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Original Article

Prognostic relevance of dynamic hyperinflation during cardiopulmonary exercise testing in adult patients with cystic fibrosis

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Abstract

Background: Dynamic hyperinflation during cardiopulmonary exercise testing (CPET) in cystic fibrosis (CF) has not been well characterized, and little is known regarding its prevalence, risk factors and clinical associations.
Methods: CPET data from 109 adult patients with mild-to-moderate CF was used, in this retrospective study, to characterize and determine the prevalence of dynamic hyperinflation, and evaluate its relationship with lung function and exercise tolerance, clinical symptoms, and prognosis over a two-year period.
Results: 58% of patients responded to CPET with dynamic hyperinflation. These patients had significantly lower lung function (FEV_1 66 ± 19 versus 79 ± 18%pred., $p < 0.01$) and exercise tolerance (peak oxygen uptake 28.7 ± 8.1 versus 32.9 ± 6.1 $mL \cdot kg^{-1} \cdot min^{-1}$, $p = 0.02$), and experienced greater shortness of breath at peak exercise (7 ± 3 versus 5 ± 2 Modified Borg scale, $p = 0.04$) compared to patients who responded without dynamic hyperinflation. Significant relationships between FEV_1, FVC, FEV_1/FVC, FEF_{25-75} and dynamic hyperinflation were shown ($p < 0.01$; $p = 0.02$; $p < 0.01$; $p < 0.01$, respectively). Dynamic hyperinflation was also significantly correlated with oxygen uptake, tidal volume, work-rate and shortness of breath at peak exercise ($p = 0.03$; $p < 0.01$; $p < 0.01$; $p = 0.04$, respectively). Responding to CPET with or without dynamic hyperinflation did not significantly predict FEV_1 at 2 years beyond the FEV_1 at baseline ($p = 0.06$), or increase the likelihood of experiencing a pulmonary exacerbation over a two-year period ($p = 0.24$).
Conclusion: The prevalence of dynamic hyperinflation during CPET in adult patients with mild-to-moderate CF is high, and is associated with reduced lung function and exercise tolerance, and increased exertional dyspnea. However, identifying dynamic hyperinflation during CPET had limited prognostic value for lung function and pulmonary exacerbation.

Keywords: Cardiopulmonary exercise testing; Dynamic hyperinflation; Prevalence; Clinical utility; Prognosis

1. Introduction

The assessment of exercise tolerance, through cardiopulmonary exercise testing (CPET), is used in clinical practice to provide an objective measure of exercise capacity, monitor disease progression and/or response to interventions, predict prognosis, and identify the mechanisms that limit exercise [1]. Exercise intolerance, from a clinical perspective, can be considered a patient's inability to complete a physical task that could be achieved, ordinarily, by a healthy individual. In cystic fibrosis (CF) exercise tolerance is compromised [2,3], and mechanisms for this can be multiple [4]. These include abnormal oxygen delivery and gas exchange, [5] musculoskeletal abnormalities

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[6,7], and deconditioning [4]. In chronic obstructive pulmonary disease (COPD), dynamic hyperinflation of the lung is also considered a major limitation to exercise, through ventilatory constraints [8], and has been reported to cause characteristic symptoms such as exertional dyspnea [9]. However, the study of dynamic hyperinflation and its clinical utility in CF is limited, and patient numbers to date have been small. Furthermore, given the differences in demographics, clinical characteristics, and pathophysiology, extrapolation of data from COPD to CF is not appropriate [10].

Previous studies investigating dynamic hyperinflation in CF, measured changes in end-expiratory lung volume (EELV) by measuring inspiratory capacity (IC) during different stages of graded exercise. Alison et al. evaluated changes in EELV during leg and arm exercise in 22 patients with CF; [11] while Regnis and colleagues (1991) and (1996) studied changes in EELV during CPET in 22 [12] and 8 [13] CF patients, respectively. In the study by Regnis et al. it was reported that patients who demonstrated an increase of 100 mL or greater in EELV had significantly lower lung function, and exercise tolerance than patients whose EELV decreased by 100 mL or more [12]. Larger studies, however, are needed to confirm these findings, and further investigate the clinical utility of assessing dynamic hyperinflation during CPET in this patient group.

