise tests (CPET), respectively, V_{Tpeak}/TLC may be a convenient new marker of dynamic hyperinflation, thereby avoiding the need for dynamic IC measurements.

The aims of this study were (1) to investigate whether V_{Tpeak}/TLC is less variable and more significant in correlation with static air trapping or lung hyperinflation in subjects with COPD than V_{Tpeak}/IC, /FVC, and /SVC, and (2) to develop a new marker of dynamic hyperinflation to replace dynamic IC maneuvers by evaluation of the relationship between EELV and V_{Tpeak}/TLC and identification of a cutoff value of V_{Tpeak}/TLC.

Methods

Study design. This observational cross-sectional study enrolled healthy normal subjects and subjects with COPD at two university teaching hospitals, and analyzed lung function and cardiopulmonary exercise data for *aim 1* and *aim 2*. The Institutional Review Boards of Chung Shan Medical University Hospital (CS16174) and Chang Gung Memorial Hospital (201700899A3) approved this study, which was conducted in compliance with the Declaration of Helsinki.

Subjects. Subjects aged ≥40 years without any chronic diseases including uncontrolled diabetes mellitus, uncontrolled hypertension, anemia (hemoglobin <13 g·dL^{-1} in males and <12 g·dL^{-1} in females), and no acute illnesses in the recent 1 month were enrolled. Anthropometric measurements, leisure/sports activities, and cigarette smoking were recorded. Subjects with a body mass index ≤18 kg·m^{-2} or ≥32 kg·m^{-2} or with laboratory findings of cardiovascular, hematological, metabolic or neuromuscular diseases were excluded.

Study group. COPD was diagnosed according to the GOLD criteria[13]. Adult subjects who underwent lung function tests were enrolled only if their FEV_1/FVC was <0.7 or the flow volume curve of spirometry revealed typical concavity[13], and their forced expired volume in one second (FEV_1)% predicted was <80% and had been stable for at least 1 month. A total of 131 subjects in the study group were screened, and 123 were retained for the study (Fig. 1). The reasons for exclusion included not meeting the inclusion criteria (n = 3), meeting the exclusion criteria (n = 2), and declining to participate (n = 2). The study group was divided into two cohorts, one for *aim 1* and one for *aim 2*. To evaluate the bronchodilator effect on the relationship between V_{Tpeak}/TLC and static air trapping or lung hyperinflation, the subjects with COPD in study 1 were not allowed to use medications before measurements, whereas the subjects with COPD in study 2 were used medications as normal.
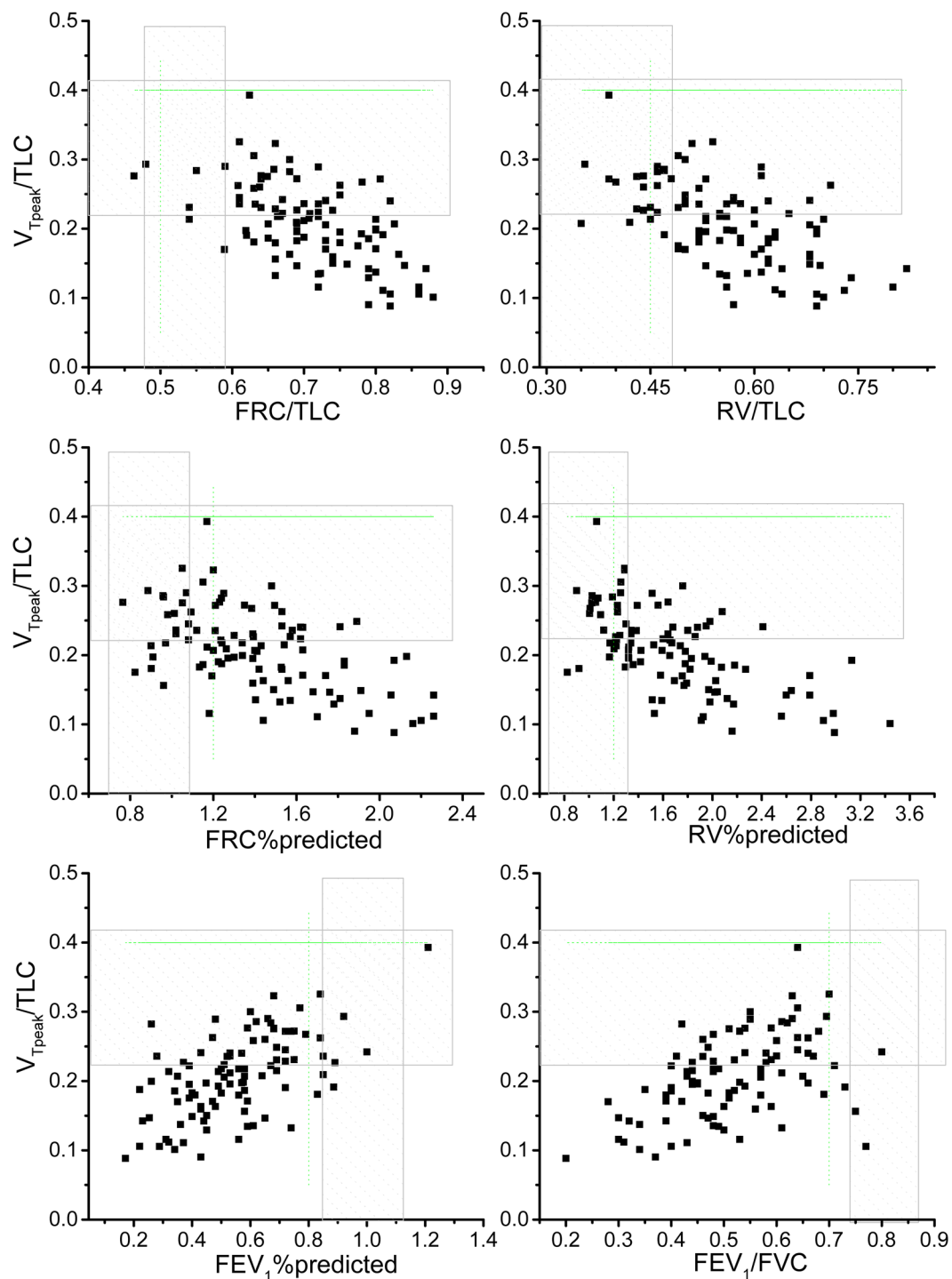
Figure 2. Tidal volume at peak exercise (V_{Tpeak}) and total lung capacity (TLC) ratio as a function of air trapping, hyperinflation and airflow obstruction in the subjects with COPD (n = 97). The hatched areas represent the 5th and 95th percentiles of each corresponding variable of the normal subjects in study 2. The vertical and horizontal dashed lines represent the mean value of each corresponding variable of the normal subjects from the literature. Each symbol represents one subject.

