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Inspiratory Fraction is Correlated with Exercise Capacity of Patients with Stable Moderate to Severe Chronic Obstructive Pulmonary Disease

Yan Zhang MD, Xing-guo Sun MD, Wen-lan Yang MD, Xiao-yue Tan MD, Jin-ming Liu MD

Yan Zhang MD, Xing-guo Sun MD, Wen-lan Yang MD, Xiao-yue Tan MD, and Jin-ming Liu MD are affiliated with the Department of Respiratory Medicine, Shanghai Pulmonary Hospital Affiliated to Tongji University, Shanghai, China. Xing-guo Sun MD is affiliated with Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, St. John's Cardiovascular Research Center, Torrance, California, USA

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Corresponding author:

Jinming Liu, MD, Department of Respiratory Medicine, Shanghai Pulmonary Hospital Affiliated to Tongji University, 507 Zhengmin Road, Shanghai 200433, China. Tel: +86-021-65115006-3005. Email address: jinmingliu_sh@hotmail.com

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BACKGROUND: Exercise intolerance is the hallmark of chronic obstructive pulmonary disease (COPD). Static lung hyperinflation and increased dynamic hyperinflation during exercise have been associated with the reduced functional capacity in these patients. Inspiratory capacity (IC) correction for the total lung capacity (TLC), defined as inspiratory fraction (IF) may be functionally more representative than other traditional indices in these patients. **OBJECTIVE**: To investigate the association between IF and the exercise capacity of patients with stable moderate to severe COPD. **METHODS:** Fifty patients and thirty-four healthy volunteers constituted the study cohort. Pulmonary function tests (PFT) and cardiopulmonary exercise testing (CPET) were performed, parameters of lung ventilation and gas exchange were measured. **RESULTS:** IF was significantly correlated with peak $\dot{V}O_2$%pred of patients with stable moderate to severe COPD($r = 0.52$, $p < 0.001$). IF was an independent factor in predicting a reduced exercise capacity of COPD patients, and was more sensitive and specific than forced expiratory volume in one second (FEV_1%pred). Statistical analysis generated the final model as: peak $\dot{V}O_2\%pred = 65.9IF + 0.45FEV_1\%pred + 35.8$ ($R_C^2 = 0.39$, $p < 0.001$). Patients with IF lower than 0.23 had more severe lung hyperinflation and less exercise capacity than the patients with IF higher than 0.23. At peak exercise, breathing frequencies of two groups were similar, whereas low IF patients had reduced peak minute ventilation and peak tidal volume relative to the patients with high IF. CONCLUSIONS: IF is a robust factor to reflect lung hyperinflation and to estimate the exercise capacity of patients with stable moderate to severe COPD

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compared to FEV_1. *Key words: chronic obstructive pulmonary disease; inspiratory fraction; lung hyperinflation; cardiopulmonary exercise test; inspiratory capacity*

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Introduction

Chronic obstructive pulmonary disease (COPD) is recognized as the fourth leading cause of death worldwide and a major chronic respiratory disorder due to different diseases causing medical disability. COPD is characterized by airflow limitation that is poorly reversible, progressive, and associated with an abnormal inflammatory response of the lung to noxious particles, such as the materials released from smoking [1]. The hallmark of COPD is exercise intolerance and exertional dyspnea, which are due to complex interactions between impaired ventilatory, cardiovascular, and peripheral muscle responses. The major abnormality of respiratory muscle dysfunction in COPD patients is the mechanical disadvantage caused by lung hyperinflation. Static lung hyperinflation at rest and increased dynamic hyperinflation (DH) during exercise have been associated with the reduced functional capacity of those patients [2]. Over the decades, it has been widely accepted that traditional measures of airflow obstruction, such as forced expiratory volume in one second (FEV_1) and the ratio of forced expiratory volume in one second to forced vital capacity (FEV_1/FVC), are repeatable and reliable for the diagnosis and prognosis of COPD. However, increasing evidence demonstrates that FEV_1/FVC does not reflect the level of lung hyperinflation and is poorly correlated with exercise capacity and exertional dyspnea of COPD patients [1, 2].

Recently, inspiratory capacity (IC) at rest and during exercise has been shown to be superior to traditional predictive parameters like FEV_1 [3]. IC reflects not only the level of lung hyperinflation, but is also associated with the functional reserve in

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patients with COPD. Moreover, IC correction for the total lung capacity (TLC) provides a better characterization of the volume fraction available for inspiration than IC alone [4]. This correction is called the inspiratory fraction (IF = IC/TLC) and has been found to be a prognostic factor for exercise capacity in moderate to severe COPD.

In the current study, we compared the functional parameters of ventilation, gas exchange, and exercise capacity of patients with stable moderate to severe COPD. We also analyzed the breathing patterns and the extent of exertional dyspnea of these patients by performing standard pulmonary function tests (PFT) and cardiopulmonary exercise testing (CPET). The objective of this study was to investigate the relationship between IC, IF, or other parameters and the exercise capacity of patients with COPD, in order to determine if IF is a robust predictive factor for the exercise capacity of COPD patients.

