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Inspiratory Fraction (IC/TLC) and Exercise Impairment in COPD Patients GOLD Stages II-III

ANDRÉ ALBUQUERQUE, MD
LUIZ EDUARDO NERY, MD, PhD
DÉBORA STROSE VILLAÇA, Nt
TAILA MACHADO
CRISTINO CARNEIRO OLIVEIRA, Pt
ÂNGELA TAVARES PAES, MSc
J. ALBERTO NEDER, MD, PhD

Pulmonary Function and Clinical Exercise Physiology Unit Department of Medicine, Division of Respiratory Diseases,
Federal University of Sao Paulo (UNIFESP), São Paulo, São Paulo, Brazil

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Running Title
IC/TLC AND EXERCISE TOLERANCE IN COPD

Address: J.A. Neder, MD, PhD. Coordinator, Pulmonary Function and Clinical Exercise Physiology Unit (SEFICE); Respiratory Division, Department of Medicine; Federal University of Sao Paulo – Paulista School of Medicine (UNIFESP-EPM). Rua Professor Francisco de Castro 54, Vila Clementino, CEP: 04020-050, Sao Paulo, Brazil. Phone: (+55-11) 5571-8384. FAX: (+55-11) 5575-2843. E-mail: albneder@pneumo.epm.br.

ABSTRACT

The inspiratory-to-total lung capacity ratio (IC/TLC or "inspiratory fraction") may be functionally more representative than traditional indexes of resting airflow limitation and lung hyperinflation in patients with chronic obstructive pulmonary disease (COPD).

On a retrospective study, we contrasted the individual performance of post-bronchodilator IC, IC/TLC and FEV_1 in predicting a severely-reduced peak $\dot{V}O_2$ (< 60% predicted) in 44 COPD patients GOLD stages II-III (post-bronchodilator FEV_1 ranging from 31% to 79 % predicted).

Patients in the lowest IC/TLC tertile (≤ 0.28) showed increased lung volumes and reduced exercise capacity as compared to other subjects ($p<0.05$). On a multiple linear regression analysis, only IC/TLC and FEV_1 remained as independent predictors of peak $\dot{V}O_2$ ($r^2 = 0.33$, $p < 0.01$). A ROC curve analysis revealed that an IC/TLC ≤ 0.28 had the highest specificity (89.6%), positive predictive value (80%) and overall accuracy (86.3%) in identifying patients with peak $\dot{V}O_2$ < 60% predicted. In addition, the area under the ROC curve tended to be higher for IC/TLC than IC ($p=0.06$).

In conclusion, post-bronchodilator TLC-corrected IC (inspiratory fraction) adds useful information to FEV_1 and IC in order to estimate the likelihood of COPD patients to present with severely-reduced maximal exercise capacity.

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INTRODUCTION

Exercise intolerance is a hallmark of chronic obstructive pulmonary disease (COPD), being ascribed to complex interactions between ventilatory, cardiovascular and peripheral muscle abnormalities (1). Amongst the pulmonary-ventilatory mechanisms which could contribute to exercise impairment in these patients, dynamic hyperinflation (DH) seems to be of special relevance (1, 2). In this context, resting and exercise inspiratory capacity (IC) have been shown to be superior to traditional measures of airflow obstruction (such as FEV_1) in predicting exercise impairment and improvement in tolerance to effort after bronchodilators, especially in patients with more advanced disease (3-5).

However, IC measurements on isolation may provide insufficient information about the actual elastic load during exercise and, therefore, to patients' ability to sustain exercise. Casanova and co-workers have argued that IC correction for the total lung capacity (TLC) would provide a better characterization of the volume fraction available for inspiration than IC alone. In fact, this so-called "inspiratory fraction" (IC/TLC) has been found to constitute an important prognostic factor in moderate-to-severe COPD (6). Another prospective study (7) showed that air trapping, expressed as increased residual volume (RV)/TLC ratio, was a powerful predictor of mortality in patients with COPD. To our knowledge, however, no previous study has systematically evaluated the value of resting IC/TLC in predicting maximal exercise tolerance in this patient population.