The objective of the present study was to investigate dynamic hyperinflation during CPET in a large cohort of adult patients with mild-to-moderate CF, to better understand which patients are at greater risk for dynamic hyperinflation, and to determine whether dynamic hyperinflation is a predictor of clinical outcomes. Specifically, our aims were to characterize and determine the prevalence of dynamic hyperinflation, and to evaluate its relationship with lung function, exercise tolerance and clinical symptoms. A secondary aim was to determine if dynamic hyperinflation during CPET could predict lung function at two years, and whether dynamic hyperinflation was associated with subsequent pulmonary exacerbations over a two-year period.

2. Methods

This is a retrospective study of 109 adults with mild-to-moderate CF who were followed at the Adult CF Program at St. Michael's Hospital (Toronto, CANADA) between 2002 and 2008. As part of routine care, CF patients who have a forced expiratory volume in one second (FEV_1) greater than 30% predicted and who are clinically stable undergo annual CPET. Patients with a FEV_1 less than 30% predicted, not clinically stable or post-transplant are excluded from exercise testing. Baseline spirometry and patient clinical parameters were taken at the time of CPET and obtained from the Toronto CF database. These included age, gender, pancreatic status (insufficiency versus sufficiency), the presence of CF-related diabetes, nutritional status as measured by body mass index, and the presence of *Pseudomonas aeruginosa* or *Burkholderia cepacia* complex. The number of hospitalizations for pulmonary exacerbations within the two years following their CPET was recorded. Patients provided written informed consent for their data to be included in the Toronto CF database and to be used for research purposes. Institutional research board ethics approval was given by St. Michael's Hospital (IRB# 04-076).

2.1. Lung volume and function

Total lung capacity was calculated from the mean functional residual capacity, determined by body plethysmography (Vmax Spectra; Viasys, Loma Linda, CA, USA), plus the highest measured IC from three acceptable and reproducible tests. Standard spirometry [14] was performed by the patient using a mass-flow sensor spirometer (Vmax Spectra; Viasys, Loma Linda, CA, USA) for the measurement of forced lung function maneuvers. The Canadian predicted normal values for spirometry of Gutierrez et al. were used [15]. Maximal voluntary ventilation (MVV) was estimated using the formula $FEV_1 \times 40$.

2.2. Cardiopulmonary exercise testing

Patients performed CPET on an electronically braked cycle ergometer (Ergometrics 800; Jaeger, Wuerzburg, Germany) using a graded protocol. Starting at 0 $W \cdot min^{-1}$ the work-rate was increased progressively every minute by 10 or 15 $W \cdot min^{-1}$. The work-rate was ramped with the goal of individuals reaching symptom limitation within 10–12 min. Verbal encouragement during exercise testing was given to all patients. Breath-by-breath pulmonary gas measurements (oxygen uptake and carbon dioxide production), as well as minute ventilation were collected continuously during exercise and recorded by a metabolic gas analyser (Vmax Encore; Viasys, Loma Linda, CA, USA). Flow volume measurements (i.e., IC and EELV) and shortness of breath and muscular leg fatigue scores, measured by a modified Borg scale [16], were recorded at rest and every 2 min of the exercise test.

2.3. The IC maneuver

The IC maneuver was measured by spirometry (Vmax Encore; Viasys, Loma Linda, CA, USA) and was performed by patients at rest and every 2 min of the CPET. The patients were instructed to inspire, at the end of normal exhalation, until their lungs were full. The maneuver ended with unforced exhalation. Patients received verbal encouragement during the IC maneuver to inspire maximally. The IC represents the volume inhaled from the end of normal exhalation to maximal inhalation (i.e., total lung capacity). EELV was calculated by subtracting the IC from the total lung capacity. It is assumed that total lung capacity remains unchanged during exercise which is supported by literature in health [17] and COPD [18]. The change in the IC from rest to peak exercise was calculated ($IC\Delta$). Patients were categorized into two groups, using established cut-off criteria [12], those with evidence of dynamic hyperinflation (a *decrease* in $IC\Delta \geq 100$ mL) and those without evidence of dynamic hyperinflation (an *increase* in $IC\Delta \geq 100$ mL). Individuals with no change or a decrease or increase in the $IC\Delta \leq 99$ mL were not included in the between group analyses.