Methods

Patients diagnosed as COPD stage II (n = 16) and stage III (n = 34) at the Department of Respiratory Medicine Shanghai Pulmonary Hospital between July 2010 and June 2011 were recruited for this study. Diagnosis and classification were based on the criteria of Global Initiative for Chronic Obstructive Lung Disease 2010 Guidelines (http://www.goldcopd.org/, *Accessed March 17, 2013*). All patients accepted regular treatment and maintained stable disease for at least four weeks prior to enrollment. More than 400 patients were screened for this study, by analyzing the

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reports of case history, PFT, heart color doppler ultrasound, computed tomography scanning, patients with diseases causing breathing discomfort and impairing exercise capacity, such as asthma, pulmonary arterial hypertension, interstitial lung disease, other concomitant lung disease, heart failure, metabolic disorders, and/or skeletal muscle diseases, were excluded from the study. As a control group, thirty-four healthy volunteers of similar ages participated in the study. Professional athletes and laborers were excluded. The protocol was approved by the hospital's ethics review board. All subjects signed the written informed consent before enrollment.

Age, sex, body weight, and height of all subjects were recorded and body mass index (BMI) was calculated. PFTs were performed using pulmonary function equipment (Mastercreen-PFT, Jaeger Corp., Hoechberg, Germany) pre and post bronchodilator. Every subject completed at least three acceptable tests, with an interval of one minute. The variability between the 3 tests was less than 5%, and the results of the best trial were reported. Collected parameters included FVC, FEV_1, FEV_1/FVC, maximal voluntary ventilation (MVV), IC, TLC, residual volume (RV), RV/TLC, and diffusing capacity of the lung for carbon monoxide (DL_{CO}) (corrected for Hemoglobin). PFT parameters were expressed as percentage of predicted values (%pred), which were calculated using the equations designed for Chinese adult pulmonary function in 1988 [5].

Symptom-limited CPET was conducted on a cycle ergometer using a cardiopulmonary exercise testing system (Mastercreen-CPX, Jaeger Corp., Hoechberg, Germany) and a gas analysis system (SBx/CPX, Jaeger Corp., Hoechberg, Germany)

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[6]. The increasing work rate was individually selected from 10 to 25 W/min, to provide a total exercise duration of 8 to 12 min. During the whole procedure, we monitored a 12-lead online electrocardiogram, blood pressure, pulse oximetry (Sp_{O_2}), and gas exchange. Gas exchange data were recorded, breath-by-breath, and averaged over 10-second intervals followed by further analysis [7-9]. The tests were terminated if the patient had any of the following conditions: ischemic ECG changes (ST depression of 2 mm with chest pain, or ST depression of 3 mm without chest pain), frequent premature ventricular contractions, conduction disorders, systolic pressure higher than 250 mmHg, diastolic pressure higher than 120 mmHg, a fall in systolic pressure more than 20 mmHg from the highest value obtained during the test, and/or a SpO_2 lower than 80%. Typical symptoms for stopping were leg fatigue, weakness, or shortness of breath. The CPET variables were peak load, peak $\dot{V}_{O_2}$, peak O_2 pulse, minute ventilation ($\dot{V}_E$), breathing frequency (BF), tidal volume (V_T), heart rate (HR) and heart rate reserve [HRR, $HRR=HR_{predict}$- peak HR, $HR_{predict}$=220-Age(year)]. Anaerobic threshold (AT) was determined by the V-slope method [10]. The intensity of dyspnea at peak exercise was described as peak $\dot{V}_E$/MVV. CPET parameters were expressed as percentage of predicted values (%pred), which were calculated using the equations released by ATS/ACCP in 2003 [11].

All statistical analyses were performed using SPSS19.0 software. Data were expressed as mean ± standard deviation (SD). *p*-values between groups were calculated using the χ^2 test or the unpaired student *t*-test. Pearson's correlation coefficients were used to assess the level of association between variables. A

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backward stepwise multiple linear regression was performed to define the independent predictors. Receiver operating characteristic (ROC) curves were obtained for selected variables, in order to evaluate the sensitivity and specificity of PFT parameters as predictors for peak $\dot{V}O_2$%pred [12]. The Youden index was calculated to decide the cut-offs of variables. Youden index is defined as the maximum vertical distance between the ROC curve and the diagonal or chance line and is calculated as maximum (sensitivity + specificity −1) [13]. P-value of < 0.05 was considered to be statistically significant.

Results

PFTs and CPET parameters of COPD patients and normal subjects

Fifty patients with stable moderate or severe COPD and thirty-four healthy volunteers participated in this study. Table 1 shows the demographics of all subjects and the results of PFTs and CPET. There were no significant differences between the two groups for sex, age, and BMI ($p > 0.05$). FEV_1 %pred in the Spirometric measurements in the COPD patients demonstrated moderate to very severe obstruction, with FEV_1 %pred ranging from 32% to 75%. Nearly all COPD patients had lung volume measurements suggestive of air trapping (RV%pred ranging from 129% to 296%, n=48) and DL_{CO} was decreased in nearly half (DLco%pred 37% to 79%, n = 24).

In the CPET, we observed significant reductions in peak Work, peak Work%pred, peak $\dot{V}O_2$, peak $\dot{V}O_2$%pred and AT in COPD patients, compared to normal subjects (p

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< 0.001). Twenty six percent of COPD patients displayed a severe reduction in peak $\dot{V}O_2$%pred (lower than 65%, n = 13) [9]. $\dot{V}E/\dot{V}CO_2$ at AT in COPD patients was significantly higher than normal subjects. At peak exercise, gas exchange analysis showed that there was no significant difference for peak BF between the two groups ($p = 0.33$). However, peak $\dot{V}E$ (44.95 ± 12.94 L/min) and peak V_T (1.43 ± 0.39 L) of COPD patients were dramatically decreased compared to control group (60.74 ± 15.27 L/min and 1.83 ± 0.47 L, respectively, $p < 0.001$). The peak $\dot{V}E$/MVV of 98% of the COPD patients was more than 0.7, suggesting a severely reduced breathing reserve of COPD patients at peak exercise [11]. Moreover, the peak $\dot{V}E$/MVV of COPD patients was worse than the control group (1.04 ± 0.19 and 0.71 ± 0.21, respectively, $p < 0.001$).

