Determining the Role of Dynamic Hyperinflation in Patients with Severe Chronic Obstructive Pulmonary Disease

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Key Words

Chronic obstructive pulmonary disease · Dynamic hyperinflation · Static hyperinflation · Inspiratory capacity · Exercise capacity

Abstract

Background: Dynamic hyperinflation due to increased respiratory frequency during exercise is associated with limitations in exercise capacity in patients with moderately severe chronic obstructive pulmonary disease (COPD). **Objectives:** The present study assessed whether the manually paced tachypnea (MPT) test, sitting at rest, induces dynamic hyperinflation correlating with exercise capacity in patients with very severe COPD. **Methods:** Dynamic hyperinflation was induced by the MPT test, using a breathing frequency of 40/min for 1 min. Dynamic hyperinflation was defined as a 'change' in inspiratory capacity (IC) before and directly after the MPT test. At baseline, static hyperinflation by body plethysmography was measured, as well as the 6-min walking test and spirometry. **Results:** We studied 74 patients with severe COPD (age 59 ± 9 years, FEV_1 $28 \pm 10\%$ predicted). All patients tolerated the MPT test well. It induced a significant decrease in IC: -0.65 ± 0.33 liters, $p < 0.001$, correlating with the 6-min walking distance ($\rho = -0.246$, $p = 0.034$). Static hyperinflation [IC/total lung capacity (TLC)] at baseline cor-

related stronger with the 6-min walking distance ($r = 0.582$, $p < 0.001$). Multiple regression analysis showed that IC/TLC, but not dynamic hyperinflation, was the only independent predictor of walking distance. **Conclusions:** In patients with very severe COPD, dynamic hyperinflation measurement by the MPT test is feasible and contributes less importantly to exercise performance than static hyperinflation.

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Introduction

Dyspnea and subsequent limitation of exercise capacity are the hallmark of clinical symptoms in patients with advanced stages of chronic obstructive pulmonary disease (COPD) [1]. These symptoms can either be caused by generic factors like anxiety, muscle weakness and general fitness, or may be due to direct disease-related mechanical impairments such as ventilation-perfusion mismatch or reduced lung elastic recoil and increased airway resistance leading to airflow obstruction and subsequent static and further dynamic hyperinflation [2–7].

Static hyperinflation is defined by an increase in end-expiratory lung volume (EELV) at rest being accompanied by a decreased inspiratory capacity (IC), the volume from end expiration to full inspiration. In patients with

Fig. 1. Schematic overview of the dynamic hyperinflation measurement. f = Frequency (40 times in 1 min).

COPD, the elevated resting EELV is caused by increased airway resistance, due to airway inflammation and airway wall thickening, and/or reduced lung elastic recoil due to alveolar destruction and emphysema. This so-called static hyperinflation correlates well with several important patient-reported outcomes, such as dyspnea, poor exercise performance, and reduced quality of life [3, 4]. Static hyperinflation is also an independent risk factor for mortality in subjects with COPD [8].

Dynamic hyperinflation is defined by a further increase in EELV associated with elevations in the respiratory rate, as occurs during exercise [4]. Young healthy subjects normally do not show hyperinflation during heavy exercise, but elderly subjects and particularly COPD patients, who have limitations in their expiratory flow rates, may show dynamic hyperinflation during exercise [7, 9, 10]. In severe COPD, this dynamic hyperinflation is superimposed on top of the already existing static hyperinflation, leading to a significantly reduced IC. This cumulative process of hyperinflation particularly takes place during exercise, as severely obstructed patients mainly increase their minute ventilation by increasing their breathing frequency (BF). The increases in respiratory frequency, and thus shortened expiratory time, associated with exertion in the setting of expiratory flow limitation results in progressively increasing hyperinflation, a vicious cycle leading to ventilatory limitation during exertion [11, 12].