2.4. Statistical analysis

The independent student's *t*-test was used to investigate differences in continuous variables between groups at rest and during CPET. Differences in categorical variables were evaluated using a Chi-square (X^2) test. To determine whether responding to exercise testing with or without dynamic hyperinflation can predict FEV_1 at 2 years (FEV_{1y2}) beyond the FEV_1 at baseline, linear regression was used and a partial F test was employed to compare the following two models:

$$FEV_{1y2} = \beta_0 + \beta_1 FEV_1 + \varepsilon \quad (1)$$

$$FEV_{1y2} = \beta_0 + \beta_1 FEV_1 + \beta_2 IC\Delta + \varepsilon \quad (2)$$

where ε represents the error term, β_0 is the intercept of the line, β_1 is the coefficient of the FEV_1 and β_2 is the coefficient of the ICΔ. The ICΔ was coded 0 if the patient responded to CPET with dynamic hyperinflation and 1 if the patient responded without dynamic hyperinflation. A Fisher's Exact Test was used to assess the frequency distribution of pulmonary exacerbations over 2 years post CPET between the two groups.

Simple linear regression was used to explore relationships between lung function, CPET parameters and the ICΔ and the IC Δ expressed as a percentage change from rest to peak exercise (IC Δ%). Multiple regression analysis was performed to determine which lung function and exercise parameters best predict exercise tolerance (i.e., peak oxygen uptake). Statistical significance was set a priori at $p < 0.05$ for all statistical analyses. All data were analyzed using the Statistical Package for the Social Sciences (SPSS; version 11.0, Chicago, IL).

3. Results

3.1. Characteristics of the study patients and cardiopulmonary exercise testing parameters

Characteristics of the overall study population (n = 109), and the dynamic (n = 63) and non-dynamic (n = 25) hyperinflation groups are presented in Tables 1 and 2. The mean age of the study patients was 30.2 ± 9.5 years, and 64% were male. The overall study population included individuals with a mean FEV_1 of 72 ± 18% predicted, with a range in FEV_1 of 34–115% predicted. Fifty-eight percent (63/109) of patients demonstrated evidence of dynamic hyperinflation during CPET. There were no significant differences in the frequency distribution of patients with CF-related diabetes, pancreatic insufficiency/sufficiency, and *P. aeruginosa* or *B. cepacia* complex between the dynamic hyperinflation and non-dynamic hyperinflation groups. However, the frequency distribution of males in the non-dynamic hyperinflation group was significantly greater than females ($p < 0.05$). No significant differences were shown for age and body mass index between the dynamic hyperinflation and non-dynamic hyperinflation groups, or for tidal volume, oxygen saturation, shortness of breath and muscular leg fatigue at rest. However, between groups, patients with evidence of dynamic hyperinflation demonstrated a significant reduction in FEV_1 ($p < 0.01$), forced vital capacity (FVC) ($p = 0.04$), forced expiratory volume in one second and forced vital capacity ratio (FEV_1/FVC) ($p < 0.01$), forced expiratory flow between 25 and 75% of the forced vital capacity ($FEF_{25–75}$) ($p < 0.01$) and estimated MVV ($p < 0.01$).

Table 1
Characteristics of the study group.

	All (n = 109)	Dynamic hyperinflation (n = 63)	Non-dynamic hyperinflation (n = 25)
Age (y)	30.2 ± 9.5	31.3 ± 10.2	28.6 ± 7.2
BMI ($kg \cdot m^2$)	22.9 ± 2.8	23.1 ± 3.4	22.9 ± 2.9
% Male	64	59	88 *
% with CFRD	29	27	16
% with PI	73	73	64
% with *Pseudomonas aeruginosa*	68	70	68
% with *Burkholderia cepacia*	16	18	8

Values are means ± SD.
BMI, body mass index; CFRD, cystic fibrosis related diabetes; PI, pancreatic insufficiency.
* $p < 0.05$, between the dynamic hyperinflation and non-dynamic hyperinflation groups.

