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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.