

## Role of inspiratory capacity on exercise tolerance in COPD patients with and without tidal expiratory flow limitation at rest

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*Role of inspiratory capacity on exercise tolerance in COPD patients with and without tidal expiratory flow limitation at rest. O. Diaz, C. Villafranca, H. Ghezzi, G. Borzone, A. Leiva, J. Milic-Emil, C. Lisboa. ©ERS Journals Ltd 2000.*

**ABSTRACT:** Expiratory flow limitation promotes dynamic hyperinflation during exercise in chronic obstructive pulmonary disease (COPD) patients with a consequent reduction in inspiratory capacity (IC), limiting their exercise tolerance. Therefore, the exercise capacity of patients with tidal expiratory flow limitation (FL) at rest should depend on the magnitude of IC. The presented study was designed to evaluate the role of FL on the relationship between resting IC, other respiratory function variables and exercise performance in COPD patients.

Fifty-two patients were included in the study. Negative expiratory pressure (NEP) technique was employed to assess FL. Maximal work rate ( $\dot{W}R_{max}$ ) and oxygen uptake ( $\dot{V}O_{2,max}$ ) were measured during an incremental symptom-limited cycle exercise.

Twenty-nine patients were FL at rest. The IC was normal in all non-FL patients, while in most FL subjects it was decreased. Both  $\dot{W}R_{max}$  and  $\dot{V}O_{2,max}$  were lower in FL patients ( $p < 0.001$ , each). A close relationship of  $\dot{W}R_{max}$  and  $\dot{V}O_{2,max}$  to IC was found ( $r = 0.73$  and  $0.75$ , respectively;  $p < 0.0001$ , each). In the whole group, stepwise regression analysis selected IC and forced expiratory volume in one second (FEV<sub>1</sub>)/forced vital capacity (FVC) (% predicted) as the only significant contributors to exercise tolerance. Subgroup analysis showed that IC was the sole predictor in FL patients, and FEV<sub>1</sub>/FVC in non-FL patients.

Detection of flow limitation provides useful information on the factors that influence exercise capacity in chronic obstructive pulmonary disease patients. Accordingly, in patients with flow limitation, inspiratory capacity appears as the best predictor of exercise tolerance, reflecting the presence of dynamic hyperinflation. *Eur Respir J 2000; 16: 269–275.*

Patients with chronic obstructive pulmonary disease (COPD) show widely variable exercise capacities. The relationship between resting lung function and exercise tolerance has been extensively studied in this group of patients [1–5]. In most previous studies, it was found that forced expiratory volume in one second (FEV<sub>1</sub>) was a poor predictor of exercise capacity [1–3]. Recently, however, it has been shown that indices related to dynamic hyperinflation, such as the inspiratory capacity (IC), are more closely related to exercise tolerance than FEV<sub>1</sub> [4, 5].

Even at rest, patients with COPD often exhibit tidal expiratory flow limitation (FL) [6, 7], promoting an increase in end-expiratory lung volume (EELV) due to dynamic hyperinflation with a concomitant decrease in inspiratory capacity and inspiratory reserve volume (IRV) [8, 9]. During exercise, normal subjects increase the tidal volume ( $\dot{V}_T$ ) at the expense of both the IRV and the expiratory reserve volume [8, 9]. In contrast, in flow-limited COPD patients,  $\dot{V}_T$  increases only at the expense of their reduced IRV and eventually it impinges into the flat portion of the static volume-pressure relationship of

the respiratory system [8, 9]. Thus, in flow-limited COPD patients the maximal  $\dot{V}_T$  ( $\dot{V}_{T,max}$ ) achieved during exercise should depend on the magnitude of IC. Since the exercise capacity is related to  $\dot{V}_{T,max}$  [8], a close association of maximal work rate ( $\dot{W}R_{max}$ ) and oxygen uptake during exercise ( $\dot{V}O_{2,max}$ ) to IC should be expected in patients who exhibit tidal expiratory flow limitation already at rest. In contrast, in COPD patients without tidal FL (non-FL) at rest other factors should play a prominent role in determining exercise capacity.

Accordingly, in the present study the role of tidal expiratory flow limitation on the relationships of  $\dot{W}R_{max}$  and  $\dot{V}O_{2,max}$  to IC and other resting lung function variables in COPD patients has been investigated. Assessment of FL was made using a simple noninvasive method that consists of applying a negative expiratory pressure (NEP) at the mouth during a tidal expiration and comparing the ensuing expiratory flow-volume curve with that of the previous control expiration [6]. The NEP technique has been extensively applied and validated, and has been used in stable COPD patients both at rest and during exercise [7, 8, 10].