Control group. Healthy subjects without any of the aforementioned chronic diseases were screened. Twenty such subjects were screened, and 19 were enrolled (one subject did not meet the inclusion criteria) (Fig. 1). All eligible subjects were enrolled after signing informed consent forms.

Definitions. *Static and dynamic air trapping and hyperinflation.* Definitions of pulmonary hyperinflation and air trapping of the lung in the literature are inconsistent. In this study, static air trapping and hyperinflation

	COPD1		COPD2		Normal		P	
	mean	SD	mean	SD	mean	SD	COPD Study 1 vs 2	Study 2 COPD vs normal
N=	100		23		19			
Age, years	67.8	7.6	68.2	7.7	64.9	9.9	0.93	0.22
Sex: M:F	97:3		23:0		20:0			
Height, cm	164.2	6.1	164.8	5	167.1	5.2	0.63	0.14
Weight, kg	61.1	9.6	61.1	10.7	70.5	8.5	0.91	0.003
Body mass index, kg/m^2	22.7	3.1	22.5	3.7	25.5	2.7	0.69	0.01
Cigarette smoke, pack × year	46	22.8	69.2	38.5	37.8	40.8	0.0001	0.14
Total lung capacity, TLC, L	6.1[#]	1	6.25	0.89	5.88	0.81	0.62	0.16
%predicted, %	120	23	115	17	104	13	0.282	0.03
FRC, L	4.4[#]	1	4.19	1.06	3.14	0.51	0.47	0.0002
%predicted, %	141	35	138	34	102	16	0.69	0.0003
FRC/TLC	0.71[#]	0.09	0.67	0.1	0.53	0.05	0.04	<0.0001
Residual volume, RV, L	3.5[#]	1	3.6	1.1	2.42	0.55	0.61	0.0001
%predicted, %	168	54	166	48	112	22	0.83	<0.0001
RV/TLC	0.56[#]	0.1	0.57	0.11	0.41	0.07	0.77	<0.0001
Inspiratory capacity, IC, L	1.78[#]	0.55	2.01	0.54	2.75	0.48	0.06	<0.0001
%predicted, %	88	27	82	21	108	19	0.29	0.0004
IC$_{dynamic}$, L	—	—	2.22[^]	0.66	3.03[^]	0.69	—	0.003
IC/TLC	0.29[#]	0.09	0.33	0.09	0.47	0.05	0.09	<0.0001
D$_L$CO, mL/mm Hg/min	14.5	5.2	13.3	5.1	19.2	3.2	0.26	<0.0001
%predicted, %	75[#]	27	78	21	102	16	0.66	0.0001
Forced vital capacity, FVC, L	2.51	0.65	2.62	0.66	3.45	0.58	0.45	<0.0001
%predicted, %	83	22	83	14	101	13	0.99	0.0002
FEV$_1$, L	1.29	0.46	1.53	0.54	2.76	0.47	0.02	<0.0001
%predicted, %	55	19	64	16	104	12	0.03	<0.0001
FEV$_1$/FVC	0.52	0.12	0.57	0.11	0.8	0.05	0.02	<0.0001
Slow vital capacity, SVC, L	2.7[&]	0.66	2.66	0.64	3.46	0.57	0.88	<0.0001
%predicted, %	88	24	80	14	99	13	0.11	<0.0001
MVV, L/min	43	17.8	63.5	22.4	108.6	21.1	<0.0001	<0.0001

Table 1. Demographics and lung function in 100 subjects with chronic obstructive pulmonary disease (COPD) in Study 1 and another 23 subjects with COPD and 19 healthy subjects in Study 2. Functional residual capacity, FRC; Inspiratory capacity, IC; Diffusing capacity for carbon monoxide, DLCO; Forced expired volume in one second, FEV$_1$; MVV. Maximum voluntary ventilation, GOLD I, n = 10; GOLD II, n = 49; GOLD III, n = 32; GOLD IV, n = 9. [#]n = 97, ICdyn: IC dynamic, measured during incremental exercise testing, [&]n = 99, *Study 1 vs 2 on subjects with COPD; [^]p = 0.12 and 0.14, respectively, intra-group comparison.

were defined as RV/TLC > 0.45[14,15], FRC%pred > 120%, or RV%pred > 120%; dynamic air trapping or hyperinflation was defined as V$_{Tpeak}$/TLC < 0.4[2,3,5].