The association between PFTs parameters and peak $\dot{V}O_2$%pred of COPD patients

Peak $\dot{V}O_2$%pred was significantly related to some PFTs' parameters, as IC%pred (r = 0.43, $p = 0.002$), RV%pred (r = -0.52, $p < 0.001$), TLC%pred (r = -0.25, $p = 0.08$), IF (r = 0.52, $p < 0.001$, Figure 1), FEV_1%pred (r = 0.54, $p < 0.001$). Backward stepwise multiple linear regression analysis generated the model as:

$$\text{peak } \dot{V}O_2\text{\%pred} = 65.9IF + 0.45FEV_1\text{\%pred} + 35.8 \ (R_C^2 = 0.39, p < 0.001)$$

The results revealed that IF and FEV_1%pred act as independent factors in predicting the exercise capacity of COPD patients.

IF is an important factor in predicting the exercise capacity of COPD patients

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Based on the above findings, we then compared the sensitivity and specificity of IF, IC%pred, and FEV_1%pred as predictors of peak $\dot{V}O_2$%pred in COPD patients through analyzing ROC curves. The areas under the curve (AUCs) were 0.933 (95% CI, 0.862-1.000, $p < 0.001$), 0.849 (95% CI, 0.737-0.962, $p < 0.001$), and 0.853 (95% CI, 0.751-0.955, $p < 0.001$), respectively (Figure 2). When we chose 0.23 as the cut-off for IF, the sensitivity, specificity, and Youden index of IF as an independent factor were 0.923, 0.837, and 0.76, respectively. Similarly, the cut-off for FEV_1%pred was 43%, and the sensitivity, specificity, and Youden index were 0.722, 0.929 and 0.651, respectively. The cut-off of IC%pred was 63% and the sensitivity, specificity, and Youden index were 0.722, 0.929, and 0.651, respectively. The data revealed that IF is the best factor among PFT parameters in predicting the exercise capacity of COPD patients.

The comparison of PFTs and CPET parameters of COPD patients with high or low IF

According to the calculated Youden index, we chose 0.23 as the cut-off for IF and divided the COPD patients into two groups: Group 1 consisted of patients with IF < 0.23 (n = 18) and Group 2 consisted of patients with IF ≥ 0.23 (n = 32). Table 2 shows the PFTs' parameters of the two groups: FEV_1% were 39.59 ± 5.81% and 50.36 ± 12.7%, TLC%pred were 138.04 ± 29.66% and 116.89 ± 14.48%, RV%pred were 222.58 ± 35.77% and 170.87 ± 34.27%, and IC%pred were 52.97 ± 11.25% and 72.09 ± 21.77%. These data suggest that Group 1 COPD patients had worse airflow obstruction and higher lung hyperinflation than Group 2 patients.

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CPET results revealed that peak $\dot{V}O_2$%pred of six patients from Group 1 COPD patients were higher than 65% and the rest was lower than 65%. Peak $\dot{V}O_2$%pred of one patient from COPD Group 2 was lower than 65% and the rest was higher than 65%. Breathing pattern analysis at peak exercise showed that peak BF was not significantly different between the two COPD groups ($p = 0.29$). However, peak $\dot{V}_E$ (36.47 ± 4.87 L/min) of Group 1 was significantly lower than that of Group 2 (44.93 ± 11.03 L/min)($p = 0.001$), and V_T at AT and peak exercise (1.05 ± 0.14 L and 1.13 ± 0.25 L) of Group 1 were significantly lower than those (1.23 ± 0.28 L and 1.45 ± 0.37 L) of Group 2 ($p = 0.01$ and 0.001, Figure 3.). The patterns of the change of V_T and BF in CPET (Figure 4) revealed that the V_T of COPD patients with IF lower than 0.23 did not increase substantially when the exercise load was increasing, and that V_T at peak exercise almost reached the IC at rest. In contrast, the V_T of COPD patients with IF higher than 0.23 increased when the exercise load was increasing, and the V_T at peak exercise was lower than the IC at rest. The pattern of V_T change in Group 2 patients was comparable to normal subjects, whereas the peak V_T of Group 2 was smaller than that of control subjects. Gas exchange analysis showed that although AT was not statistically different between the two COPD groups ($p = 0.092$), $\dot{V}_E/\dot{V}CO_2$ was higher in Group 1 than Group 2 (37.93 ± 4.69 vs. 34.33 ± 4.76, $p = 0.045$). In addition, 72% of COPD Group 1 patients and 34% of Group 2 patients stopped exercise due to shortness of breath. 2% of Group 1 patients and 47% of Group 2 patients stopped the exercise because of leg fatigue. The results suggested that the

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reason for stopping exercise was significantly different between COPD patients with high or low IF ($p < 0.05$).

