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Resting and ADL-induced dynamic hyperinflation explain physical inactivity in COPD better than FEV_1

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Summary
Background: Physical activity and health status deteriorate early in the course of chronic obstructive pulmonary disease (COPD). This can only partially be explained by the degree of airflow limitation. Changes in (resting and dynamic) lung volumes are known to be associated with functional impairments and thus might influence physical activity level. The aim of the present cross-sectional study was to explore the contribution of dynamic hyperinflation during daily life activities (ADL) in the decline in physical activity.
Methods: Airflow limitation and inspiratory capacity at rest to total lung capacity ratio (IC/TLC) as a measure of resting hyperinflation were measured in 59 patients with COPD (GOLD I–IV). Mean daily physical activity was assessed with a tri-axial accelerometer. Measurements of dynamic hyperinflation during ADL (ΔIC and inspiratory reserve volume at end ADL) were performed at patients' home using a portable breath-by-breath system.
Results: Multiple regression analysis showed that resting as well as ADL-induced dynamic hyperinflation independently contributed to decreased daily physical activity, together explaining 45.8% of the variance in physical activity. In contrast to hyperinflation, the severity of airflow limitation (FEV_1) appeared to have no unique part in explaining how physically (in-) active patients were.

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Conclusions: The presence of resting hyperinflation and occurrence of dynamic hyperinflation during ADL contribute to reduced physical activity levels in patients with COPD, independently of the degree of airflow limitation.

Introduction

Deterioration in physical activity level and health status (HS) in patients with chronic obstructive pulmonary disease (COPD) are important patient related outcomes, which not necessarily follow the progressive airflow limitation that characterizes the disease. Although physical activity level declines with worsening of airflow limitation, there is great variability in physical activity as well as in HS within a certain degree of airflow limitation.[1–3] Part of the variability in physical activity might be explained by dynamic hyperinflation. Dynamic hyperinflation as well as the subsequent decrease in inspiratory reserve volume (IRV) is known to induce dyspnea and to limit exercise capacity in COPD.[4] One study showed that patients who hyperinflated during cardiopulmonary exercise testing had a lower level of physical activity than patients who did not hyperinflate.[5] Although ADL is less likely to require maximal exercise capacity, it has been shown that dynamic hyperinflation also occurs during dyspnea-causing activities of daily life (ADL).[6,7] A certain amount of dynamic hyperinflation may be accommodated when inspiratory capacity (IC) is preserved. But patients also may have resting hyperinflation due to the changes in lung compliance associated with COPD. This leaves them less room for dynamic hyperinflation and a critical decrease in inspiratory reserve volume (IRV) may occur even during ADL. Whether hyperinflation or a decrease in IRV during ADL is associated with physical inactivity is unknown. We hypothesized that patients who are less active would experience more hyperinflation during daily life activities (ADL).

The aim of the present study was to investigate whether ADL-induced dynamic hyperinflation additionally explains the level of physical activity in patients with COPD, next to the variance that can be explained by FEV_1. Because it depends on the amount of resting hyperinflation and the remaining IRV if dynamic hyperinflation leads to mechanical constraints, these factors were included in the analysis. Therefore, we measured physical activity level with an electronic accelerometer and measured dynamic hyperinflation and IRV during dyspnea-causing ADL. Additionally, we investigated the relations between physical activity level and HS.

Materials and methods

Subjects

Between November 2009 and March 2012, 57 patients were recruited from the outpatient population of the Radboud University Nijmegen Medical Centre and the University Centre for Chronic Diseases Dekkerswald and from general practices in close proximity of Nijmegen, The Netherlands.

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, neuromuscular or musculoskeletal disorders).

The study was approved by the local Medical Research Ethics Committee (CMO Arnhem-Nijmegen, no NL25920. 091.08) and all patients gave their written informed consent.

During a visit to the hospital, pulmonary function was measured according to the guidelines of the American Thoracic Society and European Respiratory Society.[8–10] Reference equations for the calculation of predicted values were those produced by the European Community for Steel and Coal.[11] Severity of airflow limitation was classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages.[12] Predicted normal values for inspiratory capacity (IC) were calculated as predicted total lung capacity (TLC) minus predicted functional residual capacity (FRC). Because TLC as well as FRC may increase due to changing lung compliance associated with COPD, thus preserving IC, the ratio between IC and TLC was used to reflect resting hyperinflation. Maximal voluntary ventilation (MVV) was estimated at $37.5 \times FEV_1$.[13] Additionally, a symptom-limited cardiopulmonary bicycle exercise test was performed to assess maximal exercise capacity.[13]