Measurements. *Pulmonary function testing.* FEV$_1$, TLC, RV, and diffusing capacity for carbon monoxide were measured using spirometry and body plethysmography (6200 Autobox DL, Yorba Linda, CA, USA or MasterScreen Body™, Carefusion, Wuerzburg, Germany) according to recommended standards[16–21]. V$_T$/TLC, V$_T$/SVC, V$_T$/FVC, and V$_T$/IC were derived when V$_T$ was obtained at peak exercise.

CPET. Each subject completed an incremental exercise test to the limit of the symptom (MasterScreen CPX™, Carefusion, Wuerzburg, Germany). Work rate was selected at a rate of 5–20 W/min based on a derived protocol formula according to the oxygen-cost diagram scores[22]. $\dot{V}O_2$ (mL/min), CO$_2$ output ($\dot{V}CO_2$) (mL/min), and minute ventilation ($\dot{V}_E$) were continuously measured. $\dot{V}O_{2peak}$ was symptom-limited and $\dot{V}O_{2peak}$ predictions were performed as reported previously[22]. Cardiovascular stress level or exercise intensity was defined as heart rate at peak exercise/heart rate predicted maximum. The definition of ventilatory limitation was a breathing reserve of either <30% or <11–15 L/min[23].

Dynamic inspiratory capacity measurement. The techniques used for performing and accepting IC measurements were as previously reported[9]. Dynamic IC was measured at the end of a steady-state resting baseline and unloaded cycling, and near the middle of loaded exercise and near end exercise. The middle of the loaded exercise was approximately 5–6 minutes after the start of loaded exercise, when dynamic IC near anaerobic threshold was measured. EELV was calculated as TLC minus dynamic IC. O'Donnell threshold was calculated as dynamic IC minus V$_T$ at peak exercise[7].

	COPD1		COPD2		Normal		P	
	mean	SD	mean	SD	mean	SD	Study1 vs 2 COPD	Study2 COPD vs normal
N=	100		23		19			
Work rate, watts	83.2	36.3	95.9	38.5	141.4	33.9	0.14	0.0002
% pred	72	28	85	25	113	25	0.04	0.0008
Oxygen uptake (VO_2), l/min	1.03	0.33	1.27	0.47	1.56	0.37	0.005	0.03
% pred	67	20	74	20	84	14	0.18	0.06
Anaerobic threshold, l/min	0.67	0.18	0.82	0.23	0.99	0.32	0.002	0.07
$\%VO_{2max}$pred, %	44	13	48	13	53	12	0.18	0.28
Respiratory exchange ratio	1.05	0.11	1.03	0.1	1.17	0.11	0.46	0.0001
Cardiac frequency, b/min	128	19.5	127.7	19.3	147.9	18.9	0.97	0.001
% pred max, %	82	12	84	11	95	11	0.49	0.001
Oxygen pulse, mL/min	8.1	2.4	9.7	2.7	10.6	2	0.004	0.27
% pred	82	23	87	18	88	15	0.36	0.8
Minute ventilation (V_E)/VO_{2nadir}	39.7	7.7	32.4	6.8	29.6	3.9	0.0002	0.12
S_pO_2,%	92	5	92	8	97	1	0.71	0.02
V_E, l/min	41.5	12.2	49.3	16.7	65.6	16.4	0.01	0.003
VE/MVV	1.03	0.31	0.82	0.1	0.59	0.11	0.002	<0.0001
Breathing frequency, b/min	33.4	5.8	33	7.5	33.6	5.7	0.77	0.77
Tidal volume (V_T), L	1.25	0.35	1.48	0.35	1.97	0.41	0.005	0.0002
V_T/TLC	0.21[#]	0.06	0.24	0.07	0.33	0.05	0.01	<0.0001
V_T/SVC	0.48[&]	0.13	0.56	0.12	0.57	0.1	0.004	0.76
V_T/FVC	0.51	0.16	0.57	0.12	0.57	0.1	0.11	0.98
V_T/inspiratory capacity (IC)	0.74[#]	0.21	0.77	0.14	0.72	0.13	0.55	0.33
V_T/dynamic IC	—	—	0.71[^]	0.13	0.65[^]	0.14	—	0.28
EELV @ rest, L	—	—	3.34	2.46	3	0.9	—	0.75
EELV @ unloading, L	—	—	3.54	2.0	2.70	1	—	0.17
EELV @ AT, L	—	—	3.37	2.1	2.68	0.9	—	0.27
EELV @ peak, L	—	—	4.17	1.29	2.75	0.8	—	0.001

Table 2. Cardiopulmonary exercise test at peak exercise in 100 subjects with chronic obstructive pulmonary disease (COPD) in Study 1 and another 19 healthy subjects and 23subjects with COPD in Study 2. Maximum voluntary ventilation, MVV; TLC, total lung capacity; SVC or FVC, slow or forced vital capacity; EELV, end-expiratory lung volume; [#]n = 97, [&]n = 99, [^]Intra-group comparison of V_T/IC and V_T/dynamic IC, p = 0.12 and 0.11, respectively.

