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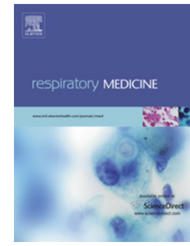

Dynamic hyperinflation after metronome-paced hyperventilation in COPD— A 2 year follow-up

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Summary
In contrast to the decline in FEV_1, the behavior of dynamic hyperinflation (DH) over time is unknown in patients with COPD. Metronome-paced hyperventilation (MPH) is a simple applicable surrogate for exercise to detect DH.
Objective: To evaluate changes in MPH-induced DH during two years follow-up in mild-to-severe COPD patients. Additionally, influence of smoking status on DH and the relation between DH and other lung function parameters were assessed.
Methods: Patients were recruited from a randomized controlled trial conducted in general practice. Measurements of lung function and DH were performed at baseline and after 12 and 24 months. DH was assessed by MPH with breathing frequency set at twice the baseline rate. Change in inspiratory capacity after MPH was used to reflect change in end-expiratory lung volume and therefore DH, presuming constant total lung capacity.
Results: During follow-up, 68 patients completed all measurements. DH increased by 0.23 $\pm$ 0.06 L ($p \leq 0.001$). No significant changes in FEV_1 %pred were seen. Smokers had lower FEV_1 and a more rapid decline than non-smokers. DH in smokers increased more over time compared to non-smokers. The amount of DH correlated positively with resting inspiratory capacity.
Conclusion: After two years, a significant increase in MPH-induced DH in COPD patients was demonstrated, which was not accompanied by a decline in FEV_1. It might be that DH is a sensitive measure to track consequences of changes in airflow obstruction.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive disease with major impact on individual patients' quality of life. According to ATS/ERS consensus statements, forced expiratory volume in 1 s (FEV_1) is used worldwide to diagnose and stage COPD.[1] FEV_1 and the rate of its decline are both predictors of mortality.[2,3] However, this parameter of disease progression fails to be a reliable predictor of patient centred outcomes like exercise tolerance, dyspnoea or health related quality of life.[4] In these outcomes, changes in operating lung volumes appear to play a more important role.[5] The origin of these changes in lung volumes is dynamic hyperinflation (DH), which is defined as a transient increase in end-expiratory lung volume (EELV) as a result of increasing ventilation with concomitant expiratory flow limitation. In contrast to the decline in FEV_1 over time, reflecting the progression in disease, the behavior of dynamic lung volumes over time is unknown.

One explanation for this lack of information might be that measurements of DH during exercise are quite time consuming. DH is commonly estimated by measuring change in inspiratory capacity (IC) during exercise, which reflects change in EELV. Gelb et al. compared DH after incremental cycle ergometry and metronome-paced hyperventilation (MPH) in COPD patients.[6] IC was measured at rest and immediately after 20 s MPH with breathing frequency set at twice the resting rate.[6] The change in IC after MPH was comparable to the change in IC after incremental cycle ergometry. Therefore, MPH is a simple applicable surrogate for exercise to detect DH. This offers a practical solution to study changes in DH over time. The purpose of the present study was to evaluate changes in MPH-induced DH during two years of follow-up in patients with COPD. In addition, the influence of smoking status on DH was explored and the relation between DH and other lung function parameters was assessed.

Methods

Subjects

Patients were recruited from a randomized controlled trial comparing three different modes of COPD disease management in general practice, conducted by the Department of Primary and Community Care of the Radboud University Nijmegen Medical Centre. Details of this trial are described at http://ClinicalTrials.gov, identifier NCT00128765.

Inclusion criteria were mild-to-severe COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification[1] and age $\geq$35 years. Exclusion criteria were GOLD stage IV, treatment by a chest physician and severe co-morbidity with reduced life expectancy. An additional exclusion criterion for the present study was the inability to visit our pulmonary function unit. This study was approved by the local medical ethics committee. All participants gave written informed consent.

Study design

In the present study, IC measurements and spirometry were the primary outcomes. Measurements were performed at baseline and after 12 and 24 months. Patients were free of exacerbation during testing. Prescriptions for pulmonary medication during the study were extracted from the general practitioners' medical records.

Spirometry and IC measurements

Patients were instructed to continue their usual medication, but to withhold short-acting β_2-agonists and/or anti-cholinergics for 6 and 8 h respectively and long-acting β_2-agonists and/or anti-cholinergics for 12 and 24 h respectively prior to testing. Pulmonary function was measured using a spirometer (Masterlab®, Jaeger, Würzburg, Germany) according to the guidelines of the ATS/ERS.[7] IC maneuvers were performed before and immediately after 20 s MPH with breathing frequency set at twice the current resting rate.[6] Patients were instructed to take a deep breath in after normal exhalation and encouraged to inspire maximally (to the total lung capacity (TLC)). During MPH, patients were encouraged to maintain a tidal volume (VT) equal to resting VT. Performance of the test was monitored by the real-time display of breathing volumes. Any inconsistency in the last breath preceding the IC was manually corrected to obtain a true EELV.[8]

Repeatability of the IC's has been tested in a subgroup. In 18 patients, the mean coefficients of variation of resting IC (IC_{rest}) and IC after MPH (IC_{MPH}) were $2.6 \pm 1.8\%$ and $3.3 \pm 3.1\%$ respectively.

Spirometry and IC maneuvers were repeated after administration of 80 µg ipratropium/400 µg salbutamol. If not stated otherwise, post-bronchodilation values are presented in the results.

Predicted IC_{rest} was calculated as predicted TLC minus the predicted functional residual capacity. Change in IC (ΔIC: $IC_{MPH} - IC_{rest}$) was used to reflect DH, presuming constant TLC.[9,10] Inspiratory reserve volume (IRV) was calculated as IC $-$ VT. Minute ventilation was calculated by breathing frequency $\times$ VT.

Statistical analysis

Data are expressed as mean $\pm$ se. Changes in lung function parameters and DH over time were analysed with general linear models for repeated measures (two-factor mixed design: time and group). Post hoc analyses were performed with Bonferroni (time) and Scheffé (group) corrections for multiple comparisons. Differences between pre- and post-bronchodilation values were tested with a two-way repeated measures design. Pearson correlation coefficient was used to evaluate associations between lung function parameters and DH. Statistical significance was set at $p < 0.05$. Data were analysed with SPSS, version 16.0 (SPSS, Chicago, IL).

Results

Study population

After initial screening, 124 patients were included in the current study. During two years of follow-up, 68 patients completed all measurements (Fig. 1). Reasons for drop-out