ADL assessment was performed during a visit at patients' home, within ten days from the hospital visit. Patients selected their individual most dyspnea-causing activity and performed this ADL until symptom limitation, task completion or for a maximum of 10 min. Measurements during ADL were performed using a portable breath-by-breath system (Oxycon Mobile, Jaeger®, CareFusion GmbH, Hoechberg, Germany).[7] This system also allows investigators to reliably track changes in IC, which reflect changes in end-expiratory lung volume due to dynamic hyperinflation.[14] IC was measured at rest[9] and at the end of ADL. The change in IC relative to resting IC ($\%\Delta IC = (IC\ end - IC\ rest)/IC\ rest \times 100$) was used to reflect the amount of dynamic hyperinflation. IRV was calculated as the difference between IC and tidal volume (VT) at end ADL and expressed as percentage of TLC. To quantify oxygen consumption (VO_2), heart rate, minute ventilation (VE), VT and peripheral oxygen saturation (SpO_2) the mean values of the last minute of ADL were used. ADL-induced dyspnea was measured with a Borg scale.

Between the hospital visit and ADL testing, patients wore a tri-axial accelerometer (Actometer)[15] for seven consecutive days to assess mean daily physical activity. The accelerometer was worn at the ankle and users were asked to wear the device day and night, except during showering, swimming etc. Minimal wearing time is 22 out of 24 h for a day to be included in the analyses. Mean physical activity was expressed as vector magnitude units (VMU).

HS was assessed by the Nijmegen Clinical Screening Instrument (NCSI), a validated instrument, described

elsewhere in detail.[16] In literature, HS is defined as covering physiological functioning, symptoms, functional impairment in daily life and quality of life as main domains.[17,18] These domains were shown empirically to be subdivided into many independent sub-domains.[19] The NCSI is an empirically composed battery of validated generic and disease-specific instruments that provide a detailed and comprehensive assessment of these sub-domains of HS. In the present study, the NCSI covered eight sub-domains of the main domains 'symptoms', 'functional impairment' and 'quality of life'. For each sub-domain, the scores of the respective instruments were summed to a sub-domain total score. Based on normative data of healthy subjects and patients with COPD, these sub-domain total scores indicated normal functioning, mild problems or severe problems for each sub-domain.[16] This allows HS evaluation on the level of the individual patient.

Statistical analyses

The One-Sample Kolmogorov–Smirnov Test was used to verify normal distribution of the variables. Normally distributed data are expressed as mean ± standard deviation. Distribution of categorical variables is described in numbers and percentages. Pearson correlations were used to investigate univariate associations between physical activity on the one hand and FEV_1%pred, resting hyperinflation (ICrest/TLC), ADL-induced dynamic hyperinflation (%ΔIC) and IRV/TLC at end ADL on the other hand.

The impact of ICrest/TLC, %ΔIC and IRV/TLC at end ADL on physical activity was analyzed by performing standard multiple linear regression analyses. First, we analyzed FEV_1 (%pred) as explanatory variable for physical activity. Then, ICrest/TLC, %ΔIC and IRV/TLC at end ADL were added in a second model to evaluate whether they additionally explained the variance in physical activity. Statistical significance was set at a p-value < 0.05.

Results

Characteristics

In Table 1, anthropometrics, pulmonary function and exercise capacity of the study population are described. Age ranged from 48 to 77 years and 63% of the patients was male. Twenty percent of the patients was current smoker. Forty-two percent of the patients used either short- or long-acting β_2-agonists, 73% used anticholinergics, 10% used a combination preparation of β_2-agonist and anticholinergic, and 71% used inhaled corticosteroids.

Level of physical activity and health status

Mean activity level was 39.8 ± 12.2 vector magnitude units (range 12–70). Fig. 1 depicts the large variance in physical activity within GOLD stages.

The number of patients experiencing normal functioning, mild or severe problems respectively for each sub-domain of HS are described in Table 2. Seventy-eight percent of the patients experienced severe problems in one or more sub-domains of HS.

Table 1 Characteristics of the study population (n = 57 patients).

	Mean ± sd
Anthropometrics	
Age, year	64.1 ± 7.1
Sex, M/F	35/22
Weight, kg	79.3 ± 17.2
Height, cm	171.1 ± 8.0
BMI, kg/m^2	27.0 ± 5.0
Pulmonary function	
GOLD stage I/II/III/IV, n	15/22/14/6
FEV_1 post-bronchodilator, L (%pred)	1.81 ± 0.74 (64 ± 24)
FEV_1/FVC post-bronchodilator, %	46 ± 14
TLC, L (%pred)	7.27 ± 1.48 (114 ± 22)
RV, L (%pred)	3.55 ± 1.07 (153 ± 43)
IC/TLC, %	38 ± 9
RV/TLC, %	49 ± 10
DL_{CO}, %pred	58 ± 24
Exercise capacity	
Peak work load, W	106 ± 45
Peak VO_2, L/min (%pred)	1.54 ± 0.52 (81 ± 21)
Peak VE, L/min (%MVV)	58.9 ± 17.8 (90 ± 24)
Peak HR, beats/min	137 ± 18
Dyspnea (Borg)	6.6 ± 2.2
Leg discomfort (Borg)	5.4 ± 2.2

BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; IC: inspiratory capacity; DL_{CO}: diffusion capacity of the lung for carbon monoxide; VO_2: oxygen consumption; VE: minute ventilation; MVV: maximal voluntary ventilation; HR: heart rate; %pred: percentage of predicted normal values.