Statistical analysis.
Data were summarized as mean ± standard deviation and percentage and 5th and 95th percentiles. The Student's *t* test was used for comparisons between two groups. Correlations were based on Pearson's correlation coefficients. A *p* value < 0.05 was considered to be significant. An ROC curve was generated to identify a cut off value for V_{Tpeak}/TLC by comparisons with dynamic EELV at peak exercise. Statistical analyses were performed using SAS statistical software (SAS Institute Inc., Cary, NC, USA) and Origin v4.1 (Northampton, MA, USA). The sample size of study 2 was estimated to be 23 based on calculations with a 0.1 between-group difference and 0.1 of standard deviation for each group in V_{Tpeak}/TLC with a power of 0.9 and significance level of 0.05.

Results
One hundred subjects (97 men) with COPD in study 1 and 23 (23 men) with COPD and 19 healthy subjects (19 men) in study 2 were analyzed (Fig. 1 and Table 1). The majority of the subjects in study 1 had moderate airflow obstruction with hyperinflation and air trapping, and mild exercise hyperventilation and exercise ventilation limitation with mild exercise impairment (Tables 1 and 2). Compared to study 1, most of the subjects with COPD in study 2 had less severe airflow obstruction and hyperinflation and exercise impairment (Tables 1 and 2). V_{Tpeak}/TLC and V_{Tpeak}/SVC were significantly lower in the subjects in study 1 than in the COPD group in study 2, while V_{Tpeak}/FVC and V_{Tpeak}/IC were similar between the two COPD groups.

Correlation of V_{Tpeak}/TLC, /SVC, /FVC, and /IC with static air trapping and spirometry.
V_{Tpeak}/TLC was 0.21 ± 0.06 (Table 2) and was most significantly correlated with air trapping or hyperinflation parameters and FEV_1/FVC and FEV_1%pred compared to the other three variables (Table 3, |r| = 0.45–0.62 vs. 0.001–0.49). Twelve of 99 (12%) subjects had a V_{Tpeak}/SVC > 0.63 (mean cut-off value of normal and COPD groups ≤0.63[1,4,5]), 18 of 100 subjects had a V_{Tpeak}/FVC > 0.63, and 31 of 97 (32%) subjects had a V_{Tpeak}/IC > 0.79 (cut-off value: ≤0.79[1-3,5]), while none of 97 subjects had a V_{Tpeak}/TLC > 0.4 (re-measured normal value: 0.4–0.42[2,3,5], Table 4) and only two (2%) had a V_{Tpeak}/TLC > 0.33 (Table 2, normal cut-off value in study 2).

Study 1, n = 100	V_{Tpeak}/TLC	V_{Tpeak}/SVC	V_{Tpeak}/FVC	V_{Tpeak}/IC
FRC/TLC	−0.53[‡]	0.001	−0.09	0.49[‡]
RV/TLC	−0.59[‡]	0.21[¶]	0.14	0.08
FRC%pred	−0.50[‡]	−0.05	−0.03	0.26[*]
RV%pred	−0.61[‡]	0.01	0.002	0.04
FEV$_1$/FVC	0.45[‡]	0.26[*]	0.31[†]	0.15
FEV$_1$%pred	0.62[‡]	0.02	−0.06	0.11
Study 2, n = 23				
FRC/TLC	−0.73[‡]	0.001	0.13	0.52*
RV/TLC	−0.67[†]	0.28	0.39	0.36
FRC%pred	−0.77[‡]	−0.03	0.11	0.22
RV%pred	−0.65[†]	0.12	0.24	0.14
FEV$_1$/FVC	0.76[‡]	0.45[*]	0.33	−0.01
FEV$_1$%pred	0.79[‡]	0.15	0.01	−0.16

Table 3. Correlation coefficients of the ratios of tidal volume at peak exercise (V_{Tpeak}) and TLC, SVC, FVC, and IC with markers of air trapping or lung hyperinflation and spirometry at rest in subjects with chronic obstructive pulmonary disease. Forabbreviations, please refer to Table 1. *p < 0.05, †<0.01, †<0·001, ‡<0.0001, ¶<0·1.

Relationship between V_{Tpeak}/TLC and static air trapping and airflow obstruction.

The normal subjects could expand V_{Tpeak}/TLC from 0.25 to 0.41 during incremental exercise (Fig. 2). The area under ROC curve was 0.861 and V_{Tpeak}/TLC of 0.27 had the highest sensitivity (88%) and specificity (77%) to predict elevated EELV. Nineteen of 112 (17%) subjects with FRC/TLC > 0.59 (Table 1, 95th percentile of the normal subjects in study 2) could expand their lungs to ≥ V_{Tpeak}/TLC of 0.27. Sixteen 13 of 97 (13%) subjects with RV/TLC > 0.48 (95th percentile of normal), 28of 119 (24%) subjects with FEV$_1$%pred < 88% (5th percentile of normal), and 21 of 120 (18%) subjects with FEV$_1$/FVC < 0.73 (5th percentile of normal) could expand their lungs to ≥V_{Tpeak}/TLC of 0.27.