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## Methods

### Patients

The study was performed on 52 patients with mild to severe COPD. Diagnosis was made according to American Thoracic Society (ATS) guidelines [11]. Patients were receiving chronic care at the authors' institution, and were familiarized with all respiratory measurements, dyspnoea evaluation, and symptom-limited incremental exercise test. Their clinical and functional state was stable at the time of the study, *i.e.*, there was absence of exacerbations and significant changes in spirometry during the preceding four weeks. All patients had stopped smoking for at least 2 yrs before the study, and were receiving regular treatment with inhaled bronchodilators, with no systemic or inhaled steroids. Twelve patients were on long-term oxygen therapy. None was participating in a respiratory training programme nor was receiving home noninvasive mechanical ventilation. No change in the routine medical and oxygen therapy was made in the four weeks before the study. Patients with history of asthma, obstructive sleep apnoeas, other concomitant lung disease, cardiovascular disorders, inability to cooperate, or oxygen desaturation to <80% during exercise on room air were excluded. All agreed to participate in the study, which was approved by the Ethics Committee of our Institution.

### Pulmonary and respiratory muscle function tests

Spirometry was performed with a calibrated dry spirometer (Vitalograph®, London, UK) according to ATS standards [12]. Absolute lung volumes were measured with the nitrogen washout method (SensorMedics, Corp., Yorba Linda, CA). Reference values from (for spirometry) KNUDSON *et al.* [13] and (for lung volumes) from the European Community for Steel and Coal [14] were used. For IC, predicted values were calculated as the difference between predicted total lung capacity (TLC) and predicted functional residual capacity (FRC). Airflow ( $\dot{V}$ ) was measured with a heated Fleisch No. 2 pneumotachograph (Fleisch, Lausanne, Switzerland) and a differential pressure transducer (MP45,  $\pm 2$  cmH<sub>2</sub>O; Validyne Corp., Northridge, CA). Volume was obtained by numerical integration of the flow signal. Maximal inspiratory pressure ( $P_{I,max}$ ) was measured at FRC with a differential pressure transducer (Validyne MP45,  $\pm 100$  cmH<sub>2</sub>O). Reference values were those of Harik-KHAN *et al.* [15]. Arterial blood gas tensions were measured with a Ciba. Corning 238 gas analyser (Ciba Corning Diagnostic Corp., MA, USA). Tidal expiratory flow limitation (FL) was assessed with the NEP technique, which has been previously described in detail [6–8].

### Procedure and data analysis

Subjects studied were seated upright in a comfortable chair, breathing room air through the equipment assembly while wearing a nose clip. After regular breathing had been achieved, minute ventilation ( $\dot{V}_E$ ), tidal volume ( $V_T$ ), inspiratory time ( $t_I$ ), expiratory time ( $t_E$ ), total cycle dura-

tion ( $t_{tot}$ ), duty cycle ( $t_I/t_{tot}$ ) and mean inspiratory flow ( $\dot{V}_T/t_I$ ) were obtained as average values from 1-min records of flow and volume. A series of 5 NEP tests were then applied using a pressure of  $\sim 5$  cmH<sub>2</sub>O. Subjects in whom application of NEP did not elicit an increase of flow over part or all of the control tidal expiration were considered flow limited (FL) (fig. 1). By contrast, subjects in whom flow increased with NEP over the entire range of the control tidal expiration were considered as not flow limited (non-FL) (fig. 1). The FL portion of the tidal expiration was expressed as a percentage of the control  $\dot{V}_T$  (FL, % $\dot{V}_T$ ) [7]. The latter is presented as average of the five NEP tests.

### Exercise test

An incremental symptom-limited exercise test was performed using an electrically braked cycle ergometer (ER 800®; Erich Jaeger, GmbH, Hoerschberg, Germany) connected to a metabolic chart (Q-Plex®; Quinton, WA, USA). Subjects cycled at 50 revolution·min<sup>-1</sup> (rpm) with the external power increased in 1-min steps of 5–10 watts to the limit of their tolerance, either by dyspnoea or leg fatigue. They were familiarized with the Borg Scale [16] and were capable of quantifying their level of dyspnoea or leg discomfort. Oxygen saturation, heart rate and arterial pressure were continuously monitored with a Dina-map™ Plus vital signs monitor (Critikon, Tampa, FL). The maximal mechanical power output and oxygen uptake were determined. The predicted normal values for  $\dot{W}R_{max}$  and  $\dot{V}O_{2,max}$  were those of JONES [17].