Therefore, the primary objective of this study was to investigate whether inspiratory fraction (IC/TLC) would be useful to predict maximal exercise capacity in COPD patients presenting with increased static lung volumes at rest.

METHODS

Subjects

The study population comprised 44 patients (33 males and 11 females) who had participated in a non-published investigation on the effects of neuromuscular electrical stimulation on peripheral muscle function and structure. All subjects had a clinical and functional diagnosis of COPD according to the GOLD criteria (stage II= 24 and stage III= 20) (8), presenting with FEV_1/FVC ratio < 0.7 and FEV_1 < 80 % but > 30% predicted; in addition, all patients were required to present with increased static lung volumes at rest (see below). Patients were clinically stable for at least 4 weeks and they were optimized in terms of medical therapy, including short- and long-acting β_2-adrenergics, short- and long-acting anticholinergics and inhaled steroids. Exclusion criteria were: suspected asthma, other systemic conditions that could contribute to dyspnoea or exercise limitation as heart failure or metabolic disorders, and resting oxihemoglobyn desaturation (SpO_2 < 90%). Patients gave an informed consent and the study protocol was approved by the Medical Ethics Committee.

Measurements

Anthropometry

Height was obtained with subjects standing barefoot and was determined to the nearest 0.5 cm; body mass was measured with subjects in light clothing and was established to the nearest 0.1 kg. Body mass index (BMI= weight/height^2, kg/m^2) was then calculated.

Pulmonary Function

Spirometric tests were performed by using the CPF System™ (Medical Graphics Corporation - MGC, St Paul, Minn, USA) with airflow being measured by a calibrated Pitot tube (PreVent Pneumotach™). The subjects completed at least three acceptable maximal forced and slow expiratory manoeuvres: in order to assess exercise capacity under improved ventilatory conditions, the patients were tested 20 min after the inhalation of 400 µg of salbutamol via MDI. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and inspiratory capacity (IC) were recorded in body temperature and pressure, saturated conditions (BTPS). Predicted values were those for the adult Brazilian population (9).

Carbon monoxide diffusing capacity (DL_{CO}) was measured by the modified Krogh technique (single breath): the subjects performed two acceptable and reproducible tests, with the results being within 10% or 3 mL.CO.min^{-1}.mmHg^{-1}(10). Total lung capacity (TLC, L) and residual volume (RV, L) were obtained by constant-volume, different-pressure body plethysmography and expressed as percent of the predicted value according to Brazilian standards (11). Air trapping was defined as increased RV/TLC and RV (>0.4 and >140% predicted, respectively): TLC values > 120% predicted were assumed as indicative of lung hyperinflation (12). Arterial partial pressure for oxygen and carbon dioxide were measured in anaerobic conditions (PaO_2 and $PaCO_2$, mmHg).

Cardiopulmonary exercise test (CPET)

Symptom-limited, ramp-incremental cycle ergometer exercise tests were performed on a digital computer-based exercise system (CardiO_2 System, Medical Graphics Corp.) with breath-by-breath analysis of metabolic, ventilatory, and cardiovascular variables. The rate of power increment was individually selected (usually 5 to 10 W/min) to provide an exercise duration of more than 8 but less than 12 min. The following data were recorded as mean of 15 seconds: pulmonary oxygen uptake ($\dot{V}O_2$, mL/min), minute ventilation ($\dot{V}E$, L/min), respiratory rate (RR), and tidal volume (VT, L). Peak $\dot{V}O_2$ was the highest value found at exercise cessation: predicted values were those of Neder et al. for the adult Brazilian population (13). In the present study, a peak $\dot{V}O_2$ lower than 60% predicted was considered as indicative of a severely-reduced maximum aerobic capacity (13). Heart rate (HR, bpm) was determined using the R-R interval from a 12 lead on-line electrocardiogram. Subjects were also asked to rate their "shortness of breath" at peak exercise using the 0-10 Borg's category-ratio scale (14). Dyspnoea ratings were also corrected for the ongoing level of total ventilatory stress (dyspnoea/$\dot{V}E$, Borg unities/L/min).