Correlation of V_{Tpeak}/TLC and EELV or other variables.

In study 2, the levels of EELV at rest, unloading exercise, and near anaerobic threshold and near peak exercise were significantly larger in the subjects with COPD than in the normal subjects (Table 2). V_{Tpeak}/TLC was significantly correlated with EELV/TLC in the subjects with COPD but not in the normal subjects (Fig. 3, r = −0.83, p < 0.0001 vs. r = −0.13, p = 0.36). V_{Tpeak}/TLC was also significantly correlated with $\dot{V}O_{2peak}$% (r = 0.73, p < 0.0001) in the COPD group but not in the normal group (r = 0.24, p = 0.33). However, V_{Tpeak}/TLC was not significantly correlated with Borg score (r = −0.03 vs. −0.03, both p = NS) or O'Donnell threshold (r = −0.43 vs. 0.2, both p = NS) in either groups.

Discussion

The key findings of this study were that V_{Tpeak}/TLC was the best marker for dynamic expandability of lungs compared to V_{Tpeak}/SVC, V_{Tpeak}/FVC, and V_{Tpeak}/IC in the subjects with COPD (Table 3, |r| = 0.45–0.62 vs. 0.001–0.49). These findings were noted in the subjects with COPD with or without withdrawal of bronchodilators before the test (Table 3 in study 2, |r| = 0.65–0.79 vs. 0.001–0.52). V_{Tpeak}/TLC was highly correlated with EELV in the subjects with COPD but not in the normal subjects (Fig. 3, r = −0.83 vs. −0.13). A V_{Tpeak}/TLC cutoff value of <0.27 further identified approximately 82% of the subjects with airflow obstruction and static air trapping or hyperinflation who developed dynamic air trapping during incremental exercise (Fig. 2). As V_{Tpeak}/TLC can easily be obtained without the need for any maneuvers during exercise, the need for dynamic IC maneuvers during exercise test may be avoided.

V_{Tpeak}/TLC, /SVC, /FVC, and /IC.

V_{Tpeak}/SVC and /IC have been used to differentiate normal and obstructive ventilation from restrictive ventilation during CPET[24,25]. V_{Tpeak}/FVC has also been used as an alternative due to the ease of obtaining FVC. However, these variables are not recommended by the American Thoracic Society for such purposes[8]. In this study, V_{Tpeak}/SVC, /FVC, and /IC showed much higher variability than V_{Tpeak}/TLC in the correlation with static air trapping (Table 3). This may be because TLC changes little during exercise in normal subjects and those with airflow obstruction and interstitial lung disease[10–12]. As dynamic air trapping develops, V_T is restricted and air cannot be removed sufficiently, thereby limiting the increase in V_{Tpeak}/TLC. In contrast, static SVC, FVC, and IC may be variable due to pseudorestriction of lung volume even in subjects with the same TLC, so that dynamic hyperinflation cannot be precisely predicted by V_{Tpeak}/SVC, /FVC, and /IC. Pseudorestriction is not uncommon in subjects with airflow obstruction, small airway obstruction and emphysema.

O'Donnell et al. reported that changes in dynamic IC were larger (−14%) during exercise in subjects with airflow obstruction than in normal subjects (4%, p < 0.0005)[4], meaning that V_{Tpeak}/dynamic IC was larger than V_{Tpeak}/static IC (74% vs. 65%)[4]. However, in the current study, V_{Tpeak}/dynamic IC was smaller but not significantly smaller than V_{Tpeak}/static IC (71% vs. 77%) in the subjects with COPD, suggesting that dynamic IC was larger than static IC. This was also noted in the normal subjects in study 2 (i.e., 0.72 vs. 0.65; Table 2). This may be due to different severities of COPD in these two studies. In O'Donnell's study[4], the patients with COPD had 37%pred FEV$_1$ in contrast to study 2 where the subjects with COPD had 55–68%pred FEV$_1$.

	COPD						Normal				
	This study1, 2	IPO[26] (−)	IPO[26] (+)	O'Donnell 1993, 2001	Ciavaglia[27], obese	Faisal[2], obese	This study2	Spiro[6]	O'Donnell[3–5]	Amann[28]	Faisal
N=	100, 23	33	14	23, 105	12	16	19	20	10, 12, 25	5	16
V_{Tpeak}/TLC, mean	0.21^–0.24	0.2^	0.14^	0.15–0.17	0.24	0.24	0.31	—	0.4–0.42	0.3	0.41
5%tile	0.11–0.14	0.13	0.09	—	—	—	0.23	—	—		—
95%tile	0.3–0.36	0.27	0.24	—	—	—	0.42	—	—		—
V_{Tpeak}/VC, mean	0.48*–0.56	0.48^	0.37*	0.44–0.6	0.46	0.46	0.57	0.58	0.61–0.66		0.56
5%tile	0.3–0.39	0.31	0.24	—	—	—	0.39	—	—		—
95%tile	0.72–0.8	0.72	0.52	—	—	—	0.70	—	—		—
V_{Tpeak}/VC$_{dyn}$, mean (SD)	—	—	—	0.31 (0.1)	—	—	—	—	0.63 (0.19)		—
V_{Tpeak}/IC, mean	0.74–0.77	0.78	0.61*	0.65	0.56	0.66	0.72	—	0.78		0.76
5%tile	0.47–0.57	0.5	0.40	—	—	—	0.49	—	—		—
95%tile	1.08–0.92	1.05	0.78	—	—	—	0.86	—	—		—
V_{Tpeak}/IC$_{dyn}$, mean (SD)	0.71 (0.13)	—	—	0.74 (0.14)	0.77	0.76 (0.13)	0.65 (0.14)	—	0.74–0.78 (0.04SE–0.15)		0.78 (0.08)