CPET data in the dynamic and non-dynamic hyperinflation groups are presented in Table 3. Patients with evidence of dynamic hyperinflation had significantly lower oxygen uptake ($p = 0.02$), minute ventilation ($p = 0.04$), tidal volume ($p < 0.01$) and work-rate ($p < 0.01$) at peak exercise, and experienced greater shortness of breath ($p = 0.04$) and minute ventilation to estimated MVV ratio to those without evidence of dynamic hyperinflation ($p = 0.02$). No significant differences were noted at peak exercise for oxygen saturation, heart-rate and muscular leg fatigue between groups. At the gas exchange threshold, the dynamic hyperinflation group had a significantly greater ventilatory equivalent for carbon dioxide ($p < 0.01$) than patients who did not respond to exercise with dynamic hyperinflation.

Table 2
Physiological characteristics of the study group.

	All (n = 109)	Dynamic hyperinflation (n = 63)	Non-dynamic hyperinflation (n = 25)
FEV_1 (%pred.)	72 ± 18	66 ± 19	79 ± 18**
FVC (%pred.)	90 ± 18	87 ± 18	96 ± 15*
FEV_1/FVC (%pred.)	65 ± 11	62 ± 11	69 ± 9**
$FEF_{25–75}$ (%pred.)	37 ± 21	31 ± 19	47 ± 23**
MVV ($L \cdot min^{-1}$)	105.1 ± 36.4	97.8 ± 33.9	126.6 ± 32.6**
V_{Trest} (L)	0.88 ± 0.59	0.96 ± 0.63	0.72 ± 0.47
SpO_{2rest} (%)	96 ± 2	96 ± 1	97 ± 1
$BorgSOB_{rest}$	0 ± 1	1 ± 1	0 ± 1
$BorgLEG_{rest}$	0 ± 1	0 ± 1	0 ± 1

Values are means ± SD.
FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEV_1/FVC, forced expiratory volume in one second and forced vital capacity ratio; $FEF_{25–75}$, forced expiratory flow between 25 and 75% of the forced vital capacity; MVV, estimated maximal voluntary ventilation; V_{Trest}, tidal volume at rest; SpO_{2rest}, oxygen saturation at rest; $BorgSOB_{rest}$, Borg shortness of breath score at rest. $BorgLEG_{rest}$, Borg muscular leg fatigue at rest.
*$p < 0.05$, **$p < 0.01$ between the dynamic hyperinflation and non-dynamic hyperinflation groups.

Table 3
Cardiopulmonary exercise testing parameters.

	Dynamic hyperinflation (n = 63)	Non-dynamic hyperinflation (n = 25)
$\dot{V}O_{2\ peak}$ (mL·kg^{-1}·min^{-1})	28.7 ± 8.1	32.9 ± 6.1 *
$\dot{V}_{E\ peak}$ (L·min^{-1})	72.4 ± 20.5	83.4 ± 29.7 *
HR_{peak} (b·min^{-1})	176 ± 14	173 ± 16
WR_{peak} (W·min^{-1})	140 ± 49	177 ± 53 **
SpO_{2peak} (%)	93 ± 3	93 ± 3
$BorgSOB_{peak}$	7 ± 3	5 ± 2 *
$BorgLEG_{peak}$	7 ± 2	8 ± 3
$\dot{V}_E/\dot{V}CO_{2GET}$	33.2 ± 4.5	29.8 ± 3.9 **
$\dot{V}_{E\ peak}$/MVV	0.79 ± 0.22	0.67 ± 0.18 *
$V_{T\ peak}$ (L)	1.73 ± 0.56	2.20 ± 0.57 **
ICΔ (L)	−0.44 ± 0.26	+0.40 ± 0.28 **
EELVΔ (TLC-IC) (L)	+0.44 ± 0.26	−0.40 ± 0.28 **