Statistical analysis

Data are presented as mean and standard deviations (SD) for normally distributed variables (Kolmogorov-Smirnov): median (range) was used otherwise. A commercially-available statistical software was used for the calculations (SPSS 13.0, SPSS, Chicago, IL, USA). Pearson's correlation coefficient was used to assess the level of association between continuous variables. Backward stepwise multiple linear regression was performed to define the independent predictors of peak $\dot{V}O_2$ (%

predicted): resting variables which were significantly related to peak $\dot{V}O_2$ at 10% level ($p<0.10$) were considered for inclusion in the model. In the regression analysis, however, only variables independently related to peak $\dot{V}O_2$ at 5% level ($p<0.05$) were allowed to remain in the final model. Non-paired t test was used to compare variables between patients separated by IC/TLC values. Receiver operating characteristic (ROC) curves were obtained for selected resting physiological variables in order to predict a severely-reduced maximal exercise capacity (peak $\dot{V}O_2$ $<60\%$ predicted). Their areas were then compared according to Delong et al (15) for pairwise differences. Sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, and accuracy were calculated for the cutoffs derived from the ROC curves. The level of statistical significance was set at 5% for all hypothesis tests ($p< 0.05$).

RESULTS

Population characteristics

Resting and exercise characteristics are presented in Table 1. On average, patients had moderate-to-severe airflow obstruction with evidences of air trapping (N = 44) and lung hyperinflation (N = 18) (see Methods). Maximal exercise capacity (peak $\dot{V}O_2$) was below the lower limit of normality in 38 patients (86.3%) (12): 16 subjects (36.3%) had a severe reduction in peak $\dot{V}O_2$ (< 60% pred). Pulmonary-ventilatory limitation, as indicated by increased $\dot{V}$Emax/MVV ratio (>0.8), was found in all subjects; accordingly, dyspnoea was the main exercise limiting symptom (Table 1).

Relationship between resting parameters and maximal exercise capacity

Maximal exercise capacity (peak $\dot{V}O_2$, % predicted) was significantly related to a number of resting variables, including: IC/TLC (r = 0.45, Figure 1), IC (r = 0.26), TLC (r = 0.38), RV (r = 0.48), and FEV_1 (r = 0.58). After a multiple regression analysis which considered all of these variables, only IC/TLC and FEV_1 remained as independent predictors in the final model: peak $\dot{V}O_2$ (% pred) = 78.9 IC/TLC + 26.1 FEV_1 (% predicted) + 29.4 ($p<0.01$; $r^2 = 0.334$).

Lung function predictors of a severely-reduced maximal exercise capacity

Considering that IC/TLC was an independent predictor of peak $\dot{V}O_2$, we examined more carefully this relationship. As shown in Figure 1, all but two patients in the lowest IC/TLC tertile (≤ 0.28; Group I) had peak $\dot{V}O_2$ values < 60% pred. On the other hand, only three patients in the upper IC/TLC tertiles (Group II, IC/TLC >

0.28) had peak VO_2 values <60% pred. In fact, there were several between–group differences either at rest or during exercise (Table 2). Therefore, Group I patients had reduced body mass index, worse lung function (airflow obstruction, air trapping and lung hyperinflation) and, as expected, lowest exercise capacity ($p<0.05$). Importantly, these patients tended to present with reduced tidal volume and increased ventilation-corrected dyspnoea scores (Table 2).

In order to compare the resting physiological variables in their ability to predict a severely-reduced peak $\dot{V}O_2$, we contrasted the area under the ROC curves (AUC) for IC/TLC, IC (% pred) and FEV_1 (% pred). As shown in Figure 2, IC/TLC had the highest AUC (0.92): this value, however, tended to differ statistically only from IC ($p=0.06$). Based on this analysis, we selected the cutoff points with the best sensitivity and specificity for each functional variable (14): IC/TLC= 0.28, IC = 75% pred, and FEV_1= 50% pred. As shown on Table 3, IC/TLC ≤ 0.28 presented with the highest specificity, positive predictive value, likelihood ratio for positive and negative test results, and overall accuracy to predict a peak $\dot{V}O_2$ < 60% pred as compared to other variables.