Table 4. Summary from this study and the literature regarding the ratio of operating tidal volume at peak exercise and total lung capacity (VTpeak/TLC) and other relevant ratios in subjects with chronic obstructive pulmonary disease (COPD) and subjects with interstitial lung disease (ILD) and normal healthy subjects. IPO[26]: impaired peripheral oxygenation. ^$P < 0.0001$ vs the normal subjects of the study 2, *$P = 0.02$ vs study 2 norm, SEStandard error.
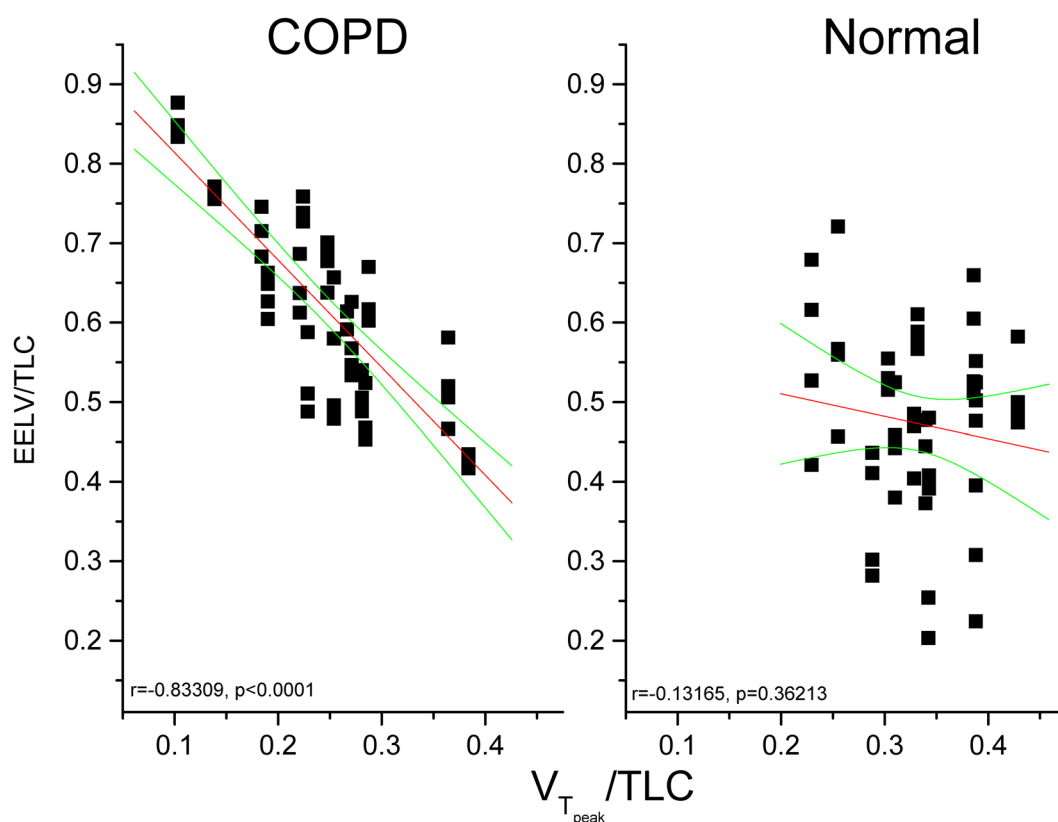
Figure 3. End-expiratory lung volume and total lung capacity ratio (EELV/TLC) at rest, unloading, near anaerobic threshold, and near peak exercise as a function of tidal volume at peak exercise and TLC ratio (V_{Tpeak}/TLC) in 23 subjects with COPD and 19 normal subjects. The solid line represents the linear regression line ($r = -0.83$, $p < 0.0001$ for the COPD group and $r = -0.13$, $p = 0.36$ for the normal subjects) and the curved lines are the 95% CI lines.

V_{Tpeak}/TLC ratio and EELV or other variables. EELV is calculated as TLC minus dynamic IC. As TLC changes little during exercise[10–12], changes in EELV must be inversely associated with changes in IC[4]. As mentioned, V_{Tpeak}/TLC changed in line with dynamic IC, and was thus inversely related to EELV (Fig. 4, $r = -0.83$,