Values are means ± SD.
$\dot{V}O_{2\ peak}$, oxygen uptake at peak exercise; $\dot{V}_{E\ peak}$, minute ventilation at peak exercise; HR_{peak}, heart-rate at peak exercise; WR_{peak}, work-rate at peak exercise; SpO_{2peak}, oxygen saturation at peak exercise; $BorgSOB_{peak}$, Borg shortness of breath score at peak exercise; $BorgLEG_{peak}$, Borg muscular leg fatigue at peak exercise; $\dot{V}_E/\dot{V}CO_{2GET}$, ventilatory equivalent for carbon dioxide at the gas exchange threshold; $\dot{V}_{E\ peak}$/MVV, minute ventilation at peak exercise and estimated maximal voluntary ventilation relationship; V_{Tpeak}, tidal volume at peak exercise; ICΔ, inspiratory capacity delta from rest to peak exercise; EELVΔ, end-expiratory lung volume delta from rest to peak exercise.
* $p < 0.05$.
** $p < 0.01$.

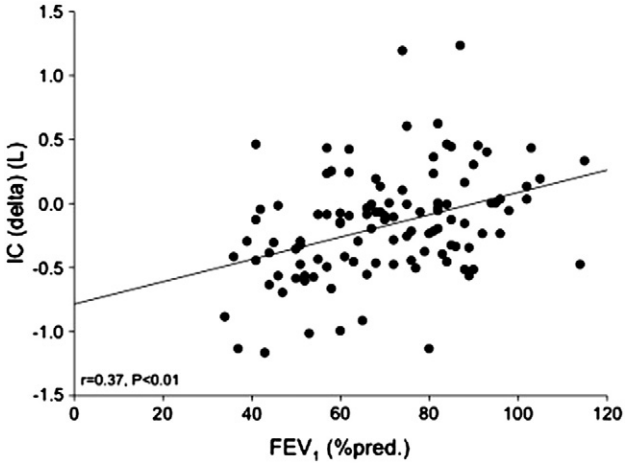

Fig. 1. Relationship between FEV_1 (%pred.) and IC(Δ) during CPET (r = 0.37, $p < 0.01$; n = 109).

Simple linear regression analysis between lung function, CPET parameters and the ICΔ and ICΔ% are presented in Table 4. Lung function parameters, FEV_1 (Fig. 1), FVC, FEV_1/FVC (Fig. 2), $FEF_{25–75}$ (Fig. 3) and estimated MVV were all significant predictors of the ICΔ ($p < 0.01$; $p = 0.02$; $p < 0.01$; $p < 0.01$; $p < 0.01$, respectively). CPET parameters at peak exercise, oxygen uptake (Fig. 4), tidal volume, work-rate and shortness of breath were also significant predictors of the ICΔ ($p = 0.03$; $p < 0.01$; $p < 0.01$; $p = 0.04$, respectively). Minute ventilation at peak exercise was not a significant predictor of the ICΔ ($p = 0.07$). When expressed as a percentage change from rest to peak exercise the ICΔ% was significantly predicted from the FEV_1, FVC, FEV_1/FVC, $FEF_{25–75}$ and estimated MVV ($p < 0.01$). The ICΔ% was also significantly predicted from the oxygen uptake, minute ventilation, tidal volume and work-rate at peak exercise ($p = 0.01$; $p = 0.01$; $p < 0.01$; $p < 0.01$, respectively). Shortness of breath at peak exercise did not significantly predict the ICΔ% ($p = 0.08$).

A multiple linear regression analysis of the lung function and CPET parameters showed that the strongest predictors of peak oxygen uptake (exercise tolerance) were FEV_1, FEV_1/FVC and either the ICΔ or ICΔ%, respectively. These parameters combined in a multiple linear regression model explain 31% of the variance between the independent variables and peak oxygen uptake ($r^2 = 0.31$, $p < 0.01$).

3.2. Prognostic value of exercise induced dynamic hyperinflation

Whether patients responded to CPET with or without dynamic hyperinflation did not explain any significant additional variance of the FEV_1 at two years, beyond the FEV_1 at baseline. The difference between the R^2 of the two models was 0.01, which was not clinically or statistically significant ($p = 0.06$). Furthermore, the frequency distribution of pulmonary exacerbations over two years following exercise testing was not significantly different between the two groups ($p = 0.24$).