DISCUSSION

The main original finding of the present study was that post-bronchodilator inspiratory-to-total lung capacity ratio (IC/TLC or "inspiratory fraction"), an index of increased lung volumes, was an independent predictor of maximal exercise capacity in patients with COPD. More specifically, an IC/TLC ≤ 0.28 was likely to be related to a severely-reduced peak $\dot{V}O_2$ (<60% predicted); conversely, higher IC/TLC values were commonly found in less disabled patients. These data, in association with those previously reported by Casanova and co-workers (6) in relation to mortality, indicate that the IC/TLC should be valued as a relevant index of prognosis (≤ 0.25) and disability (≤ 0.28) in patients with COPD.

Lung hyperinflation and exercise tolerance in COPD

It has long been recognized that the main pathophysiological abnormality during dynamic exercise in COPD is expiratory flow limitation: its consequences, however, are largely inspiratory and elastic as a result of DH (16). Not surprisingly, several authors have found that decrease in the operating volumes with bronchodilators, specially the end-expiratory lung volume (EELV), are more likely to be related to clinically meaningful changes in this patient population than traditional measures of airflow (17-20). Similarly, improvement in exercise capacity and dyspnoea after lung volume reduction surgery was better associated with changes in EELV than with FEV_1 (21). In the present study, measures of increased lung volumes (IC, RV, and IC/TLC) were all associated with worsening maximum exercise capacity (Table 2). Reduction in exercise tolerance in patients in the lowest IC/TLC tertile (Group I) tended to be associated with lower tidal volume and increased ventilation-corrected dyspnoea at peak exercise (Table 2). These results seem to indicate that, with exercise progression, in patients breathed at near-maximum (and less compliant) lung volumes – although exercise IC values were not measured in the present study (see *Study Limitations*).

Physiological significance of IC/TLC

The theoretical advantage of IC/TLC over IC on isolation may be related to the fact that a lower IC/TLC seems to better reflect the deleterious combination of air trapping (increased RV and RV/TLC) *plus* lung hyperinflation (increased TLC) (Table 2). Therefore, two patients may present with similar IC which is a widely-different fraction of their maximal available volume for lung expansion. In this context, the combination of lower IC/TLC with increased TLC (i.e., a very high EELV) is potentially more harmful than the isolated reduction in IC, since the patient should breath at his/her near-maximum (and increased) TLC - with negative consequences on the elastic work of breathing and dyspnoea.

A noticeable finding of the present study was the close similarity between the IC/TLC cutoffs for severe reduction in peak $\dot{V}O_2$ described herein and that found by Casanova et al. for mortality in COPD (6). Although the exact nature of the relationship between lung hyperinflation and mortality in COPD is still elusive, it is interesting to note that a low IC/TLC was related to reduced BMI, worse exercise capacity and, marginally ($p= 0.10$), to decreased D_LCO (Table 2)– all indicators of poor prognosis in COPD (22).

Clinical implications

Exercise capacity has been associated with disability, increased usage of health care resources and even mortality in patients with COPD (23). Resting lung function measurements may be useful in estimating the likelihood of a severe reduction in exercise tolerance (5). Our results show that IC/TLC is a readily-available alternative for the prediction of severe disability in COPD with the advantage to be also associated with mortality (6). On a practical point-of-view, if a COPD patient presents with an IC/TLC ≤ 0.28 (or ≤ 0.25) he/she should be considered at increased risk of respiratory-related disability and death.