Discussion

Although many factors contribute to exercise intolerance of COPD patients, such as impairment of pulmonary function, cardiovascular diseases, metabolic disorders, skeletal muscle diseases, or the combination of several diseases, one major reason is the limitation of pulmonary function [14]. In the present study, we excluded the COPD patients with certain severe systemic diseases leading to impaired pulmonary function and reduced exercise capacity.

As a key characteristic of decreased pulmonary function in COPD patients, expiratory flow reduction progressively promotes air trapping and lung hyperinflation during the development of COPD. Thus, patients display decreased IC and increased RV and TLC in PFTs. At rest, these patients are able to extend the expiratory duration in order to fully expire. However, during exercise, the only way for these patients to increase their $\dot{V}_E$ is to enhance breathing frequency, due to the limitation of the V_T increment caused by a reduced IC. Therefore, the expiratory time is further decreased and lung hyperinflation and air trapping get worse [15]. Meanwhile, increased end-expiratory lung volume (EELV) in COPD patients leads to a positive end-expiratory pressure (PEEP), i.e., intrinsic positive end-expiratory pressure (PEEPi), which eventually causes an increased loading of breathing, respiratory

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muscle fatigue, and insufficient gas exchange during exercise. The combination of these events lead to limited exercise capacity and dyspnoea [16].

CPET with gas exchange analysis is a powerful technique to evaluate cardiovascular and pulmonary function [6]. It has the potential of non-invasively grading the heart and lung function, as well as assess the severity of exercise limitation, quantify the hypoperfusion of the lung and systemic circulation, assess the response to therapy，diagnose early pulmonary hypertension, and ultimately evaluate surgery risks. The increase of $\dot{V}O_2$ measured at external respiration during exercise provides information of dynamic changes of internal metabolize. Moreover, peak $\dot{V}O_2$ and peak $\dot{V}O_2$%pred collected from symptom-limited CPET have been considered the gold standard in evaluating exercise capacity [11]. Our previous studies also demonstrated that dynamic oxygen uptake parameters during exercise are effective indices in evaluating the heart and lung function of COPD patients [17, 18]. We chose peak $\dot{V}O_2$%pred as a potential factor to evaluate exercise capacity. As an index for lung hyperinflation, IC is better than other PFT parameters in reflecting and predicting a reduction of exercise capacity and ventilation impairment of COPD patients [19-21]. However, COPD patients with similar IC might have very different TLC, therefore IC/TLC is better than IC alone to reflect the increase of EELV.

Our findings showed that IF was significantly correlated with peak $\dot{V}O_2$%pred and could be employed as an independent factor to predict a reduction of exercise capacity in moderate or severe COPD patients. In addition, IF was more sensitive than IC%pred in predicting exercise capacity of COPD patients, according to the ROC

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curve analysis. In the current study, ROC curve analysis and Youden index calculation indicated that IF was also more sensitive than FEV_1%pred in predicting the exercise capacity of COPD patients. This suggests that the change of lung hyperinflation is more predictive of the improvement of ventilation impairment than the change of expiratory airflow in stable COPD patients after treatment with bronchodilators. A group of studies showed that IC was a potential factor in evaluating the effects of bronchodilators on COPD patients compared to FEV_1 [22-24]. Our study revealed that the sensitivity, specificity, and Youden index of IF in predicting exercise capacity of COPD patients were 0.861, 0.929, and 0.79 when 0.23 served as the cut-off of IF. This suggested that 0.23 was a proper cut-off for IF as a predictor. Further comparison showed that COPD patients with low IF displayed worse lung hyperinflation, ventilation impairment, and exercise capacity reduction, indicating that IF is a robust factor in reflecting the severity of COPD patients.

Our findings are consistent with those of Albuquerque *et al.*, who reported that an IF value of 0.28 was a good factor in predicting exercise intolerance of COPD patients [4]. Also, Vassaux *et al.* found that COPD patients with an IF value lower than 0.25 possessed worse peak $\dot{V}O_2$%pred and peak O_2 pulse than the patients with an IF value higher than 0.25 [25]. Another study also showed that IF was an independent factor in predicting the risk of mortality of COPD patients and that COPD patients with an IF value lower than 0.25 had worse pulmonary function and higher mortality risk [26]. It is necessary to point out that the cut-off of IF in our study was different from

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these other reports. The reasons for the variation might be a different cohort size, a variable nationality of the subjects, and variable phenotypes of COPD patients.

Our CPET results showed that there was no significant difference for peak BF between two COPD groups. However, the peak V_T and peak $\dot{V}_E$ of COPD patients with an IF lower than 0.23 were lower than those of patients with high IF. Seventy two percent of Group 1 patients stopped the exercise due to shortness of breath, indicating that limited enhancement of V_T was not sufficient to meet the ventilation demand during exercise, and the increased neuromuscular dissociation. We also noticed that (Figure 4), due to the reduction of IC, the increment of V_T in Group 1 was significantly smaller than that in Group 2. Also, the V_T in Group 1 was very close to their IC, indicating that patients of Group 1 had more severe dynamic hyperinflation (DH). Therefore, an increased respiratory muscle work of Group 1 patients was required to overcome the lung dynamic elastance caused by gradually enhanced EELV [27]. Clearly, the only way of increasing exercise capacity in Group 1 was to increase breathing frequency earlier, and they would stop exercise earlier because the respiratory distress. Meanwhile, worse pulmonary ventilation to perfusion ratio could have caused exertional dyspnea, thereby dramatically reducing exercise capacity. Because the minute ventilation and carbon dioxide production were simultaneously limited in the exercise, it was difficult to compare $\dot{V}_E/\dot{V}_{CO_2}$ at AT between the two COPD groups. In addition, we also observed that peak O_2 pulse%pred of COPD patients with an IF lower than 0.23 was less than that of COPD patients with high IF. This might be caused by severe lung hyperinflation-induced

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reduction of left ventricular end-diastolic volume, reduced right heart blood volume, and/or increased left ventricular after load [25, 28].