4. Discussion

Our data show that dynamic hyperinflation is common in adult patients with mild-to-moderate CF. Over half of our patients (58%) responded to exercise with dynamic hyperinflation. These patients

Table 4
Simple linear regression between lung function, CPET parameters and the ICΔ and ICΔ%.

	FEV_1 (%pred.)	FVC (%pred.)	FEV_1/FVC (%pred.)	$FEF_{25–75}$ (%pred.)	MVV (L·min^{-1})	VO_{2peak} (mL·kg^{1}·min^{-1})	V_{Epeak} (L·min^{-1})	V_{Tpeak} (L)	WR_{peak} (W)	SOB_{peak} (Borg)
ICΔ (L)	0.37 **	0.22 *	0.37 **	0.35 **	0.35 **	0.19 *	0.17	0.30 **	0.25 **	0.28 *
ICΔ%	0.44 **	0.30 **	0.41 **	0.39 **	0.43 **	0.24 *	0.22 *	0.39 **	0.30 **	0.26

Values are *r*. FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEV_1/FVC, forced expiratory volume in one second and forced vital capacity ratio; $FEF_{25–75}$, forced expiratory flow between 25 and 75% of the forced vital capacity; MVV, estimated maximal voluntary ventilation; $\dot{V}O_{2\ peak}$, oxygen uptake at peak exercise; $\dot{V}_{E\ peak}$, minute ventilation at peak exercise; V_{Tpeak}, tidal volume at peak exercise; WR_{peak}, work-rate at peak exercise; $BorgSOB_{peak}$, Borg shortness of breath score at peak exercise; ICΔ, change in inspiratory capacity from rest to peak exercise; ICΔ%, percentage change in inspiratory capacity from rest to peak exercise.
* $p < 0.05$.
** $p < 0.01$.

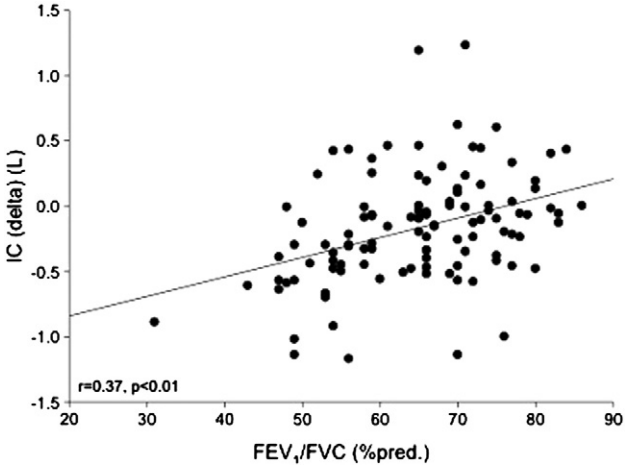

Fig. 2. Relationship between FEV_1/FVC (%pred.) and IC(Δ) during CPET (r = 0.37, p < 0.01; n = 109).

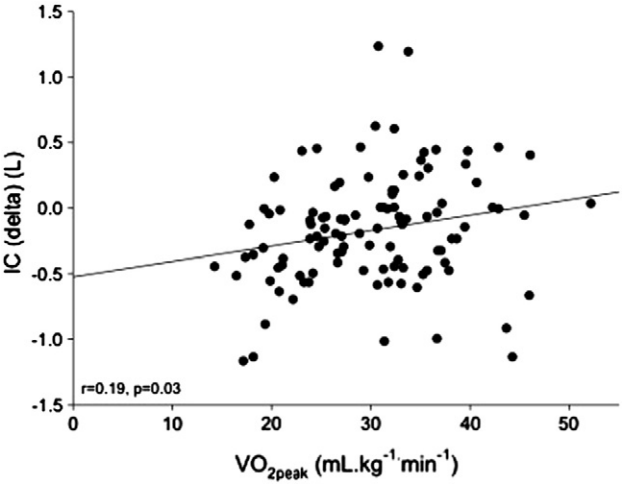

Fig. 4. Relationship between VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$) and IC(Δ) during CPET (r = 0.19, p = 0.03; n = 109).

had significantly lower lung function than patients who exercised without evidence of dynamic hyperinflation, confirming the findings of an earlier, smaller study [12]. Patients with dynamic hyperinflation during CPET also had lower exercise tolerance and greater breathlessness at peak exercise than those without dynamic hyperinflation. The identification of dynamic hyperinflation, despite identifying patients with more severe lung disease, did not predict the two-year clinical outcomes studied here. Specifically, whether the patient responded to CPET with or without dynamic hyperinflation did not predict lung function at two years beyond the FEV_1 at baseline, or whether the patient would experience a pulmonary exacerbation over a two-year period.