The fact that there are patients without severe problems in any sub-domain, but also patients with severe problems in all sub-domains, shows that there was a large heterogeneity regarding HS in this population.

Measurements during ADL

Patients chose different dyspnea-causing activities. These ADL varied from household activities to gardening

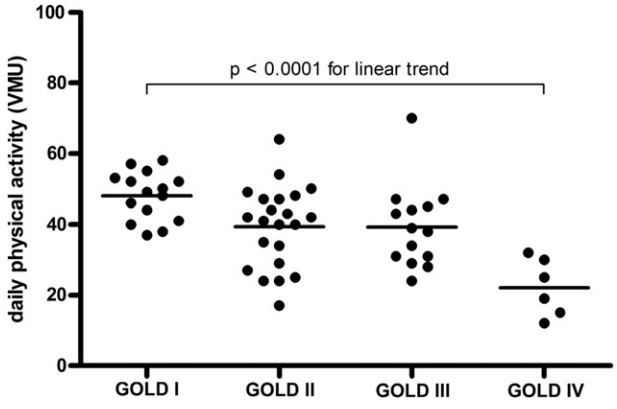

Figure 1 Physical activity data of the individual subjects per GOLD stage.

Table 2 The number of patients experiencing normal functioning, mild or severe problems in each sub-domain of the Nijmegen Clinical Screening Instrument.

Main domain	Normal scores	Mild problems	Severe problems
Sub-domain (normal, mild problems, severe problems)	*N* (%)	*N* (%)	*N* (%)
Symptoms			
Subjective pulmonary symptoms ($\leq$2, $>$2$\leq$9, $>$9)	3 (5)	26 (46)	28 (49)
Dyspnea emotions ($\leq$8, $>$8$<$12, $\geq$12)	20 (35)	19 (33)	18 (32)
Fatigue ($<$27, $\geq$27$<$35, $\geq$35)	14 (25)	13 (234)	30 (53)
Functional impairment			
Behavioral impairment ($\leq$2.91, $>$2.91$\leq$17.38, $>$17.38)	14 (25)	26 (46)	17 (30)
Subjective impairment ($\leq$4, $>$4$\leq$11, $>$11)	2 (4)	26 (46)	29 (51)
Quality of life			
General quality of life ($\leq$11.36, $>$11.36)	22 (39)	–	35 (61)
Health-related quality of life ($\leq$3, $>$3$\leq$5, $>$5)	19 (33)	24 (42)	14 (25)
Satisfaction relations ($\leq$2, $>$2$\leq$4, $>$4)	28 (49)	20 (35)	9 (16)

For each sub-domain of HS the cut-off values for normal scores, mild problems and severe problems are described between brackets.[16]

(online attachment e-Table 1). Mean duration of ADL was 07:51 $\pm$ 02:53 min. Mean dyspnea score at end ADL was 5.1 on the Borg scale and varied between 0.5 and 10 (ΔBorg 3.6 $\pm$ 2.0). Physiologic responses to ADL are presented in Table 3. Eighteen percent of the patients ($N = 10$) had a decreased breathing reserve (VE/MVV > 0.85 and/or MVV-VE < 11L) during ADL. In 32% of the patients ($N = 18$) IRV decreased to less than 0.5L[20] or less than 10% of TLC.[13] Oxygen desaturation ($\Delta SpO_2 \leq -4\%$) during ADL occurred in 20 patients; only one patient had $SpO_2 \leq 80\%$ at end ADL.

Associations

Mean daily physical activity was associated with airflow limitation (FEV_1%pred) and ICrest/TLC as well as with %ΔIC and IRV/TLC at end ADL (Table 4).

Table 5 shows the changes in total variance (R^2) with these variables added into the multiple regression model, as well as the contribution of each independent variable to the variance in physical activity (B). In the first model FEV_1%pred explained 24.5% of R^2 in daily physical activity in the study population. The second model explained an additional 21.3% of R^2. However, in this second model, FEV_1%pred and IRV/TLC appeared to have no unique part in physical activity ($p = 0.939$ and $p = 0.940$ respectively). Resting and dynamic hyperinflation were independent explanatory variables ($p < 0.05$ for B). This means that resting and dynamic hyperinflation explained 45.8% of the variance in physical activity ($R = 0.677$).