Due to the study including small sample size, it cannot be ruled out that another cut-off value of IF and other physiological variables were superior to IF (0.23) to evaluate exercise capacity in stable moderate to severe COPD patients. Statistical analysis revealed that the reasons for stopping exercise were significantly different between the two COPD groups, whereas no difference for peak $\dot{V}_E$/MVV was noticed. It is possible that the cohort size was not big enough, or the specificity of peak $\dot{V}_E$/MVV is not significant. Therefore, it is critical to further study the effects of dynamic hyperinflation on exercise capacity.

Conclusions

The current study showed that IF was significantly correlated with the exercise capacity of stable moderate to severe COPD patients and that IF served as an independent factor in predicting reduced exercise capacity. Compared to COPD patients with IF higher than 0.23, the patients with low IF had worse lung hyperinflation, less exercise capacity, and more reduced peak V_T, peak $\dot{V}_E$, and peak O_2 pulse%pred. Our findings provide evidence to support the hypothesis that IF is an effective index in predicting exercise capacity of COPD patients, which would be helpful information for physicians when they choose individual treatment plans.

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Figure Legends

Fig. 1. IF is correlated with peak $\dot{V}O_2$%pred in COPD patients. Statistical analysis revealed a significant correlation between IF and exercise capacity of COPD patients ($r = 0.52$, $p < 0.001$).

Fig. 2. IF is a proper factor, compared to IC%pred and FEV_1%pred, in predicting a reduction of exercise capacity of COPD patients. ROC curve analysis revealed the sensitivity and specificity of IF, IC%pred, and FEV_1%pred in predicting the change of peak $\dot{V}O_2$%pred (lower than 65%). The AUCs were 0.933 (95% CI, 0.862-1.000, $p < 0.001$), 0.849 (95% CI, 0.737-0.962, $p < 0.001$), 0.853 (95% CI, 0.751-0.955, $p < 0.001$) and the cut-offs were 0.23, 43%, and 60%, respectively.

Fig. 3. COPD patients with an IF lower than 0.23 had decreased V_T in CPET. We compared the V_T of two groups of COPD patients at different stages of CPET. Duration of rest was an average of 120 s before ending the period. Duration of warm-up was an average of 30 s before ending the period. AT was determined by the V-slope method. The duration of peak exercise was an average of 30 s before the peak loading. 95% CI of each data with statistical analysis was shown (*$p < 0.05$).

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Fig. 4. The patterns of V_T and BF of COPD patients and normal subjects during CPET. A representative V_T and BF pattern of a COPD patient, **a)** IF = 0.15, IC = 1.27, protocol: 15W/min increase, **b)** IF = 0.35, IC = 2.49, protocol: 20W/min increase, and a control subject, **c)** IF = 0.44, IC = 2.73, protocol: 20W/min increase. □: V_T, △: BF, --- : IC.

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Table 1. Summary of demographics, PFT, and CPET of COPD patients and normal subjects.

	COPD patients	Normal Subjects	*p*-value
Demographics			
n	50	34	-
Sex (M/F)	45/5	26/8	0.09
Age (y)	63 ± 6	60 ± 7	0.08
BMI (kg/m^2)	23 ± 3	24 ± 3	0.12
PFT			
FVC%pred	84.82 ± 14.5	102.44 ± 11.49	$<$0.001
FEV_1%pred	46.48 ± 11.88	98.30 ± 11.51	$<$0.001
FEV_1/FVC(%)	44.05 ± 7.42	77.55 ± 4.51	$<$0.001
TLC%pred	124.5 ± 23.31	103.27 ± 7.82	0.002
IC%pred	65.2 ± 20.73	91.34 ± 21.0	0.001
IF	0.25 ± 0.07	0.43 ± 0.10	$<$0.001
RV%pred	189.49 ± 42.61	109.82 ± 10.18	$<$0.001
RV/TLC(%)	58.89 ± 7.7	38.87 ± 5.07	$<$0.001
DLco%pred	83.89 ± 25.57	108.0 ± 25.0	0.004
PaO_2 (mmHg)	79 ± 10	90 ± 2	$<$0.001
$PaCO_2$ (mmHg)	38 ± 4	36 ± 2	0.334
CPET			
Peak Work (W)	93 ± 29	137 ± 33	$<$0.001
Peak Work%pred	82.76 ± 23.57	115.68 ± 20.89	$<$0.001
Peak $\dot{V}O_2$ (ml/min)	1279.72 ± 301.86	1643.85 ± 331.52	$<$0.001
Peak $\dot{V}O_2$%pred	73.41 ± 13.75	91.71 ± 12.13	$<$0.001
Peak HR (beats/min)	133 ± 19	151 ± 16	$<$0.001
Peak $\dot{V}_E$ (L/min)	41.88 ± 10.1	60.74 ± 15.27	$<$0.001
Peak BF (breaths/min)	32 ± 6	34 ± 6	0.33
Peak V_T (L)	1.33 ± 0.36	1.83 ± 0.47	$<$0.001
Peak O_2 pulse(ml/beats)	9.62 ± 1.68	10.98 ± 2.24	0.002
Peak O_2 pulse%pred	91.31 ± 13.53	100.56 ± 16.23	0.006
Peak $\dot{V}_E$/MVV	1.04 ± 0.19	0.71 ± 0.21	$<$0.001
AT (ml/min)	956.48 ± 215.69	1136.91 ± 242.63	$<$0.001
$\dot{V}_E/\dot{V}CO_2$ @ AT	35.23 ± 4.94	30.69 ± 3.67	$<$0.001

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Table 2. Summary of demographics, PFT, and CPET of COPD patienets with different IF.