Dynamic hyperinflation can be measured by performing IC maneuvers during a cycle ergometry test, but this test requires logistics, is time consuming and, most importantly, is uncomfortable for patients [13], especially for those with very advanced stages of COPD. An alternative method to investigate the pathophysiology of dynamic hyperinflation, the so-called manually or metronome-paced hyperventilation or tachypnea (MPT) test,

can be performed by applying a mandatory tachypnea for a short period while sitting at rest [14, 15]. This test is designed to mimic the dynamic respiratory pattern that occurs during exertion, without the inconvenience of putting the subject through a progressive exercise maneuver [12].

To date, the MPT test to investigate dynamic hyperinflation has been used predominantly in patients with mild-to-moderate COPD. The present study was designed to investigate the feasibility of the MPT test in patients with more severe COPD and to determine the relationship between dynamic hyperinflation and exercise capacity as assessed by the 6-min walking test (6MWT) as well as quality of life.

Methods

Study Design and Population

This was a single-center prospective cohort study in patients with severe COPD who were being evaluated for bronchoscopic lung volume reduction treatment at the Pulmonary Department of the University Medical Center Groningen, the Netherlands. All subjects were clinically stable, on optimal medication, had stopped smoking at least 6 months before the study and participated in one of our bronchoscopic lung volume reduction trials (clinical trial identifiers: NCT01421082; NCT01101958; NTR2876), which were approved by the local ethics committee, and all gave written informed consent.

Measurements

The subjects were instructed to use their regular medications, and an additional 400 µg of salbutamol was administered 15 min before the pulmonary function measurements. Spirometry, body plethysmography and diffusion capacity were measured using the Jaeger MasterScreen™ body plethysmograph (CareFusion, Germany) and were performed according to the ATS/ERS guidelines [16, 17] using the reference values from the European Community for Coal and Steel workers [18]. The 6MWT was done accord-

Table 1. Patient demographics and baseline characteristics

Variable	Absolute value
Patients, n	74
Male/female	25/49
Age, years	59±9
Smoking history, pack years	39±16
BMI	23.7±3.5
BODE index (n = 73)	5.4±1.5
FEV ₁ , l	0.77±0.32
FEV ₁ , % predicted	28±10
FVC, l	2.53±0.83
FVC, % predicted	75±7
FEV ₁ /FVC, %	31±7
RV, % predicted	233±49
TLC, % predicted	136±14
RV/TLC, %	62±9
R _{aw} , kPa/l/s	0.73±0.28
R _{aw} , % predicted	245±94
DL _{CO} , mmol/min/kPa (n = 63)	3.31±1.13
DL _{CO} , % predicted	38±12
6MWD, m	357±92
SGRQ, points (n = 73)	60.3±13.6
mMRC, points (n = 73)	2.8±0.8

Results are presented as means ± SD or numbers. FVC = Forced vital capacity; RV = residual volume; R_{aw} = airway resistance; DL_{CO} = carbon monoxide diffusion capacity single breath.

ing the ATS recommendations [19]. Quality of life and symptoms were measured using the St. George's Respiratory Questionnaire (SGRQ) [20, 21] and the modified Medical Research Council dyspnea scale (mMRC), respectively [22].

Measurement of Dynamic Hyperinflation

Dynamic hyperinflation was measured using a manually paced tachypnea test with the breath-by-breath method (Oxycon Pro™, CareFusion, Germany) during a 15-min protocol (see fig. 1 for a schematic overview of the MPT procedure). The subjects were given a demonstration to familiarize them with the pacing protocol. During tidal breathing, the subjects were asked to perform at least 3 slow maximum inspirations (IC maneuver) with a 1-min rest in-between each. The technician then coached the subjects to increase their BF to a rate of 40 times/minute for 1 min. The subjects were provided vocal feedback of their BF by the technician who used a computer screen displaying real-time registration of the BF. Immediately following 60 s of tachypnea, the subjects performed an IC maneuver and resumed resting tidal breathing. The MPT procedure was repeated at least 3 times with a 3-min period of resting tidal breathing between maneuvers. To obtain the baseline IC (IC_{baseline}), we calculated the mean value of 3 reproducible ICs (within 150 ml), and to establish the IC following tachypnea (IC_{MPT}), we calculated the mean value of the 2 highest and reproducible ICs (within 150 ml) [16]. Pulmonary function measurements, questionnaires, 6MWT and the MPT test were all performed on the same day.