Study limitations

A major limitation of the present study is related to the sample size. Therefore, we cannot rule out that a potential superiority of IC/TLC over other physiological variables has not been demonstrated due to an insufficient number of patients with severe-to-very severe lung hyperinflation. In fact, our results should not be extrapolated for patients with more advanced or milder disease. Another relevant limitation was the lack of IC measurements during exercise, a physiological outcome which has been shown to be superior to resting IC in estimating exercise tolerance in patients with COPD (1). It could be speculated, however, that as patients with lower IC/TLC had substantially increased operating lung volumes at rest – as discussed above – they would tend to present with lower exercise IC. However, recent studies using optoelectronic plethysmography have found a variable behaviour of exercise lung volumes in individual COPD patients with DH being poorly related to static lung volumes (24, 25). Future studies, therefore, are warranted to evaluate how IC/TLC compares to exercise IC in these patients. Also importantly, submaximal exercise tolerance has been found to be more closely related to patients´ functional capacity than peak exercise: it remains to be investigated the accuracy of IC/TLC in identifying patients with reduced tolerance to endurance exercise (26). Moreover, it is currently unknown whether pre-bronchodilator IC/TLC also presents with functional significance. Finally, as mentioned, exercise intolerance is a multi-factorial construct where pulmonary-ventilatory, cardiovascular and peripheral factors interact in a complex way: IC/TLC (as any lung function variable) should always be used in association with other indices to estimate the degree of effort intolerance in the individual patient.

Conclusion

The present study has shown, for the first time, that post-bronchodilator IC/TLC ("inspiratory fraction") is an independent predictor of severely-reduced maximal exercise capacity in patients with COPD. Considering that this variable has also been previously found to constitute a significant prognostic index in COPD (6), IC/TLC should be valued in the functional evaluation of this patient population.

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Table 1. Patients characteristics at rest and maximal exercise (N=44).

Variables	Values
Demographic/ Anthropometric	
Gender (M/F)	33/11
Age (yrs)	64.1 (7.5)
Body mass index, $kg.m^{-2}$	23.7 (4.0)
Pulmonary function	
FEV_1, L	1.24 (0.49)
FEV_1, % pred	49.0 (16.4)
FVC, % pred	89.3 (21.8)
FEV_1/FVC	0.43 (0.09)
TLC, % pred	116.8 (16.4)
RV, % pred	205.2 (60.7)
RV/TLC	0.55 (0.09)
IC, % pred	79.4 (17.2)
IC/TLC	0.31 (0.07)
D_LCO, % pred	55.8 (18.9)
P_aO_2, mmHg	66.5 (8.6)
P_aCO_2, mmHg	41.3 (6.2)
Maximal exercise	
Peak $\dot{V}O_2$, % pred	68.4 (16.5)
Peak $\dot{V}O_2$, $mL.min^{-1}$	998 (342)
Power, W	64 (29)
$\dot{V}E$, $L.min^{-1}$	38.0 (13.5)
$\dot{V}E$/MVV	0.83 (0.18)
Respiratory rate, $breaths.min^{-1}$	31.5 (5.1)
Tidal volume, L	1.20 (0.37)
Tidal volume/resting IC	0.57 (0.15)
Heart rate, % pred	85.9 (11.5)
Dyspnoea score	7 (5-10)
Dyspnea/$\dot{V}E$	0.18 (0.10)

Definition of abbreviations: FEV_1= forced expiratory volume in one second; FVC= forced vital capacity; TLC= total lung capacity; RV= residual volume; IC= inspiratory capacity; D_LCO= lung diffusing capacity; $\dot{V}O_2$ = oxygen consumption; $\dot{V}E$ = minute ventilation;

MVV – maximal voluntary ventilation. *Mean (SD) with exception of sdyspnoea scores (median and range).

Table 2. Resting and exercise parameters of patients separated by tertiles of IC/TLC.