### Statistical analysis

Results are expressed as mean  $\pm$  SEM. Comparisons between non-FL and FL patients were performed through unpaired t-test. A Bonferroni-type adjustment was carried out using Hommel's procedure [18]. Linear regression analysis was performed using the least squares method. This analysis was carried out using  $\dot{W}R_{max}$  and  $\dot{V}O_{2,max}$  as dependent variables while the possible independent variables included the resting pulmonary and respiratory muscle function variables together with the anthropometric characteristics of the subjects. Independent variables of pulmonary and muscle function were expressed both as absolute values and percent of predicted. The strongest significant contributors to  $\dot{W}R_{max}$  and  $\dot{V}O_{2,max}$  were selected by stepwise multiple regression analysis. This analysis was first performed for the entire population and then separately for non-FL and FL patients. A similar analysis was also made using arterial oxygen ( $P_{a,O_2}$ ) and carbon dioxide pressure ( $P_{a,CO_2}$ ) as dependent variables. The SPSS/PC statistical software package was used (Release 9.0, 1999; SPSS Inc., Chicago, IL). A p-value <0.05 was considered significant.

## Results

Twenty-three COPD patients were non-FL while the other 29 exhibited tidal FL at rest, the FL (% $\dot{V}_T$ ) ranged

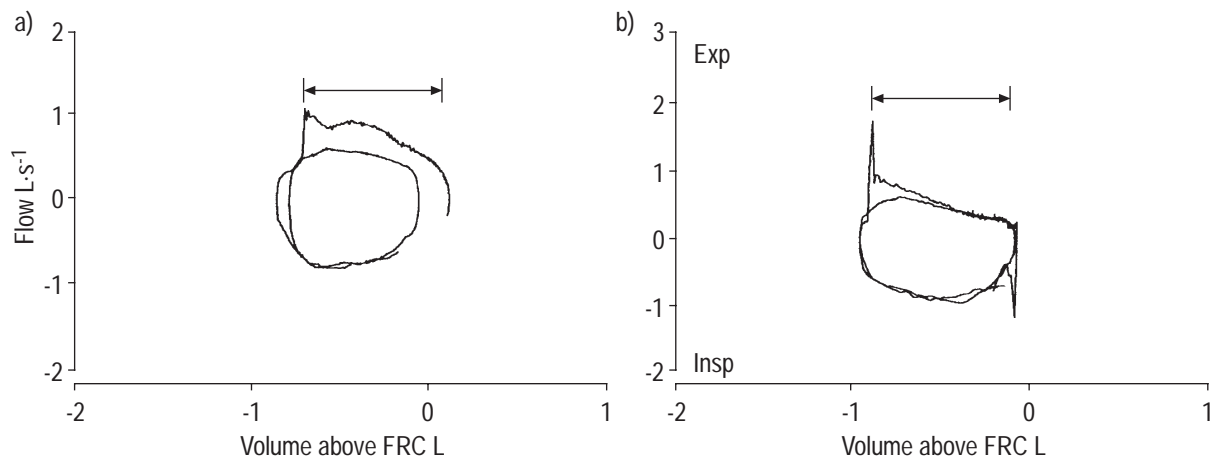


Fig. 1. – Flow-volume loops of negative expiratory pressure (NEP) test breaths and preceding control breaths of a patient a) without flow-limitation (flow limitation (FL), 0% tidal volume ( $V_T$ ); inspiratory capacity (IC) 89% pred and b) with flow-limitation encompassing 45% of the tidal control tidal volume (FL, 45%  $V_T$ ; IC 70% pred). Horizontal arrows indicate volume range over which NEP was applied. Zero volume is end-expiratory lung volume of control breaths. FRC: functional residual capacity; Exp: expiration; Insp: inspiration.

42–80%. Table 1 shows the relevant anthropometric and lung function characteristics of the 23 non-FL and 29 FL COPD patients. The values for FEV<sub>1</sub>, FVC, FEV<sub>1</sub>/FVC, FRC, RV and IC (% pred) differed significantly between non-FL and FL patients.