Table 2. Dynamic hyperinflation measurement characteristics (n = 74)

Variables	Baseline	During MPT
BF, breaths/min	16 (8–27)	40 (36–43)*
VT, l	0.75 (0.4–1.4)	0.54 (0.34–1.53)*
VE, l/min	12 (6–24)	21 (13–61)*
FETCO ₂ , %	4.67 (2.70–7.19)	3.69 (1.92–6.14)*
Ti/Tot, %	34 (21–58)	40 (32–58)*

Results are presented as median (range). VT = Tidal volume; VE = ventilation; FETCO₂ = end-tidal carbon dioxide fraction; Ti/Tot = inspiration time/total time ratio. Difference between baseline and during MPT were measured with the paired t test; * p < 0.001.

Statistics

Data were expressed as means ± standard deviations (SD) unless otherwise indicated. A p value of <0.05 was considered statistically significant. To evaluate the variability in the repeated IC measurements (IC_{baseline} and IC_{MPT}), a variation coefficient was obtained by dividing the SD of the IC measurements by the individual mean. A difference of <10% was accepted. Static hyperinflation was expressed by IC_{baseline} in proportion to the total lung capacity (TLC) assessed by body plethysmography, thereby assuming that the TLC remains constant during the MPT test [10, 23]. Dynamic hyperinflation was calculated by the absolute change in IC (IC_{MPT} minus IC_{baseline}) as well as the difference (IC_{MPT}/TLC minus IC_{baseline}/TLC) [8]. The Wilcoxon signed-ranks test was used to compare IC_{baseline} and IC_{MPT} and to compare IC_{MPT}/TLC and IC_{baseline}/TLC. Pearson correlation was used to investigate univariate associations between static or dynamic hyperinflation and pulmonary function variables, exercise performance and quality of life when data were normally distributed. In case of non-normal distribution, Spearman correlation was used. Univariate associations with a p value <0.15 were entered in the multiple regression model. Highly correlating variables (correlation coefficient >0.75) were not entered in the model. The ΔIC and IC/TLC results from the literature shown in table 5 were either directly taken from the papers, or recalculated using the available input from these papers. IBM SPSS Statistics version 22 (IBM; Armonk, N.Y., USA) was used for all analyses.

Results

Patient Characteristics

Seventy-four clinically stable patients with severe COPD (FEV₁ 28 ± 10% predicted) were included between May 2010 and July 2012 (see table 1 for demographics and baseline characteristics).

All subjects tolerated the MPT test well and were able to maintain a manually paced rate of 40/min (range 36–43) for 1 min (see table 2 for dynamic hyperinflation measurement characteristics) during all attempts. The repeat-

Fig. 2. MPT test results of dynamic hyperinflation. Results presented in boxplots: median (horizontal line) and mean (+); whiskers: range. **a** IC at baseline and directly after the MPT test. **b** IC/TLC at baseline and directly after the MPT test.

Table 3. Univariate associations between static and dynamic hyperinflation with pulmonary function, quality of life and exercise performance