One strength of the present study is the large sample size of our patient group, which adds confidence to our findings, and allowed us to create a robust clinical picture of dynamic hyperinflation in mild-to-moderate CF. Our study included a broad range of lung disease severity (FEV_1 34–115%pred.), and included patients with a variety of CF co-morbidities such as diabetes, pancreatic insufficiency, and various microbiology. Therefore, from an epidemiological perspective, the present study has characterized dynamic hyperinflation in a wide spectrum of CF disease. We did not include patients with severe CF in this study, as CPET is not routinely performed in our clinic with individuals with an FEV_1 less than 30% predicted. However, given the observed association of dynamic hyperinflation with reduced FEV_1, we would expect a greater incidence of dynamic hyperinflation during exercise in patients with more severe CF (i.e., FEV_1 <30%pred.). This would also be compatible with the reported association between exercise dynamic hyperinflation and severity of COPD [19].

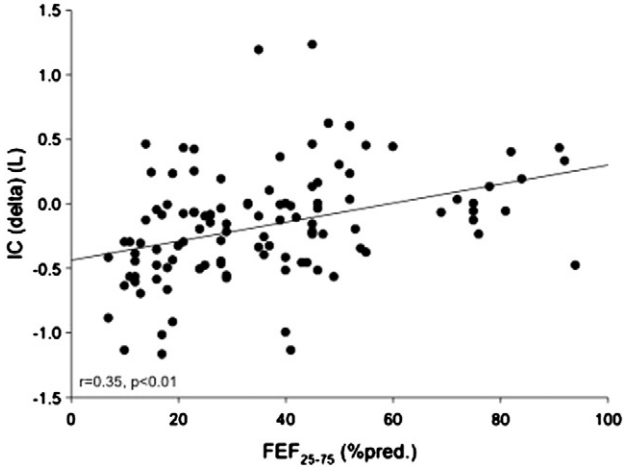

Fig. 3. Relationship between $FEF_{25–75}$ (%pred.) and IC(Δ) during CPET (r = 0.35, p < 0.01; n = 109).

At peak exercise, perceived dyspnea was significantly greater in the dynamic hyperinflation group. The increased breathlessness likely contributed to the earlier termination of exercise, with significantly lower work-rates and peak oxygen uptake observed in the dynamic hyperinflation group. Hyperinflation of the lung may have also compromised minute ventilation and tidal volume at peak exercise, and minute ventilation at peak exercise and estimated MVV ratio in these patients. At lower exercise intensities, patients in the dynamic hyperinflation group had to work at significantly greater ventilatory equivalents for carbon dioxide at the gas exchange threshold. This may have also resulted in the greater perception of exertional dyspnea in the dynamic hyperinflation group. There was, however, a greater distribution of females in the dynamic hyperinflation group. This may have possibly affected the exercise testing parameters between the two groups presented in Table 3. An analysis to control for gender would, however, not be appropriate due to the difference between the number of females in the dynamic hyperinflation (n = 26) and non-dynamic hyperinflation (n = 3) groups. At peak exercise, oxygen uptake, tidal volume and work-rate were all significant predictors of the ICΔ and ICΔ%. However, minute ventilation at peak exercise was a significant predictor of the ICΔ% but not the ICΔ; and shortness of breath was a significant predictor of ICΔ but not the ICΔ%.

The multiple regression analysis showed that the strongest model for predicting peak oxygen uptake included FEV_1,

FEV_1/FVC and either the ICΔ or ICΔ%. However, the model showed that the ICΔ or ICΔ% was the weakest dependent variable in the model for predicting peak oxygen uptake. Given that peak oxygen uptake is a strong prognostic indicator of survival in CF [20], it is of interest that our data suggest that the dynamic hyperinflation is associated with a reduction in exercise tolerance in patients with mild-to-moderate CF.