In all non-FL patients, the IC was within normal limits (>80% pred) while in almost all FL patients it was <80% of predicted normal. Accordingly, there was little overlap between the two groups of patients (fig. 2a). In contrast, in terms of both FEV<sub>1</sub> and FVC (% pred) there was

considerable overlap between the non-FL and FL patients (figs. 2b and 2c).

In the FL patients, there was a significant negative correlation of FL (% $V_T$ ) to IC (% pred) ( $r=-0.52$ ;  $p<0.05$ ).

Significant negative correlations were found of IC (% pred) to FRC (% pred) ( $r=-0.45$ ;  $p<0.005$ ) and residual volume (RV) (% pred) ( $r=-0.53$ ;  $p<0.0001$ ). The relatively poor correlation of IC to FRC may be explained by the fact that the latter was measured with the nitrogen washout method, which tends to underestimate the thoracic gas volume, particularly in patients with severe COPD.

The average ( $\pm$ SEM) values of  $WR_{max}$  and  $V'O_{2,max}$  of the non-FL and FL patients are given in table 2. In all FL patients  $V'O_{2,max}$  was <80% pred normal, while this was not the case for 8 (35%) of the 23 non-FL subjects.

According to the linear regression analysis, the strongest correlations of  $WR_{max}$  and  $V'O_{2,max}$  to the independent variables used were with IC and FEV<sub>1</sub>/FVC. Figure 3 depict the relationships of  $V'O_{2,max}$  to IC and FEV<sub>1</sub>/FVC, all variables being expressed as percent of predicted normal. The latter variables were selected by stepwise regression analysis as the only significant contributors to  $WR_{max}$  and  $V'O_{2,max}$ . The predictive equations based on these variables are, respectively:

$$WR_{max} = -7.2 + 0.43IC + 0.37FEV_1/FVC \pm 9.6 \quad (1)$$

$$V'O_{2,max} = -6.5 + 0.48IC + 0.57FEV_1/FVC \pm 10.1 \quad (2)$$

where all variables are expressed as % pred normal. The values of the correlation coefficients ( $r$ ) for these regressions were 0.79 and 0.85, respectively.

The above analysis was performed separately for FL and non-FL patients. For FL patients only IC was selected as a significant contributor by the stepwise regression analysis, while for non-FL patients only FEV<sub>1</sub>/FVC was selected. The equations for FL patients were:

$$WR_{max} = -14.7 + 0.3 IC \pm 8.3 \quad (3)$$

$$V'O_{2,max} = 20 + 0.44 IC \pm 7.6 \quad (4)$$

The values of the correlation coefficients for these regressions were 0.48 and 0.63, respectively. The equations for non-FL patients were:

Table 1. – Anthropometric, pulmonary, and respiratory muscle data at rest of 23 non-flow limited (non-FL) and 29 flow-limited (FL) chronic obstructive pulmonary disease patients

	Non-FL	FL	p-value
Subjects n	23	29	
Age yr	67±2	65±1	NS
Sex M:F	17:6	26:3	NS
Smoking history, pack-yr	48±4	54±4	NS
Weight kg	65±2	67±2	NS
Height cm	161±2	166±1	NS
Body Mass Index, kg·m <sup>-2</sup>	25±0.7	24±0.9	NS
$P_{a,O_2}$ , kPa	9.1±0.3	8.0±0.2	
(mmHg)	(68±2)	(60±2)	0.036
$P_{a,CO_2}$ , kPa	5.2±0.2	5.8±0.2	
(mmHg)	(39±1)	(44±1)	0.042
pH	7.43±0.01	7.41±0.01	NS
FEV <sub>1</sub> % pred	58±3	31±2	<0.002
FVC % pred	94±4	75±4	0.009
FEV <sub>1</sub> /FVC % pred	62±2	44±2	<0.002
TLC % pred	116±3	120±3	NS
FRC % pred	134±5	169±6	<0.002
RV % pred	150±6	198±9	<0.002
IC % pred	93±2	60±3	<0.002
$P_{I,max}$ % pred	77±4	67±3	NS

Values are means±SEM. M: male; F: female;  $P_{a,O_2}$ : oxygen tension in arterial blood;  $P_{a,CO_2}$ : carbon dioxide tension in arterial blood; FEV<sub>1</sub>: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; FRC: functional residual capacity; RV: residual value; IC: inspiratory capacity;  $P_{I,max}$ : maximal inspiratory pressure; NS: nonsignificant.

$$WR_{\max} = 16.8 + 0.6 \text{ FEV}_1/\text{FVC} \pm 10.9 \quad (5)$$

$$V'_{\text{O}_2, \max} = 4.9 + 1.1 \text{ FEV}_1/\text{FVC} \pm 9.9 \quad (6)$$

The correlation coefficients for these equations were 0.57 and 0.80, respectively.

