Can COPD Patients Who Hyperinflate During Daily Life Activities Be Identified by Laboratory Tests?

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For editorial comment see p. 177

Key Words

Dynamic hyperinflation · Metronome-paced tachypnea · Cardiopulmonary exercise testing

Abstract

Background: Identification of patients with chronic obstructive pulmonary disease (COPD) who develop dynamic hyperinflation (DH) during activities in daily life (ADL) is important, because of the association between DH and dyspnea and exercise limitation. **Objective:** We aimed to answer the question whether measurements of DH during metronome-paced tachypnea (MPT) or cardiopulmonary exercise testing (CPET) can be used to identify patients who develop DH during ADL. **Methods:** DH was measured by tracking changes in inspiratory capacity during CPET, MPT and ADL. Bland-Altman plots were used to evaluate agreement in DH between methods. With a receiver operating characteristic (ROC) analysis, the overall accuracy of MPT and CPET to identify patients who hyperinflate during ADL was assessed. **Results:** There are broad limits of agreement in DH between methods. ROC curve analyses showed good overall accuracy of both CPET and MPT to identify patients who hyperinflate during ADL. For CPET, area under the curve (AUC) = 0.956 (95% CI 0.903–1.009). For MPT, AUC = 0.840 (95% CI 0.699–0.981). Sensitivity and specificity to identify patients who hyperinflate during ADL with CPET were 96 and 83%, respectively, and with MPT, they were 89 and 77%, respectively.

Conclusion: Both CPET and MPT can serve as screening tools to identify patients who are susceptible to developing DH during ADL. In practice, MPT is the most simple and inexpensive surrogate. However, the sensitivity of MPT is not optimal. When DH does not occur during CPET, it is unlikely to occur during ADL.

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Introduction

Dynamic hyperinflation (DH) is an important phenomenon in chronic obstructive pulmonary disease (COPD). The increase in end-expiratory lung volume (EELV), which defines DH, is associated with dyspnea and exercise limitation [1, 2] which are both major complaints in COPD patients. Commonly, DH is assessed through symptom-limited or constant workload cardiopulmonary exercise testing (CPET). For study purposes, DH has also been assessed with metronome-paced tachypnea (MPT), which has been shown to be a simple, reliable alternative to CPET when it comes to comparing DH between groups [3, 4]. So far, it remains unknown whether the DH measured in laboratory settings, i.e. CPET and MPT, reflects the DH that occurs during activities in daily life (ADL) that cause dyspnea [5, 6]. From a clinical point of view, it is interesting to know whether a patient with COPD is predisposed to develop DH during ADL.

DH leads to an increase in operating lung volumes, which eventually stiffens the lungs and thus requires an increased effort to inhale. On the other hand, the diaphragm can generate less inspiratory pressure due to DH [7]. This might explain why, in COPD, DH is related to a decline of physical activity [8]. In clinical practice, however, it is not practical and often not possible to test if a patient develops DH in response to ADL.

In a previous study, we compared MPT-induced DH with CPET-induced DH [4]. It is likely that the amount of DH during ADL will be less than during CPET, as minute ventilation and breathing frequency are lower during submaximal activities [1], as seen in most ADL. The main objective of this study was to answer the question whether or not the measurement of DH during MPT or CPET can identify patients who develop DH during ADL.

Methods

Between November 2009 and March 2012, patients with mild to very severe COPD were recruited from the outpatient clinic of the Radboud University Nijmegen Medical Centre and the University Centre for Chronic Diseases in the Netherlands. Patients participated in a study on ADL.

The inclusion criteria were: a diagnosis of COPD and clinical stability (defined as no exacerbations for at least 6 weeks). Exclusion criteria were: other respiratory diseases, long-term oxygen therapy, recent participation in a pulmonary rehabilitation program and disorders which could possibly interfere with exercise testing (severe or unstable heart disease and neuromuscular or musculoskeletal disorders). The study was approved by the local medical research ethics committee and all patients gave their written informed consent.

Design

Measurements of DH were taken during CPET, MPT and ADL. During a visit to the hospital, pulmonary function was measured and CPET was performed according to the guidelines of the American Thoracic Society and the European Respiratory Society [9–11]. In addition, an MPT test [3] was performed. Measurements during ADL were scheduled at the patients' homes within 9 days of CPET.