	Group 1 (IF < 0.23)	Group 2 (IF ≥ 0.23)	*p*-value
Demographics			
n	18	32	-
Age (y)	64 ± 8	62 ± 7	0.48
BMI (kg/m^2)	22 ± 3	23 ± 3	0.18
PFT			
FVC%pred	79.03 ± 11.22	88.07 ± 15.26	0.03
FEV_1%pred	39.59 ± 5.81	50.36 ± 12.7	0.001
FEV_1/FVC(%)	40.43 ± 5.93	46.09 ± 7.47	0.008
TLC%pred	138.04 ± 29.66	116.89 ± 14.48	0.001
IC%pred	52.97 ± 11.25	72.09 ± 21.77	0.001
IF	0.18 ± 0.04	0.29 ± 0.06	<0.001
RV%pred	222.58 ± 35.77	170.87 ± 34.27	<0.001
RV/TLC(%)	63.83 ± 5.95	56.25 ± 7.27	<0.001
DLco%pred	64.98 ± 25.21	94.86 ± 22.68	<0.001
PaO_2 (mmHg)	76 ± 10	81 ± 9	0.21
$PaCO_2$ (mmHg)	39 ± 4	36 ± 4	0.04
CPET			
Peak Work (W)	71 ± 23	103 ± 29	0.001
Peak Work%pred	70.86 ± 23.06	89.46 ± 21.4	0.006
Peak $\dot{V}O_2$ (ml/min)	1061.44 ± 210.36	1402.49 ± 276.65	<0.001
Peak $\dot{V}O_2$%pred	62.57 ± 11.97	79.5 ± 10.67	<0.001
Peak HR (beats/min)	122 ± 17	139 ± 18	0.002
Peak HR%pred	72.43 ± 9.12	81.8 ± 9.72	0.002
HRR (beats/min)	34 ± 15	19 ± 16	0.002
Peak $\dot{V}E$ (L/min)	36.47 ± 4.87	44.93 ± 11.03	0.001
Peak BF (breaths/min)	33 ± 6	32 ± 6	0.29
Peak V_T (L)	1.13 ± 0.25	1.45 ± 0.37	0.001
Peak O_2 pulse (ml/beats)	8.72 ± 1.46	10.12 ± 1.6	0.003
Peak O_2 pulse%pred	86.06 ± 13.47	94.27 ± 12.84	0.04
Peak $\dot{V}E$/MVV	1.06 ± 0.16	1.04 ± 0.21	0.72
AT (L/min)	856.9 ± 210.95	989.68 ± 210.23	0.092
$\dot{V}E/\dot{V}CO_2$ @ AT	37.93 ± 4.69	34.33 ± 4.76	0.045
Stopping Reason			
Breathing discomfort (n)	13	11	
Leg fatigue (n)	3	15	0.03
Both (n)	2	6	

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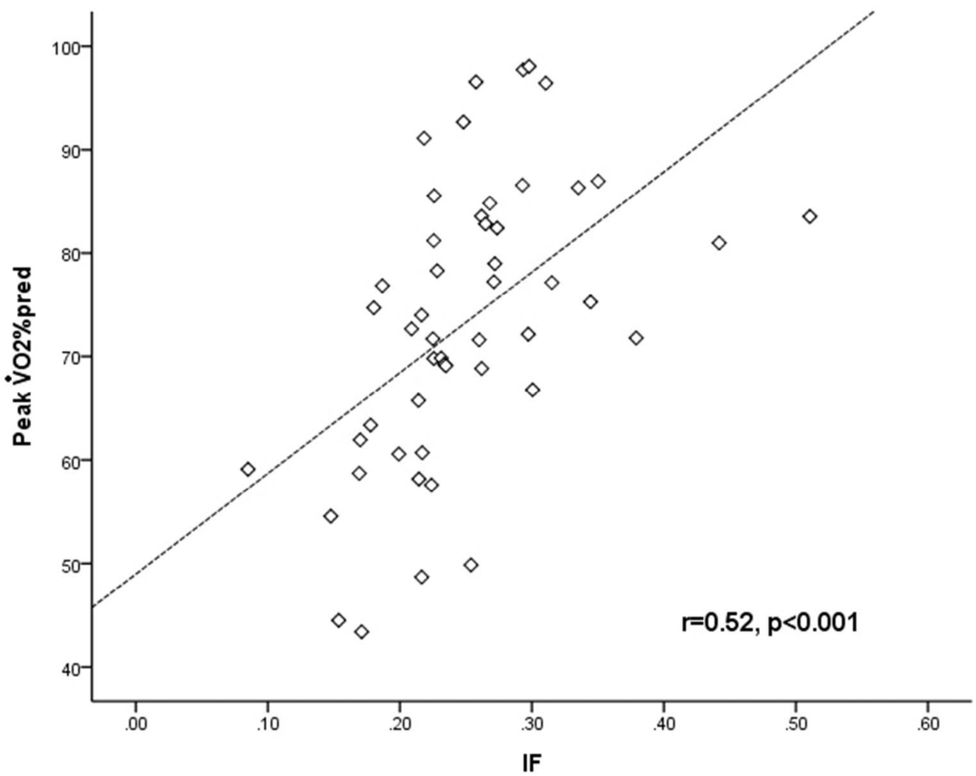