As shown in table 1, the average value of  $P_{\text{a,O}_2}$  was significantly lower in the FL than in the non-FL patients ( $p < 0.05$ ). On the other hand, the average value of  $P_{\text{a,CO}_2}$  was significantly higher in the FL patients ( $p < 0.05$ ). According to the linear regression analysis, the strongest correlation ( $p < 0.0001$ ) of  $P_{\text{a,CO}_2}$  to the independent variables used in our analysis was with FVC (% pred) and

IC (% pred), the correlation coefficients amounting to -0.55 and -0.54, respectively. These independent variables were selected by stepwise regression analysis as the only significant contributors to  $P_{\text{a,CO}_2}$ . The predictive equation based on these variables is:

$$P_{\text{a,CO}_2} = 7.9 - 0.015 \text{ FVC} - 0.015 \text{ IC} \pm 0.7 \text{ (SEM)} \quad (7)$$

where  $P_{\text{a,CO}_2}$  is in kPa, and FVC and IC are expressed as % pred. The correlation coefficient of this equation was 0.62. Predictive equations for FL and non-FL patients were, respectively:

$$P_{\text{a,CO}_2} = 8.1 - 0.04 \text{ IC} \pm 0.7 \text{ (SEM)} \quad (8)$$

$$P_{\text{a,CO}_2} = 7.2 - 0.02 \text{ FVC} \pm 0.7 \text{ (SEM)} \quad (9)$$

The correlation coefficients for these equations were 0.62 and 0.55, respectively.

There was no significant difference in breathing pattern between non-FL and FL patients (table 3). However, both  $\dot{V}_T$  and  $t_I$  were significantly lower in the 17 FL patients who were hypercapnic ( $P_{\text{a,CO}_2} > 5.7$  kPa) [19] than in the 12 nonhypercapnic FL patients ( $0.576 \pm 0.04$  versus  $0.792 \pm 0.09$  L,  $p < 0.03$ , and  $0.99 \pm 0.07$  versus  $1.35 \pm 0.08$  L,  $p < 0.005$ , respectively). In the hypercapnic FL patients, the IC (% pred) was lower than in the nonhypercapnic FL patients ( $53 \pm 2$  versus  $71 \pm 3$  % pred;  $p < 0.0001$ ).

There was no significant difference in  $P_{I, \max}$  (% pred) between the FL and non-FL patients. A weak correlation was found of  $P_{I, \max}$  (% pred) to IC (% pred) ( $r = 0.34$ ;  $p < 0.05$ ). No significant correlation was found of  $V'_{\text{O}_2, \max}$  to  $P_{I, \max}$ , while there was a significant, although loose, correlation between  $WR_{\max}$  and  $P_{I, \max}$  ( $r = 0.32$ ;  $p < 0.01$ ).

## Discussion

The main finding of the present study is that, in COPD patients, detection of expiratory FL at rest plays an important role in identifying the factors that limit exercise tolerance. In those patients with FL, the sole predictor of exercise capacity was IC, whereas in non-FL patients  $\text{FEV}_1/\text{FVC}$  was the best predictor. In addition, it was found that 1) in all non-FL patients IC was within normal limits and in the majority of FL subjects the IC was below normal limits; and 2) in all FL subjects  $V'_{\text{O}_2, \max}$  was decreased, whereas in 35% of the non-FL patients  $V'_{\text{O}_2, \max}$  was within normal limits.