	Group I (N= 15) (IC/TLC ≤ 0.28)	**Group II (N= 31) (IC/TLC > 0.28)**
Demographic/ Anthropometric		
Age (yrs)	65.2 (6.8)	63.5 (7.9)
Body mass index, $kg.m^{-2}$	21.0 (3.5)	24.9 (3.6)*
Pulmonary function		
FEV_1, % pred	38.4 (14.7)	54.5 (14.5)*
TLC, % pred	125.4 (18.7)	112.3 (13.4)*
RV, % pred	255.4 (64.3)	179.3 (39.3)*
RV/TLC	0.64 (0.07)	0.51 (0.07)*
IC, % pred	65.0 (7.0)	86.8 (16.2)*
IC/TLC	0.23 (0.03)	0.35 (0.05)*
D_LCO, % pred	47.8 (23.0)	59.6 (15.8)
P_aO_2, mmHg	65.2 (5.9)	67.1 (9.6)
P_aCO_2, mmHg	40.6 (5.0)	41.7 (6.7)
Maximal exercise		
Peak VO_2, % pred	56.8 (16.6)	74.4 (13.2)*
Peak VO_2, $mL.min^{-1}$	784 (319)	1109 (302)*
Power, W	48 (29)	71 (26)*
$\dot{V}E$, $L.min^{-1}$	29.9 (11.6)	42.2 (12.6)*
$\dot{V}E$/MVV	0.83 (0.18)	0.83 (0.18)
Respiratory rate, $breaths.min^{-1}$	28 (3)	32 (5)*
Tidal volume, L	1.04 (0.35)	1.28 (0.35)*
Tidal volume/resting IC	0.61 (0.20)	0.55 (0.11)
Heart rate, % pred	87.0 (9.5)	85.5 (12.3)
Dyspnoea/$\dot{V}E$	0.22 (0.14)	0.17 (0.07)

* $p<0.05$.
For definition of abbreviations see Table 1.

Table 3. Diagnosis performance of different lung function parameters in predicting a severely-reduced maximal exercise capacity (peak VO_2 < 60% pred).

	IC/TLC ≤ 0.28	**IC ≤ 75% pred**	**FEV_1 ≤ 50% pred**
Sensitivity (%)	80.0	93.3	86.6
Specificity (%)	89.6	75.8	58.2
PPV (%)	80.0	66.6	52.0
NPV (%)	89.6	95.6	89.4
Accuracy (%)	86.3	81.8	68.1
LR positive test	7.2	3.7	2.0
LR negative test	0.20	0.93	0.24

Definition of abbreviations: IC= inspiratory capacity; TLC= total lung capacity; FEV_1= forced expiratory volume in one second; PPV= positive predictive value; NPV= negative predictive value; LR= likelihood ratio.

FIGURE LEGENDS

Figure 1. Relationship between inspiratory-to-total lung capacity ratio (IC/TLC) with maximal exercise capacity (peak VO_2) in a group of 44 patients with COPD. Note that all but two patients in the lowest tertile of IC/TLC (≤ 0.28; Group I) had a severely-reduced maximal exercise capacity (peak VO_2 <60% predicted); conversely, only three patients in the higher IC/TLC tertiles (Groups II, IC/TLC > 0.28) presented with peak VO_2 <60% predicted.