Variable	Correlation coefficient: static hyperinflation	p value	Correlation coefficient: dynamic hyperinflation	p value
VC, l	0.583	<0.001	-0.495	<0.001
FEV ₁ , l	0.724	<0.001	-0.343	0.003
FEV ₁ , % predicted	0.711	<0.001	-0.212	0.070
FEV ₁ /FVC, %	0.415	<0.001	0.008	0.948
RV, % predicted	-0.714	<0.001	0.143	0.226
TLC, % predicted	-0.492	<0.001	0.019	0.872
Static hyperinflation	NA	NA	-0.489	<0.001
R _{aw} effective, kPa/l/s	-0.598	<0.001	0.182	0.121
DL _{CO} , mmol/min/kPa	0.399	0.001	-0.379	0.002
VE _{MPT} , l/m	-0.612*	<0.001	-0.323	0.005
6MWD, m	0.582	<0.001	-0.246	0.034
mMRC, points	-0.499	<0.001	0.195	0.097

Static hyperinflation: IC_{baseline}/TLC, %. Dynamic hyperinflation: IC_{MPT} minus IC_{baseline}, liters. NA = Not applicable; VC = vital capacity; FVC = forced vital capacity; RV = residual volume; R_{aw} = airway resistance; DL_{CO} = carbon monoxide diffusion capacity single breath; VE_{mpt} = ventilation during manually paced tachypnea. * Spearman correlation.

ed IC maneuvers to establish IC_{baseline} and IC_{MPT} were reproducible showing a mean $\pm$ SD variation coefficient of 4.7 ± 0.1 and $4.3 \pm 0.1\%$, respectively.

Immediately after the 60 s of tachypnea, we measured significantly lower IC values in all patients. In the total

Table 4. Multiple linear regression analyses with dynamic hyperinflation and 6MWD as dependent variable

Variable	B	Standard error	p value
<i>Dependent variable: dynamic hyperinflation</i>			
VC, l	-0.189	0.086	0.032
FEV ₁ , l	0.371	0.203	0.072
Static hyperinflation	-0.026	0.007	<0.001
R _{aw} effective, kPa/l/s	-0.289	0.161	0.077
<i>Dependent variable: 6MWD</i>			
VC, l	0.334	25.106	0.150
FEV ₁ , l	-0.045	58.609	0.828
Static hyperinflation	0.402	2.145	0.024
R _{aw} effective, kPa/l/s	-0.111	46.362	0.493
Dynamic hyperinflation	-0.108	34.670	0.390

Analyses were adjusted for age, height and sex. Dynamic hyperinflation: IC_{MPT} minus IC_{baseline}. Static hyperinflation: IC_{baseline}/TLC. VC = Vital capacity; R_{aw} = airway resistance.

group, IC_{baseline} was 1.97 ± 0.62 liters and IC_{MPT} was 1.32 ± 0.5 liters. The absolute change from baseline in IC was -0.65 ± 0.33 liters ($p < 0.001$; fig. 2a). IC_{baseline}/TLC was $25.5 \pm 7.5\%$ and IC_{MPT}/TLC was $17.1 \pm 6.2\%$. The absolute change from baseline in IC/TLC was $-8.4 \pm 4.3\%$ ($p < 0.001$; fig. 2b).

Table 3 shows the univariate associations of static hyperinflation and dynamic hyperinflation with pulmonary function tests, quality of life and exercise performance. Static hyperinflation as expressed by IC_{baseline}/TLC was as-

Fig. 3. Static hyperinflation (**a**) and dynamic hyperinflation (**b**) associated with exercise capacity. Dynamic hyperinflation: IC_{MPT} minus $IC_{baseline}$; static hyperinflation: $IC_{baseline}/TLC$.

Fig. 4. Comparison of $IC/TLC < 25\%$ versus $IC/TLC > 25\%$ with dynamic hyperinflation and 6MWD. Results presented in box-plots: median (horizontal line) and mean (+); whiskers: range. Dynamic hyperinflation: IC_{MPT} minus $IC_{baseline}$. **a** Dynamic hyperinflation in subjects with $IC_{baseline}/TLC < 25\%$ compared to subjects with $IC_{baseline}/TLC > 25\%$. **b** 6MWD in subjects with $IC_{baseline}/TLC < 25\%$ compared to subjects with $IC_{baseline}/TLC > 25\%$.

sociated with a shorter distance on the 6MWT ($\rho = 0.582$, $p < 0.001$; fig. 3a) as well as with worse quality of life (SGRQ; $\rho = -0.285$, $p = 0.015$) and greater severity of dyspnea (mMRC; $\rho = -0.499$, $p < 0.001$). Dynamic hyperinflation as defined by change in IC was associated with a longer distance on the 6MWT ($\rho = -0.246$, $p = 0.034$; fig. 3b), but no association was found with quality of life.