IF is correlated with peak V. O2%pred in COPD patients. Statistical analysis revealed a significant correlation between IF and exercise capacity of COPD patients (r = 0.52, p < 0.001).
166x130mm (96 x 96 DPI)

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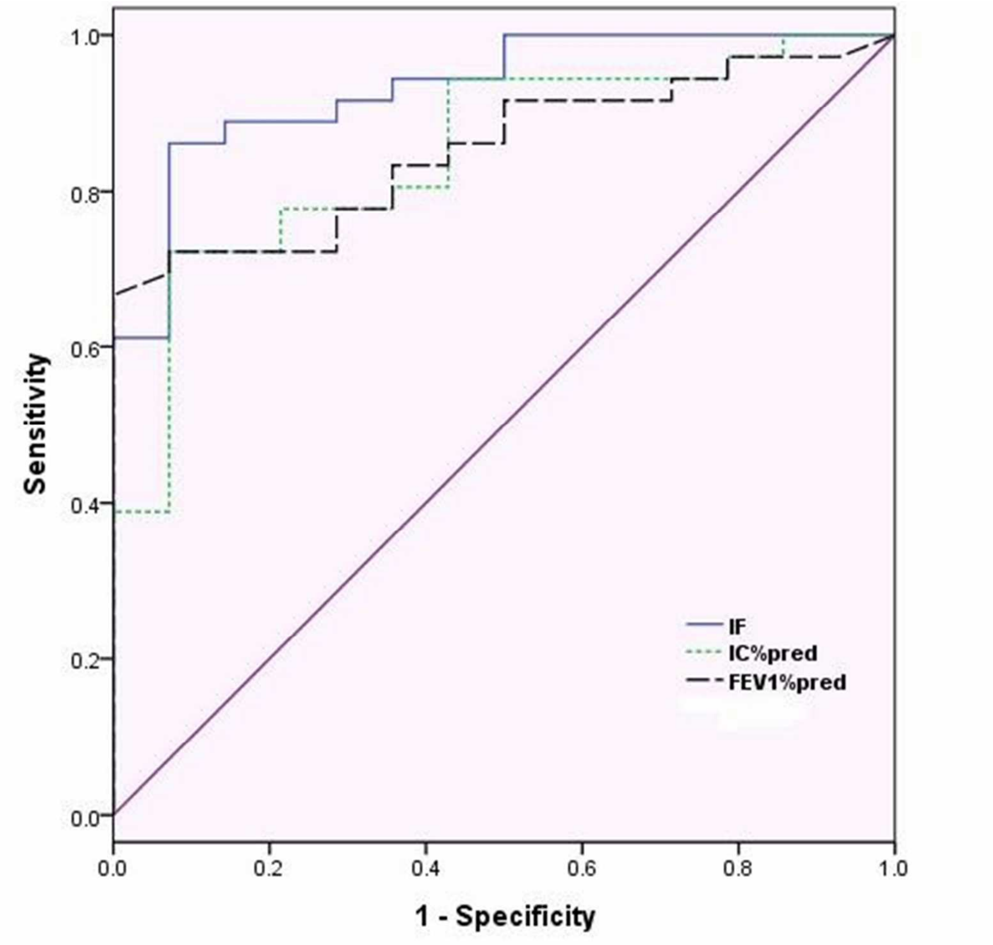

IF is a proper factor, compared to IC%pred and FEV1%pred, in predicting a reduction of exercise capacity of COPD patients. ROC curve analysis revealed the sensitivity and specificity of IF, IC%pred, and FEV1%pred in predicting the change of peak V. O2%pred (lower than 65%). The AUCs were 0.933 (95% CI, 0.862-1.000, p < 0.001), 0.849 (95% CI, 0.737-0.962, p < 0.001), 0.853 (95% CI, 0.751-0.955, p < 0.001) and the cut-offs were 0.23, 43%, and 60%, respectively.
44x41mm (300 x 300 DPI)