Measurement of DH

The amount of DH during CPET, ADL and MPT was derived from measurements of inspiratory capacity (IC). Assuming constant total lung capacity (TLC) [12, 13], a decrease in IC reflects an increase in EELV and thus DH ($EELV = TLC - IC$). All patients were instructed on the performance of the IC maneuvers prior to each test. After four consistent end-expiratory levels, monitored by the real-time display of tidal breathing, the patient was encouraged to inspire to TLC and then to return to normal breathing. At the start of each test, baseline IC was measured by taking the mean of three acceptable maneuvers while the patient was at rest (IC_{rest}) [10]. Any deviation in end-expiratory level during the last breath

preceding IC was manually adjusted during analysis of the test, considering the three preceding end-expiratory levels. IC measurements taken at peak CPET, immediately after MPT and at the end of ADL were used to assess DH. DH was thus calculated as the difference between these IC measurements and IC_{rest} and expressed as the relative change in IC compared to IC_{rest} .

Cardiopulmonary Exercise Testing

All subjects performed a symptom-limited incremental CPET [9] using an electrically braked cycle ergometer (Masterlab, Jaeger®, Wurzburg, Germany). Patients breathed through a face mask connected to a metabolic system (Oxycon Pro, Jaeger, CareFusion GmbH, Hoechberg, Germany). Breath-by-breath measurements were used to analyze expired gases. Reference equations for the calculation of predicted maximal oxygen uptake (VO_{2pred}) were those produced by Wasserman et al. [14].

Activities in Daily Life

Patients selected their individual, most dyspnea-causing ADL. This had to be an activity that was performed regularly so as to ensure we were measuring a regularly occurring phenomenon. Measurements during the ADL were performed at the patients' homes using a portable version of the Oxycon breath-by-breath system (Oxycon Mobile, Jaeger, CareFusion GmbH) [6, 15]. This allowed patients to perform their ADL in the usual way. During the ADL, there was no 'peak' value, so the mean values of the last minute of steady-state ADL were used for analyses of oxygen consumption (VO_2), minute ventilation (VE) and breathing frequency.

Metronome-Paced Tachypnea

Subjects were seated, breathing through a mouthpiece connected to the spirometer (MasterScreen-PFT, Jaeger). In accordance with earlier studies [3, 4], MPT was performed at twice the resting breathing frequency. Patients were asked to breathe at this pace for 20 s, immediately followed by a maximal inspiratory maneuver (IC_{MPT}). The procedure was repeated after patients had returned to their resting breathing level. IC_{MPT} was calculated as the mean from two acceptable maneuvers, within 10% of each other (conform [10]).

Pulmonary Function Tests

Pulmonary function tests included spirometry [10], body plethysmography [11] and determination of carbon monoxide transfer factor (DL_{CO}) [16]. Reference equations for the calculation of predicted values were those produced by the European Community for Steel and Coal [17] and normal values for IC were calculated as predicted TLC minus predicted functional residual capacity (FRC). Severity of airflow obstruction was classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages [18].

Statistics

Measurements of DH with CPET, ADL and MPT (ΔIC_{CPET} , ΔIC_{ADL} and ΔIC_{MPT} , respectively) were compared to a repeated-measures ANOVA. Post hoc analyses, with a Bonferroni correction for multiple comparisons, were used for pairwise comparisons of the test results.

A cut-off value of a 10% decrease in IC was used as a definition of ADL-induced DH and to discriminate between hyperinflators and nonhyperinflators. This cut-off was based on the repeatability

coefficient of measurements of IC [4]. A relative change in IC (Δ IC) was chosen over an absolute change, because absolute Δ IC is related to the IC value at rest, whereas relative Δ IC shows a more homoscedastic distribution [4, 5, 19, 20].

A receiver operating characteristic (ROC) analysis assessed the overall accuracy of MPT and CPET to identify the patients who hyperinflated during ADL. The optimal cut-off points for MPT and CPET were determined and, subsequently, using their optimal cut-off, the sensitivity and specificity of MPT and CPET to identify hyperinflators and nonhyperinflators were assessed.

Values are expressed as mean $\pm$ SEM, unless stated otherwise. Statistical significance was set at $p < 0.05$.

Results

Characteristics

A total of 45 patients participated in this study. Their characteristics are described in table 1. The ADL they performed are described in table 2. Based on a decrease in IC during ADL that exceeds 10%, 28 patients (62%, $n = 4, 11, 10$ and 3 for GOLD stages I, II, III and IV, respectively) were classified as hyperinflators during ADL and 17 patients ($n = 9$ and 8 for GOLD stages I and II, respectively) as nonhyperinflators.

The requirements of ADL in terms of oxygen uptake and minute ventilation were less than those of CPET. VO_2 at end ADL was $75.2 \pm 19.3\%$ of the peak VO_2 ($p < 0.001$) and VE during ADL was $65.5 \pm 18.0\%$ of the peak VE ($p < 0.001$). VE was highest during CPET and lowest during MPT (58.0 ± 2.7 l/min vs. 35.8 ± 1.3 and 31.6 ± 1.7 during ADL and MPT respectively, $p < 0.05$). Breathing frequency was similar during CPET and MPT (32.8 ± 1.1 and 30.2 ± 1.1 respectively, $p > 0.05$), but lower during ADL (26.6 ± 1.0 , $p < 0.05$). Mean ADL-induced Δ IC was $-14.8 \pm 2.4\%$ of resting IC. At peak CPET and after MPT, similar amounts of DH were measured to during ADL ($p > 0.05$) ($\Delta\text{IC}_{\text{CPET}} -16.2 \pm 2.2\%$ and $\Delta\text{IC}_{\text{MPT}} -19.3 \pm 1.9\%$).