Subjects with less severe static hyperinflation (defined as an $IC_{baseline}/TLC$ ratio of $> 25\%$) showed significantly more dynamic hyperinflation, thus a greater change in IC ($\Delta IC -0.82 \pm 0.35$ liters) compared to subjects with more severe static hyperinflation (defined as an $IC/TLC_{baseline}$ ratio of $< 25\%$; $\Delta IC -0.52 \pm 0.25$ liters, $p < 0.001$; fig. 4a). The 6MWT distance was longer in subjects with less se-

Table 5. Literature overview of previous studies investigating the MPT test

Authors [Ref.]	MPT	n	FEV ₁ , l	FEV ₁ , % predicted	IC/TLC, %	ΔIC, l
Hannink et al. [25]	2 × BF rest	68	1.61±0.07	56±2	unknown	−0.62±0.04
Lahije et al. [26]	2 × BF rest	45	1.86±0.73	65±24	37 ^a	−0.54 ^a
Cooper et al. [24]	40 Hz	35	1.76±0.5	59±9	37 ^a	−0.36±0.05
Calligaro et al. [13]	40 Hz	24	1.70±0.45	59±9	37 ^a	−0.37±0.30
Gelb et al. [2]	2 × BF rest	16	1.63±0.53	60 ^a	39 ^a	−0.39±0.29
Lahije et al. [30]	2 × BF rest	53	1.60±0.6	58±22	38 ^a	−0.53 ^a
Fujimoto et al. [15]	40 Hz	59	unknown	54 ^a	unknown	−0.32±0.03
Weigt et al. [14]	40 Hz	14	1.22±0.41	43±14	30±11	−0.54
Current study	40 Hz	74	0.77±0.32	28±10	25.5±7.5	−0.65±0.33

Data are presented as means ± SD or in numbers.

^a SD value is not available.

vere static hyperinflation [6-min walking distance (6MWD) 409 ± 68 m], compared to subjects with more severe static hyperinflation (6MWD 318 ± 89 m; $p < 0.001$; fig. 4b).

The multiple regression analyses showed that the IC_{baseline}/TLC ratio (static hyperinflation) as well as vital capacity were independent predictors of dynamic hyperinflation (change in IC) and that static hyperinflation (IC_{baseline}/TLC ratio) was the only independent predictor of the 6MWD (table 4).

Discussion

We demonstrate good feasibility for the use of the MPT test to induce dynamic hyperinflation in a group of patients with severe COPD. As expected, static hyperinflation was strongly associated with dyspnea rating, quality of life, several pulmonary function outcomes and poor exercise performance. While dynamic hyperinflation was associated with both dyspnea and exercise tolerance, contrary to what had been found in more mild COPD populations, there was no association with dyspnea severity or quality of life in our population. This indicates that subjects with more preserved airflow obstruction and less static hyperinflation had more dynamic hyperinflation, which was associated with better exercise capacity.

Dynamic hyperinflation was tested using the MPT test. The protocol used in this study was based on previously published MPT protocols [13–15, 24]. Instead of using the metronome, we chose to instruct these severe patients more personally by the technician supported by real-time monitoring of the BF. Using this approach, we

achieved an average BF of 40 Hz with a very small variation in the actual frequency (range 36–43). MPT measurements may mimic the ventilatory pattern during an exercise test in patients with severe airflow obstruction. Indeed, tidal volumes decreased during the MPT test with increasing BF being responsible for the augmentation in minute ventilation [11, 12]. Although the MPT test does not exactly reflect exercise pathophysiology in this patient group, with our approach, using the MPT test, we achieved an average decline in IC of −0.65 liters indicating that our MPT test is an appropriate method to test for dynamic hyperinflation.