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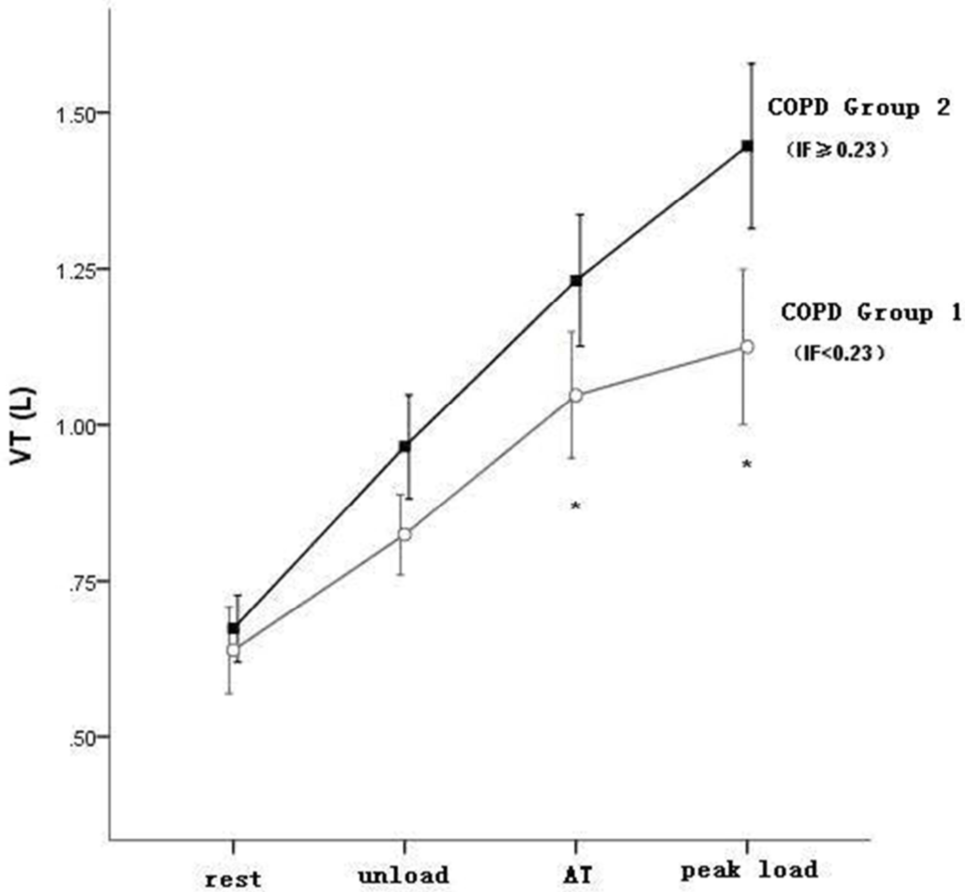

COPD patients with an IF lower than 0.23 had decreased VT in CPET. We compared the VT of two groups of COPD patients at different stages of CPET. Duration of rest was an average of 120 s before ending the period. Duration of warm-up was an average of 30 s before ending the period. AT was determined by the V-slope method. The duration of peak exercise was an average of 30 s before the peak loading. 95% CI of each data with statistical analysis was shown (*$p < 0.05$).
44x40mm (300 x 300 DPI)

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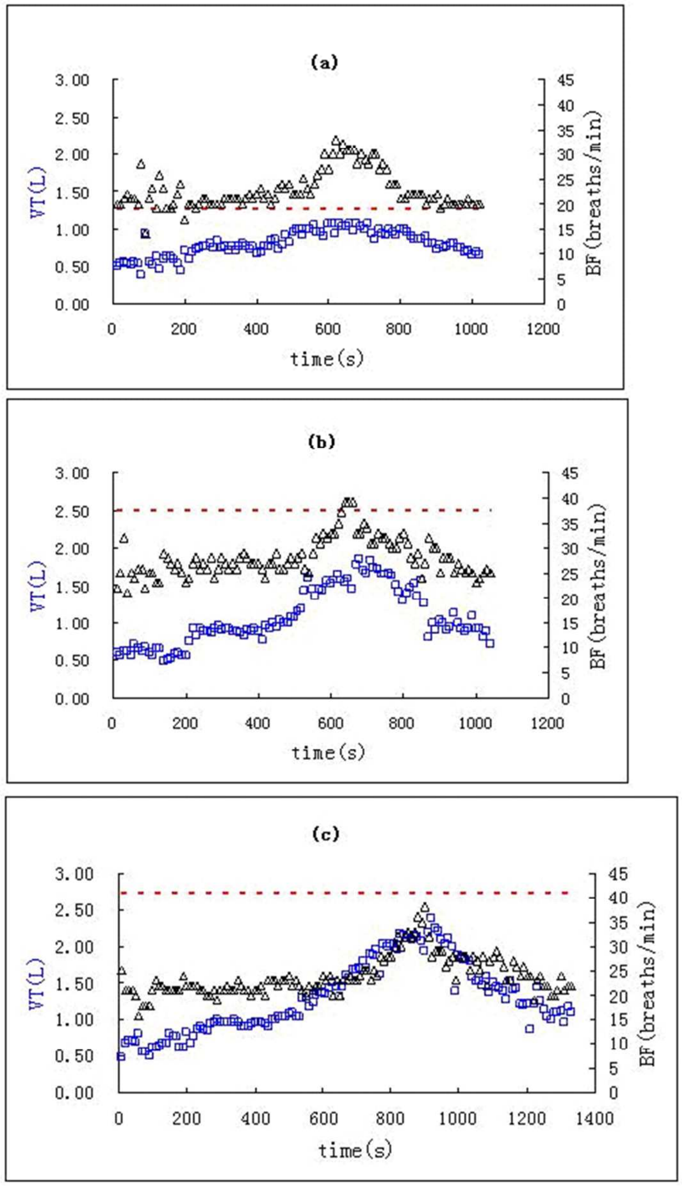

The patterns of VT and BF of COPD patients and normal subjects during CPET. A representative VT and BF pattern of a COPD patient, a) IF = 0.15, IC = 1.27, b) IF = 0.35, IC = 2.49, and a control subject, c) IF = 0.44, IC = 2.73. □: VT, △: BF, --- : IC.
129x224mm (96 x 96 DPI)