p < 0.0001). The area under ROC curve was high (0.861) and the sensitivity (88%) and specificity (77%) of VT_{peak}/TLC of 0.27 to predict elevated EELV in the current study were acceptable. The importance of V_{Tpeak}/TLC has not previously been addressed or reported, and our findings seem to suggest that V_{Tpeak}/TLC could be used as a substitute for dynamic IC maneuvers performed during exercise. One reason is that V_{Tpeak}/TLC is easily obtainable, and another is that in the ramp pattern exercise protocol but not a steady state protocol, dynamic IC maneuvers are not recommended[9]. Moreover, dynamic V_T represents the difference between dynamic end-inspiratory lung volume (EILV) and EELV, and while measuring V_{Tpeak}/TLC is straightforward, measuring EILV and EELV is more complex[5]. Interestingly, in the current study V_{Tpeak}/TLC was correlated with $\dot{V}O_{2peak}$ in the COPD group rather than in the normal group. This suggests that dynamic lung expansion played a role in the exercise capacity in patients with COPD but not in health. However, both groups reached a similar level of Borg dyspnea score (COPD vs. normal, 6 ± 3 vs. 6 ± 2, p = 0.83) but different levels of O'Donnell threshold/TLC (COPD vs. normal, 0.11 ± 0.07 vs. 0.19 ± 0.12, p = 0.02) at peak exercise. However, V_{Tpeak}/TLC was not correlated with either variable. We speculate that Borg dyspnea score and O'Donnell threshold are more related to the plateau portion of the pressure-volume curve for the lungs and chest wall whereas V_{Tpeak}/TLC involves lung volumes not only expanding to the plateau portion of the curve but also encroaching downward to expiratory reserve volume.

V_{Tpeak}/TLC ratio in this study and previous reports. Table 4 reveals that V_{Tpeak}/TLC was 0.21 ± 0.06–0.24 ± 0.07 in study 1 and 2, which is larger than in our previous report on patients with COPD (0.14–0.2)[26] and reports on COPD from other researchers (0.15–0.24, the values were not reported in their studies but were re-calculated by the current authors)[2,5,27,28]. This may be due to differences in the severity of COPD and preconditioning strategy before the measurements in these studies. We re-measured V_{Tpeak}/TLC from the figures of the previous studies, and found values of 0.31–0.42 in patients with interstitial lung disease[3,10] and 0.3–0.42 in normal healthy subjects[2,3,5,28]. In the normal subjects of this study, the V_{Tpeak}/TLC was 0.31 ± 0.06. However, it is difficult to compare this value between our study and studies in the literature as the level of V_{Tpeak}/TLC has not been reported.

Study limitations. The normal subjects had significant cigarette consumption despite having normal spirometry. In addition, subjects with restrictive ventilation were not included as interstitial lung disease is rare in our institutions. However, V_{Tpeak}/TLC in patients with interstitial lung disease as re-measured from the figures of previous studies was 0.31–0.42[2,3,10]. These values are quite different from those reported in the subjects with COPD in this study and in the literature. The number of participants in study 2 was small and the findings may not be generalizable to all populations. However, the sample size of study 2 was estimated to be 23 based on standard calculations. The cohort was all men because the incidence of COPD in women is very low in Taiwan (37:1 in our previous report[29]). Dynamic IC measurements are recommended for subjects who can achieve a steady state of exercise. The exercise protocol in this study was the ramp pattern, and the relationship between V_{Tpeak}/TLC and EELV may be different between two-minute incremental and ramp-pattern exercise. However, it can be difficult to reach a steady state in each stage of exercise despite using the two-minute incremental exercise protocol[2–5]. Lastly, the subjects did not undergo pre-test exercise testing including dynamic IC maneuvers to allow them to become familiar with the whole protocol. However, this may more accurately reflect cardiopulmonary exercise testing in the real world.

Conclusion

V_{Tpeak}/TLC may be a potential marker of dynamic hyperinflation in subjects with COPD, and its use may avoid the need for dynamic IC maneuvers during incremental exercise. This marker is simple to derive and more stable than other V_{Tpeak}-capacity ratios regarding the relationship with static air trapping or hyperinflation, and it was significantly associated with EELV. A cut-off value of V_{Tpeak}/TLC < 0.27 identified approximately 82% of the subjects with COPD who had static hyperinflation and air trapping but could not expand their tidal volume to the same extent as the normal subjects. Further large-scale studies are warranted to investigate whether V_{Tpeak}/TLC can replace dynamic IC maneuver and whether it can be used to identify the V_{Tpeak}/TLC cut-off value. As most of our participants were male, further studies are required to elucidate whether the results of this study can be applied to female patients with COPD.

References

1. Wasserman, K., Hansen, J. E., Sue, D. Y, Stringer, W. W. & Whipp, B. J. Normal values in *Principles of exercise testing and interpretation* (ed. Wasserman, K.) (Lippicott Williams & Wilkins) (Philadelphia, 2005).
2. Faisal, A. *et al.* Common Mechanisms of Dyspnea in Chronic Interstitial and Obstructive Lung Disorders. *Am. J. Respir. Crit. Care Med.* **193**, 299–309 (2016).
3. O'Donnell, D. E., Chau, L. K. & Webb, K. A. Qualitative aspects of exertional dyspnea in patients with interstitial lung disease. *J. Appl. Physiol.* **84**, 2000–9 (1998).
4. O'Donnell, D. E., Revill, S. M. & Webb, K. A. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **164**, 770–7 (2001).
5. O'Donnell, D. E. & Webb, K. A. Exertional breathlessness in patients with chronic airflow limitation. The role of lung hyperinflation. *Am. Rev. Respir. Dis.* **148**, 1351–7 (1993).
6. Spiro, S. G., Dowdeswell, I. R. & Clark, T. J. An analysis of submaximal exercise responses in patients with sarcoidosis and fibrosing alveolitis. *Br. J. Dis. Chest.* **75**, 169–80 (1981).
7. Casaburi, R. & Rennard, S. I. Exercise limitation in chronic obstructive pulmonary disease. The O'Donnell threshold. *Am. J. Respir. Crit. Care Med.* **191**, 873–5 (2015).
8. The Committee. This Joint Statement of the ATS and the ACCP was adopted by the ATS Board of Directors, March 1, 2002 and by the ACCP Health Science Policy Committee, November 1, 2001. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am. J. Respir. Crit. Care Med.* **167**, 211–77 (2003).
9. Guenette, J. A., Chin, R. C., Cory, J. M., Webb, K. A. & O'Donnell, D. E. Inspiratory Capacity during Exercise: Measurement, Analysis, and Interpretation. *Pulm. Med.* **2013**, 956081 (2013).