Table 2. – Maximal exercise data of 23 non-flow limited (non-FL) and 29 flow limited (FL) chronic obstructive pulmonary disease patients

	non-FL	FL	p-value
Subjects n	23	29	
$WR_{\max}$ , W	$73 \pm 5$	$49 \pm 3$	$< 0.001$
$WR_{\max}$ , % pred	$56 \pm 3$	$34 \pm 2$	$< 0.001$
$V'_{\text{O}_2, \max}$ , L·min <sup>-1</sup>	$1.11 \pm 0.1$	$0.79 \pm 0.04$	0.001
$V'_{\text{O}_2, \max}$ % pred	$73 \pm 3$	$47 \pm 2$	$< 0.001$
$V'_{\text{O}_2, \max}$ , mL·kg <sup>-1</sup> ·min <sup>-1</sup>	$17 \pm 0.9$	$12 \pm 0.5$	$< 0.001$
Dyspnoea, Borg	$7.9 \pm 0.4$	$8.0 \pm 0.3$	NS
Leg discomfort, Borg	$6.8 \pm 0.4$	$8.2 \pm 0.4$	$< 0.02$

Values are mean  $\pm$  SEM.  $WR_{\max}$ : maximum work rate;  $V'_{\text{O}_2, \max}$ : maximal oxygen uptake; NS: nonsignificant.

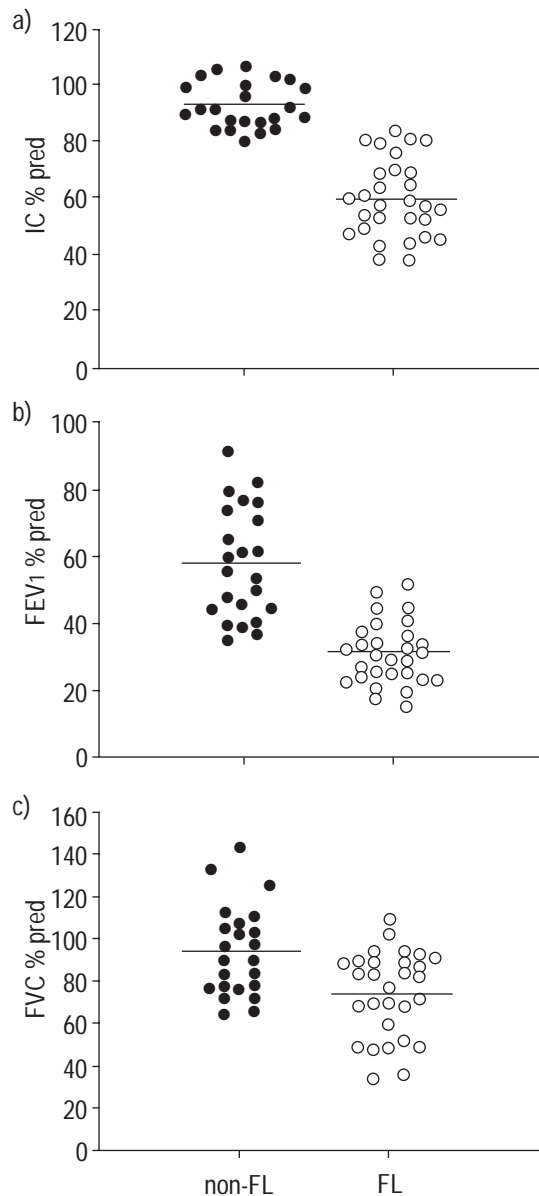


Fig. 2. – Individual and average values (bars) of a) inspiratory capacity IC; b) forced expiratory volume in one second ( $\text{FEV}_1$ ) and c) forced vital capacity (FVC), expressed as percent predicted, for chronic obstructive pulmonary disease patients without (non-FL) and with (FL) tidal expiratory flow limitation (FL) during resting breathing. p-values are  $< 0.002$ ,  $< 0.002$  and  $< 0.01$  for IC,  $\text{FEV}_1$  (FL) and FVC respectively.

Table 3. – Breathing pattern at rest of 23 non-flow limited (non-FL) and 29 flow limited (FL) chronic obstructive pulmonary disease patients

	non-FL	FL	p-value
Subjects n	23	29	
$\dot{V}_E$ L·min <sup>-1</sup>	10.3±0.7	10.9±0.4	NS
$V_T$ L	0.638±0.05	0.666±0.05	NS
$V_T$ % IC	29±3	40±2	0.018
$t_I$ s	1.25±0.06	1.14±0.06	NS
$t_E$ s	2.54±0.17	2.51±0.17	NS
$t_{tot}$ s	3.79±0.2	3.65±0.2	NS
$\dot{V}_T/t_I$ L·s <sup>-1</sup>	0.53±0.04	0.59±0.03	NS
$t_I/t_{tot}$	0.34±0.02	0.32±0.01	NS

Values are mean±SEM.  $\dot{V}_E$ : minute volume;  $V_T$ : tidal volume;  $t_I$ : inspiratory time;  $t_E$ : expiratory time;  $t_{tot}$ : total breathing cycle time;  $\dot{V}_T/t_I$ : mean inspiratory flow;  $t_I/t_{tot}$ : duty cycle; IC: inspiratory capacity; NS: nonsignificant.