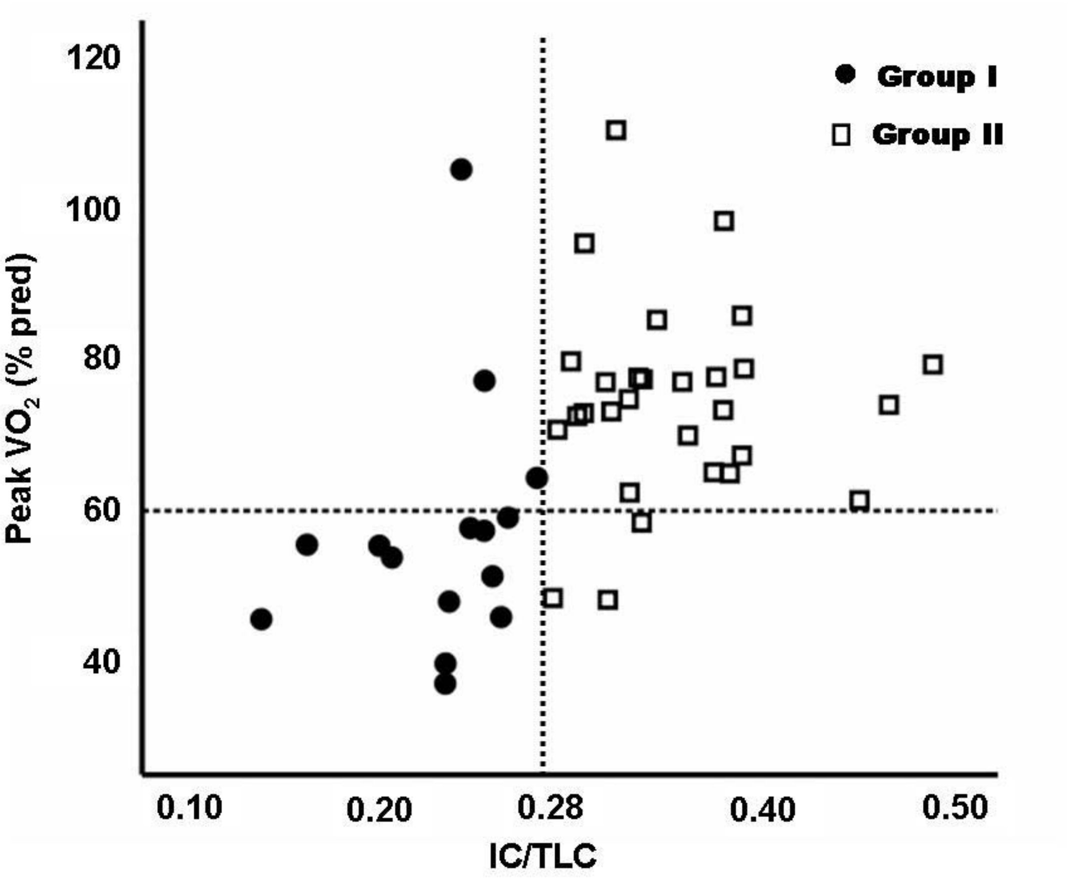
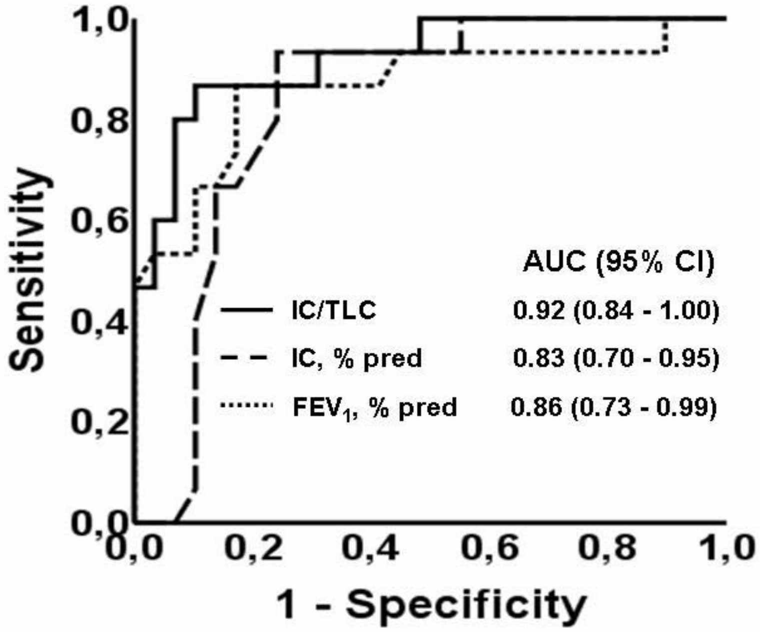


Figure 2. Receiver operating characteristic (ROC) curves of IC/TLC, IC (% predicted) and FEV_1 (% predicted) as related to a severely-reduced maximal exercise capacity (peak VO_2 < 60% predicted). The best cutoffs values were 0.28, 75% predicted and 50% predicted, respectively.



Footnotes

Definition of abbreviations: AUC= area under the curve; CI= confidence interval. Differences between AUCs= IC/TLC *vs* FEV_1 ($p = 0.30$); IC/TLC *vs* IC ($p = 0.06$); FEV_1 *vs* IC ($p = 0.66$).