10. Marciniuk, D. D., Sridhar, G., Clemens, R. E., Zintel, T. A. & Gallagher, C. G. Lung volumes and expiratory flow limitation during exercise in interstitial lung disease. *J. Appl. Physiol.* **77**, 263–73 (1994).
11. Stubbing, D. G., Pengelly, L. D., Morse, J. L. & Jones, N. L. Pulmonary mechanics during exercise in normal males. *J. Appl. Physiol. Respir. Environ. Exerc. Physiol.* **49**, 506–510 (1980).
12. Stubbing, D. G., Pengelly, L. D., Morse, J. L. & Jones, N. L. Pulmonary mechanics during exercise in subjects with chronic airflow obstruction. *J. Appl. Physiol. Respir. Environ. Exerc. Physiol.* **49**, 511–515 (1980).
13. GOLD Committees. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (revised 2015). Disclosure forms for GOLD Committees are posted on *the GOLD Website*, www.goldcopd.org (2017).
14. Ruppel, G. L. What is the clinical value of lung volumes? *Respir. Care.* **57**, 26–35 (2012).
15. Stocks, J. & Quanjer, P. H. Reference values for residual volume, functional residual capacity and total lung capacity. *Eur. Respir. J.* **8**, 492–506 (1995).
16. ATS/ERS S. ATS/ERS Statement on respiratory muscle testing. *Am. J. Respir. Crit. Care Med.* **166**, 518–624 (2002).
17. GINA Committees. Global Initiative for Asthma (UPDATED 2017) Disclosure forms for GINA Committees are posted on *the GINA Website*, www.ginasthma.org, 1–156 (2017)
18. Macintyre, N. *et al.* Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur. Respir. J.* **26**, 720–35 (2005).
19. Miller, M. R. *et al.* General considerations for lung function testing. *Eur. Respir. J.* **26**, 153–61 (2005).
20. Miller, M. R. *et al.* Standardisation of spirometry. *Eur Respir J.* **26**, 319–38 (2005).
21. Wanger, J. *et al.* Standardisation of the measurement of lung volumes. *Eur. Respir. J.* **26**, 511–22 (2005).
22. Chuang, M. L., Lee, C. H. & Lin, I. F. Using the oxygen-cost diagram in ramp-slope selection for dyspneic patients. *Intern. Med.* **49**, 1325–32 (2010).
23. McNicholl, D. M., Megarry, J., McGarvey, L. P., Riley, M. S. & Heaney, L. G. The utility of cardiopulmonary exercise testing in difficult asthma. *Chest.* **139**, 1117–1123 (2011).
24. Wasserman, K., Hansen, J. E., Sue, D. Y., Casaburi, R. & Whipp, B. J. Normal Values in *Principles of exercise testing and interpretation* p.112–131 (ed. Wasserman, K.) (Lea & Febiger) (Philadelphia, 1994).
25. Wasserman, K., Hansen, J. E., Sue, D. Y., Casaburi, R. & Whipp, B. J. Measurements during integrative cardiopulmonary exercise testing in *Principles of exercise testing and interpretation* (ed. Wasserman, K.) (Lea & Febiger) (Philadelphia, 1994).
26. Chuang, M. L., Huang, S. F. & Su, C. H. Cardiovascular and respiratory dysfunction in chronic obstructive pulmonary disease complicated by impaired peripheral oxygenation. *Int. J. Chron. Obstruct. Pulmon. Dis.* **10**, 329–337 (2015).
27. Ciavaglia, C. E. *et al.* Differences in respiratory muscle activity during cycling and walking do not influence dyspnea perception in obese patients with COPD. *J. Appl. Physiol.* **117**, 1292–301 (2014).
28. Amann, M. *et al.* Impact of pulmonary system limitations on locomotor muscle fatigue in patients with COPD. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **299**, R314–24 (2010).
29. Chuang, M. L. *et al.* Adjunctive Treatment with Rhodiola Crenulata in Patients with Chronic Obstructive Pulmonary Disease - A Randomized Placebo Controlled Double Blind Clinical Trial. *PLoS One.* **10**, e0128142 (2015).

Acknowledgements

Author Contributions

M.L.C. guarantor of the paper, initiated and designed the study, analyzed and interpreted the data, wrote the manuscript, and approved the version to be published. M.J.H. prepared and interpreted the data, reviewed the manuscript, and approved the version to be published. T.C.W. interpreted the data, reviewed the manuscript, and approved the version to be published. I.F.L. conducted statistical analysis, reviewed the manuscript, and approved the version to be published.

Additional Information

Supplementary information accompanies this paper at https://doi.org/10.1038/s41598-019-43893-1.

Competing Interests: The authors declare no competing interests.

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.