In line with ELTAYARA *et al.* [7], a high incidence of FL was found (56% versus 59%, respectively), indicating that FL is a frequent but unrecognized abnormality in these patients. The presented data also confirmed the findings of KOLOURIS *et al.* [8] that a reduced IC is a good marker of FL, as it reflects dynamic hyperinflation (DH). Accordingly, it was found that IC (% pred) was significantly lower than normal in 86% of the FL patients, while it was normal in all non-FL patients.

In our FL patients both  $\dot{W}R_{max}$  and  $\dot{V}O_{2,max}$  were significantly lower than in non-FL patients (table 2). Similar results have been reported in a previous study [8] though the differences were not significant, presumably because of the small number of individuals studied (n=14). In all of our FL patients  $\dot{V}O_{2,max}$  was lower than normal, while it was normal in 15 of the 23 non-FL patients (fig. 3). There was a close correlation of  $\dot{W}R_{max}$  and  $\dot{V}O_{2,max}$  to IC and, to a lesser extent, to FEV<sub>1</sub>/FVC (fig. 3). Both of these independent variables were selected by stepwise multiple regression analysis as the sole significant contributors to  $\dot{W}R_{max}$  and  $\dot{V}O_{2,max}$ , the coefficients of determination ( $r^2$ ) of the respective predictive equations 1 and 2

being 0.63 and 0.72. Thus, IC and FEV<sub>1</sub>/FVC explain ~70% of the variance of  $\dot{W}R_{max}$  and  $\dot{V}O_{2,max}$ , respectively. The residual variance is probably due in part to the fact that in COPD patients the exercise capacity may not be limited solely by ventilation but also by other factors, such as peripheral muscle weakness and deconditioning [20, 21]. This is suggested by the higher scores of leg fatigue found in FL patients compared to non-FL patients in our study. It should also be stressed that the presence of FL does not necessarily result in DH, if the available expiratory flow is sufficient to sustain resting ventilation without the need to increase the EELV, as was the case for 14% of our FL patients with a normal IC. This could explain that coefficients of correlation for  $\dot{W}R_{max}$  and  $\dot{V}O_{2,max}$  were lower in FL patients (equations 3 and 4) than in non-FL patients (equations 5 and 6). In addition, only part of the resting IC can be mobilized during exercise in terms of  $V_T$ . As a result,  $\dot{V}_{T,max}$  is, necessarily, somewhat lower than resting IC.

Considering the limitations of the present study to accurately predict, from their resting characteristics, all the factors involved in the exercise tolerance of COPD patients, the central point is that assessment of resting FL clearly separates two populations of patients with significant differences in exercise tolerance. More importantly, their detection provides useful information about the mechanisms limiting exercise tolerance. In presence of FL, dynamic hyperinflation appears as the main determinant of exercise performance and the magnitude of resting IC, a well recognized marker of DH, the best clinical predictor. In absence of FL, airway obstruction probably plays a key role in limiting exercise capacity, and FEV<sub>1</sub> and FVC, useful indices of these abnormalities, represented here by the FEV<sub>1</sub>/FVC ratio are the best predictors.

In our patients, the  $P_{a,O_2}$  was, on average, significantly lower, and the  $P_{a,CO_2}$  significantly higher in the FL than in the non-FL patients. Fifty-nine percent of the FL patients were hypercapnic in comparison with only 22% of the non-FL patients. IC and FVC were selected as significant contributors to  $P_{a,CO_2}$  in the whole group, but IC was the sole predictor in FL patients, suggesting that the presence of hypercapnia in this group is related to the degree of DH. The