Disease co-morbidities in CF such as pancreatic insufficiency, nutritional status (body mass index), the presence of CF-related diabetes, and the presence of *P. aeruginosa* or *B. cepacia* complex were not significantly different between the dynamic and non-dynamic hyperinflation groups, thus, making dynamic hyperinflation in mild-to-moderate CF difficult to predict. Furthermore, the FEV_1 range of the dynamic (34–114%pred.) and non-dynamic (41–115%pred.) hyperinflation groups show considerable overlap. In our study, one individual with an FEV_1 of 114% predicted and had an ICΔ of −0.48 L, while another patient with an FEV_1 of 41% predicted had an ICΔ of +0.46 L. Our data showed that the correlation between the FEV_1 and ICΔ, although significant, is weak. The FEV_1 only explains 14% of the variance of the ICΔ, and is shown by considerable spread around the regression line (Fig. 1). This relationship still holds true when the ICΔ is expressed as a percentage change from rest to peak exercise. The FEV_1 only explains 19% of the variance of the ICΔ%. Although elastic recoil of the lung, which is important to maintain ventilation during progressive exercise, is relevant to the maximum expiratory flow performance in individuals with CF, airway obstruction is a much greater determinant of the FEV_1 in these patients [21]. Whereas, the elastic recoil of the lung may be a greater determinant of dynamic hyperinflation during exercise in this patient group. Other lung function variables, FVC, FEV_1/FVC, $FEF_{25–75}$ and estimated MVV, were all significant predictors of the ICΔ and ICΔ%. Demonstrating that a reduction in these lung function variables is associated with greater dynamic hyperinflation (e.g., decrease in ICΔ or ICΔ%).

Although we have not demonstrated a prognostic role for CPET in this study, the identification of dynamic hyperinflation with exercise may help better understand exercise limitation in individual patients, may guide therapy for exertional breathlessness and may eventually be a useful therapeutic outcome measure for CF patients, as it has been shown in COPD [9,19,22,23]. The assessment of dynamic hyperinflation during CPET can refine and add to the patient's clinical profile by informing the clinician as to whether exercise capacity is limited by ventilatory mechanisms caused by progressive lung damage. This information can be used in the management of exertional dyspnea in CF, and consideration of bronchodilators or more aggressive chest physiotherapy may be beneficial in this setting to minimize bronchial obstruction, dynamic hyperinflation and exertional dyspnea. Clinically the management of exertional dyspnea is important as it causes discomfort during exercise, and may discourage individuals from taking part in physical activities. This has significant implications for patient prognosis in CF, as regular exercise participation has been shown to improve lung function, increase aerobic and anaerobic capacity, strengthen ventilatory muscles, and help airway sputum clearance [24–31]. Furthermore, increased levels of physical activity and peak oxygen uptake in CF are positively correlated to survival [20,32,33], and quality-of-life [34].

In COPD, bronchodilator use has been shown to have a significant and sustained reduction in air trapping at rest and during exercise compared to placebo, thus, allowing for greater tidal volume and, consequently, significant increases in exercise tolerance and reductions in perceptual dyspnea [35]. However, specific studies on bronchodilator use in the management of dynamic hyperinflation in CF are needed. Further work should also investigate the effects of pulmonary rehabilitation on dynamic hyperinflation. Indeed, studies in moderate-to-severe COPD have shown that reducing dynamic hyperinflation is associated with improvements in symptom limited peak oxygen uptake [35,36], constant work endurance time [37], peak tidal volume [35,37] and dyspnea [35,37,38], and a lower ventilatory demand for a given work-rate [39].

Dynamic hyperinflation is difficult to predict from disease co-morbidities in mild-to-moderate CF. Therefore, CPET is a useful tool to directly determine its presence. Our data show significant relationships between exercise induced dynamic hyperinflation and reduced lung function and exercise tolerance, and increased breathlessness during exercise. The identification of dynamic hyperinflation through CPET can identify subsets of patients who may benefit from more aggressive airway clearance treatments.

Conflict of interest

None of the authors have a conflict of interest to report.

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