Inspection of the individual responses to the three methods, in terms of DH, showed large differences in some patients, leading to wide limits of agreement between the methods, as illustrated with Bland-Altman plots (fig. 1).

Because the methods did not show good agreement, we investigated whether individuals who hyperinflated during ADL (i.e. when IC decreased more than 10%) could be identified with CPET or MPT. To evaluate the overall accuracy of CPET and MPT to identify patients showing DH during ADL, we performed ROC curve analyses. Classification of patients as hyperinflators or nonhyperinflators during ADL was taken as the reference standard. The area under the curve (AUC) and optimal

Table 1. Patient characteristics

Patients (n = 45)	Mean $\pm$ SD
Age, years	64.5 $\pm$ 7.0
Weight, kg	76.9 $\pm$ 16.1
BMI, kg/m ²	26.1 $\pm$ 4.7
<i>Pulmonary function</i>	
GOLD stage, I/II/III/IV	13/19/10/3
FEV ₁ , liters (%pred)	1.86 $\pm$ 0.73 (65.3 $\pm$ 23.7)
FEV ₁ /FVC, %	45.8 $\pm$ 13.7
TLC, liters (%pred)	7.48 $\pm$ 1.49 (116.3 $\pm$ 23.4)
IC ^a , liters (%pred)	2.80 $\pm$ 0.69 (95.1 $\pm$ 19.6)
RV, liters (%pred)	3.56 $\pm$ 1.08 (152.7 $\pm$ 45.2)
RV/TLC, %	47.2 $\pm$ 9.2
DL _{CO} , %pred	59.1 $\pm$ 24.1
<i>Peak CPET variables</i>	
Workload, W	105 $\pm$ 43
VO ₂ , liters/min (%pred)	1.50 $\pm$ 0.48 (82 $\pm$ 21)
VE, liters/min	58.0 $\pm$ 17.6

DL_{CO} = Diffusion capacity of the lung for carbon monoxide; FEV₁ = postbronchodilator forced expiratory volume in 1 s; FVC = postbronchodilator forced vital capacity; RV = residual volume; VE = minute ventilation at peak workload; VO₂ = oxygen consumption at peak workload.

^a IC was calculated as the difference between TLC and intrathoracic gas volume.

Table 2. Individually chosen dyspnea-causing ADL

	Frequency male/female
Vacuum-cleaning	11/6
Sweeping floors	5/2
Digging in the garden	4/1
Window-cleaning	2/2
Carrying bags	2/1
Stair-climbing	2/1
Changing beds	0/1
Dish-washing	0/1
Hanging laundry	0/1
Cleaning cupboards	1/0
Walking the dog	1/0
Emptying the dishwasher	0/1

cut-offs for CPET and MPT-induced DH are shown in table 3, together with the sensitivity and specificity of the cut-offs. ROC curves are depicted in figure 2.

With CPET, 4 out of 45 patients were incorrectly classified; 3 nonhyperinflators during ADL ($\Delta\text{IC}_{\text{ADL}} < 10\%$

Fig. 1. Bland-Altman plots comparing the individual responses to MPT (a) and CPET (b) with ADL. The intersection of the Y and X axes represents the bias between the 2 methods. The dotted lines represent the upper and lower limits of agreement.

decrease) did show DH during CPET ($>11.5\%$ decrease in IC) and 1 hyperinflator during ADL ($\Delta\text{IC}_{\text{ADL}} >10\%$ decrease) did not show DH during CPET. With MPT, 7 patients were incorrectly identified; 4 nonhyperinflators during ADL did show DH during MPT ($>14.3\%$ decrease in IC) and 3 hyperinflators during ADL ($\Delta\text{IC}_{\text{ADL}} >10\%$ decrease) did not show DH during MPT.

Discussion

We addressed the issue of whether an assessment of DH with laboratory tests, such as CPET and MPT, can identify patients who develop DH during ADL. Our main

Fig. 2. ROC curve plotting the probability of a true positive (Y-axis, sensitivity) against the probability of a false positive (X-axis, 1-specificity) for all possible values of the cut-off point (reference cut-off: $\Delta\text{IC}_{\text{ADL}} < -10\%$). For CPET, AUC = 0.956 (95% CI 0.903–1.009). For MPT, AUC = 0.840 (95% CI 0.699–0.981). Dotted line: AUC = 0.5. Arrows indicate optimal cut-off values for $\Delta\text{IC}_{\text{CPET}}$ and $\Delta\text{IC}_{\text{MPT}}$.