Previous MPT studies using protocols with a tachypnea period between 20 and 60 s and a BF of 40 Hz [13–15], or two times the resting BF [2, 25, 26], also achieved a decline in IC (table 5). All previous studies were performed in a population of patients with a mainly moderate severity of COPD, and with very few severe COPD patients as represented in our study. The results in table 5 show that the magnitude of dynamic hyperinflation is hardly related to the degree of airflow obstruction, although it is problematic to compare changes in IC between studies, given subtle differences in the protocol and respiratory patterns achieved. Studies enrolling patients with an average FEV₁ of 1.86 liters (65% predicted) [26] showed the same ΔIC of −0.54 liters compared with studies enrolling patients with an FEV₁ of 1.22 liters (43% predicted) [14]. In our population with patients who have more severe airflow obstruction, with an FEV₁ of 0.77 liters (28% predicted), we even found a greater change in IC (−0.65 liters). Table 5, in addition, shows that our study included patients with the lowest IC/TLC ratio at baseline, reflecting worse static hyperinflation.

How can we explain that our very severe COPD patients revealed the highest change in IC in the literature, yet a negative correlation with disease severity within the study? We hypothesize that dynamic hyperinflation during tachypnea may progress differently with increasing severity of airway obstruction and static hyperinflation. Young individuals without airway obstruction routinely lower their EELV and thus increase their IC during exertion. By contrast, aging individuals and those who progress from minimally to moderately obstructed will elevate their EELV and decrease their IC [23, 27, 28]. Finally, individuals who have progressed to very severe airway obstruction like in our study frequently have an already hyperinflated state at rest. Such individuals have little capacity to further increase their elevated EELV, and consequently show only modest decreases in IC. In our study, we included mainly very severe COPD patients, and, therefore, we were able to demonstrate a negative correlation between dynamic hyperinflation and disease severity. Future studies might also include a comparative group of less severe COPD patients.

As expected, we found a strong inverse correlation between static hyperinflation and exercise performance [3, 4]. Contrary to our expectations, however, we observed that a greater dynamic hyperinflation as reflected by a greater reduction in IC was associated with a longer 6MWD. This finding contrasts with observations in previous studies, which included mainly moderate COPD patients [29]. These previous studies demonstrated that the presence or magnitude of dynamic hyperinflation was either unrelated to exercise endurance and dyspnea [13, 28] or that dynamic hyperinflation was associated with a decline in physical activity [29]. In our population with severe COPD patients, 57% of these patients had an IC/TLC ratio below 25% [8], reflecting more severe static hyperinflation. These individuals thus have very little capacity

to decrease their IC even further during the MPT test or during exercise. Interestingly, the 6MWD correlated significantly with both static and dynamic hyperinflation; however, the correlation was stronger with static hyperinflation, and static hyperinflation was the only independent predictor of 6MWD in a multiple regression model. We believe that the observed negative association between dynamic hyperinflation and the 6MWD is attributable to the greater disease severity of our population and the associated severe static hyperinflation.

In conclusion, the 15-min MPT test is a feasible procedure to study dynamic hyperinflation in patients with severe COPD. Static hyperinflation in this severe group seems to be a more important contributor to limited exercise performance and poor quality of life than dynamic hyperinflation. Based on the data of this study, static hyperinflation seems to be a better predictor of exercise performance than dynamic hyperinflation. The negative correlation between the static and dynamic hyperinflation reflects the reduced capacity of very severe COPD patients to increase their already elevated static hyperinflation. Measurements of IC or change in IC in this group made during dynamic maneuvers do not further contribute to an understanding of their exercise or functional limitations, in contrast to such observations made in patients with mild and moderate airway obstruction.

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