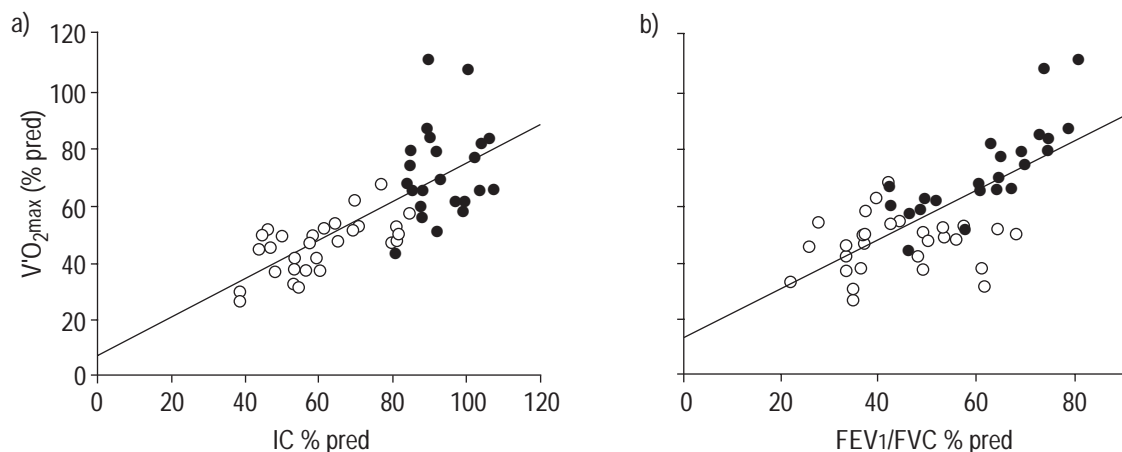


Fig. 3. – Relationship of maximal oxygen uptake  $\dot{V}O_{2,max}$  to a) inspiratory capacity IC b) and forced expiratory volume in one second (FEV<sub>1</sub>)/forced vital capacity (FVC) in chronic obstructive pulmonary disease patients without (non-FL; ●) and with (FL; ○) tidal expiratory flow limitation at rest.  $r=0.75$ ;  $p<0.0001$  and  $r=0.71$ ;  $p<0.0001$  for a) respectively and b) respectively.

coefficients of determination of these functions (equations 7–9) were, however, low. This was in part due to the presence of five hypercapnic non-FL patients (range: 6.12–6.5 kPa), in whom the IC was within normal limits. It should be noted, however, that we did not measure other important covariates, such as dead space ( $V_D/V_T$ ). Previous studies have shown that in patients with mild to moderate COPD, hypercapnia is not infrequent [22]. It should be pointed out that the above five patients were neither obese nor had history of obstructive sleep apnoeas.

There was no significant difference in breathing pattern between the non-FL and FL patients. However, in the hypercapnic FL patients,  $V_T$  and  $t_I$  were significantly lower than in the non-hypercapnic FL patients. Similar differences in the pattern of breathing have been previously reported by SORLI *et al.* [23] between hypercapnic and non-hypercapnic COPD patients, the hypercapnia being attributed to increased  $V_D/V_T$  ratio with concomitant reduction of alveolar ventilation.

### Clinical implications

The high prevalence of tidal FL at rest with concomitant DH in COPD patients, promotes increased inspiratory work due to intrinsic positive end expiratory pressure (PEEPi), impaired inspiratory muscle function, and adverse effects on haemodynamics [24]. Increased FRC due to dynamic hyperinflation is axiomatically associated with decreased IC. Because of tidal FL,  $V_{Tmax}$  (and hence maximal exercise) is closely related to resting IC [8]. This provides a reasonable mechanistic explanation for the close association between resting IC and exercise tolerance in FL patients. Assessment of IC has already been shown to provide useful information on the effects of surgical treatment [25] and bronchodilators [26] on hyperinflation in COPD patients. Recently, it has also been shown that in COPD patients the increase in IC after anticholinergic therapy best reflected the improvements in exercise endurance and dyspnoea [27].

Assessment of FL may also provide a useful guide for rehabilitation in COPD patients: in patients without FL, rehabilitation based on exercise should be particularly beneficial, while in patients with FL administration of bronchodilators and inspiratory muscle training should be preferable in order to decrease the prevailing hyperinflation [26, 27] and to increase the working capacity of the inspiratory muscles [28, 29].

In conclusion, the present results show that in chronic obstructive pulmonary disease patients there is a close association of exercise tolerance to resting inspiratory capacity in flow limited patients. A reduction in inspiratory capacity, reflecting dynamic hyperinflation and increased intrinsic positive end expiratory pressure, also plays a role in determining hypercapnia in the same group of flow limited patients.

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