Table 3. Results from ROC curve analyses with CPET and MPT used to discriminate hyperinflators and non-hyperinflators

	AUC $\pm$ SE	Optimal cut-off value	Sensitivity	Specificity
CPET	0.956 $\pm$ 0.027*	-11.5%	96%	83%
MPT	0.840 $\pm$ 0.072*	-14.3%	89%	77%

* $p < 0.001$. Cut-off value for reference standard (ADL-induced ΔIC) was -10% .

finding is that both CPET and MPT have good overall accuracy to be able to discriminate between patients who develop DH during ADL and those who do not.

Sensitivity and Specificity of CPET and MPT

The overall accuracy of CPET and MPT to discriminate between hyperinflators and nonhyperinflators was demonstrated by ROC curve analyses (fig. 2). With both methods, the AUC was high. The greater accuracy of CPET in distinguishing hyperinflators from nonhyperinflators resulted in higher sensitivity and specificity than with MPT. The high sensitivity of CPET (96%) indicates that when DH is assessed with CPET, the chances of missing patients who hyperinflate during ADL (i.e. a false-

negative result) is low. With MPT, the risk of false-negative results is higher (a sensitivity of 89%). Both CPET and MPT lack specificity, so there might be slight overdiagnosing with regard to ADL-induced DH.

Agreement between Methods Regarding DH

DH develops when ventilatory demand increases and (expiratory) airflow is obstructed, so it would seem reasonable to assume that when a patient develops DH in one instance, it would also develop under any other circumstances where there is an increase in ventilatory demand. Studies have shown that CPET and MPT induce equal amounts of DH, which makes MPT a good substitute for CPET for study purposes [3, 21]. On a group level, mean DH (Δ IC) during ADL was not different from mean DH during CPET and MPT, thus MPT-induced DH might also serve as a substitute for studying ADL-induced DH. However, although we did not find significant differences in mean DH, the Bland-Altman plots illustrated that the agreement between the methods is not enough to be able to conclude that the amount of DH measured during laboratory tests (CPET and MPT) always reflects the amount of ADL-induced DH in individual patients, i.e. for individual patient assessment, these methods cannot, in fact, be interchanged.

The Bland-Altman plots indicated that MPT, in particular, tends to induce more DH than ADL in some patients. Compared to CPET, MPT has also been shown to induce more DH in some patients [4]. The fact that, with MPT, a nonphysiological breathing rhythm is imposed on patients might have contributed to the larger amount of DH compared to CPET-induced and ADL-induced DH. Due to the use of a metronome, inspiratory and expiratory times are equal, whereas during CPET and ADL patients tend to prolong expiratory time in order to allow the lung to deflate. However, when MPT is used as a screening tool, the breathing mechanism is less important. The presence of MPT-induced DH indicates that a patient is susceptible to developing DH, whatever the circumstances.

The amount of ADL-induced DH found in our study is similar to that in earlier findings [5, 6]. Given the fact that the occurrence of DH is related to increased dyspnea, and decreased exercise capacity and level of physical activity, the fact that a large amount of DH does occur during regularly performed ADL is important [8, 22]. Even one third of the patients with mild COPD in our study showed DH during ADL. In a recent study, also including patients with mild COPD, we found that a lower level of physical activity in patients with COPD is related to hy-

perinflation during ADL, independently of the severity of airflow limitation [23]. Testing patient performance in ADL, however, is not practical in most clinical settings. Furthermore, many patients, especially those with mild-to-moderate COPD, are seen in general practices, where CPET is also difficult to perform. Here, MPT could serve as a simple screening tool to find out whether patients with COPD complaining of dyspnea and limitations during ADL are likely to develop DH.

Early detection of a patient's susceptibility to developing DH during ADL could allow early intervention to prevent or slow down further deterioration. So far, treatment options such as bronchodilation and exercise training with or without supplemental oxygen or heliox have been shown to have a positive effect on DH and consequently improve exercise capacity in patients [24, 25]. The effect of such treatments on ADL-induced DH specifically, and thus on performance of ADL as well as the effects on physical activity, still need to be confirmed.

In conclusion, both CPET and MPT can serve as a screening surrogate to identify patients who are susceptible to developing DH during ADL. In practice, MPT is the most simple and inexpensive surrogate. However, one has to keep in mind that sensitivity with MPT is not optimal and that, with a negative MPT result but symptoms and limitations in ADL, referral for CPET or, when possible, ADL testing would indeed be advisable. When DH does not occur during CPET, it is unlikely to occur during ADL.

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