Analyses of the relationships between physical activity and sub-domains of HS showed significant associations in all domains except for the sub-domains of 'fatigue' and 'satisfaction with relations'. The strongest association was found between physical activity and 'behavioural impairments' ($r = -0.56$, $p < 0.001$). A more detailed description can be found in e-Table 2.

Table 3 Measurements at start and end of ADL.

	Rest	End ADL
Borg score, au	1.5 $\pm$ 1.4	5.1 $\pm$ 2.3
VO_2, L/min (%pred)	0.34 $\pm$ 0.07	1.09 $\pm$ 0.32
	(18.9 $\pm$ 5.9)	(59.1 $\pm$ 16.5)
HRR, bpm	79.7 $\pm$ 13.8	54.5 $\pm$ 15.6
VE, L/min (%MVV)	13.8 $\pm$ 3.4	34.9 $\pm$ 8.2
	(23.8 $\pm$ 10.8)	(57.7 $\pm$ 18.9)
IC, L	2.76 $\pm$ 0.77	2.37 $\pm$ 0.79
ΔIC, %IC rest	–	−14.1 $\pm$ 15.4
IRV, L (%TLC)	1.82 $\pm$ 0.63	0.98 $\pm$ 0.52
	(25.4 $\pm$ 7.6)	(13.8 $\pm$ 6.9)
SpO_2, %	96.2 $\pm$ 2.5	92.8 $\pm$ 5.5

Mean $\pm$ sd. Au: arbitrary units; VO_2: oxygen uptake; HRR: heart rate reserve (= 220−heart rate); VE: minute ventilation; MVV: maximal voluntary ventilation; ΔIC: change in inspiratory capacity from rest; IRV: inspiratory reserve volume; TLC: total lung capacity; SpO_2: oxygen saturation.

Discussion

This study shows that both resting hyperinflation and ADL-induced dynamic hyperinflation uniquely contribute to a lower level of physical activity in patients with COPD. In other words, the large variance in physical activity within patients with a given level of FEV_1 can partially be

Table 4 Pearson's correlation coefficients for the relation between physical activity and possible determinants.

	Physical activity	95% CI
FEV_1 (%pred)	0.50#	0.27−0.67
ICrest/TLC	0.60#	0.40−0.74
%ΔIC	0.42*	0.18−0.61
IRV/TLC	0.57#	0.36−0.72

FEV_1: forced expiratory volume in 1 s; ICrest/TLC: ratio between inspiratory capacity at rest and total lung capacity; ΔIC: relative change from ICrest during ADL; IRV: inspiratory reserve volume at end ADL; *$p < 0.01$; #$p < 0.001$; CI: confidence interval of the correlation coefficient.

Table 5 Results of multiple regression analyses with mean daily physical activity as dependent variable.

Model		Unstandardized coefficients		*p*-value	R^2	R^2 Change
		B	SE			
	(Constant)	23.611	4.128			
	FEV_1%pred	0.255	0.061	**<0.001**		
1					**24.5%**	–
	(Constant)	14.194	6.664			
	FEV_1%pred	−0.006	0.084	0.939		
	ICrest/TLC	78.546	24.677	**0.002**		
	%ΔIC	0.270	0.132	**0.046**		
	IRV/TLC	−0.027	0.354	0.940		
2					**45.8%**	**21.3%**

Independent determinants of physical activity in the models are marked by bold print of their respective *p*-values.

explained by the amount of resting hyperinflation these patients have and the dynamic hyperinflation that occurs during activities they perform in daily life. Additionally, a lower level of physical activity appears to be associated with worse health status.

The results showed that both resting hyperinflation and ADL-induced dynamic hyperinflation together explain almost 46% of the variance in daily physical activity of patients with COPD. With both measures for hyperinflation included in our multivariate analysis, it appeared that severity of airflow limitation does not have a unique contribution to patients' level of physical activity. Garcia-Rio et al.,[5] found lower levels of physical activity in patients who hyperinflated during incremental exercise testing, regardless of their severity of airflow limitation. Following up on these results, the present study now shows in real life that hyperinflation during daily life activities is more relevant for physical activity than airflow limitation. A characteristic feature of this study is the fact that patients chose their individual most dyspnea-causing activities themselves. Because patients were asked to select ADL that they performed regularly, the changes in lung volumes we observed are thus representative of regularly occurring phenomena.

Recently, several studies have indicated that a deterioration in physical activity starts early in the course of COPD.[2,3,21] So far, the reason for this decline is not completely understood. Airflow limitation may play a role, but correlations are weak to moderate and do not explain why deterioration starts when FEV_1 is still relatively preserved.[2,21,22] Due to the difference in algorithms that are used to convert the output signal of accelerometers into VMU's, comparison of the physical activity levels to other studies is limited. We found a decline in physical activity with increasing GOLD stage as well. Yet, with the large variance in physical activity within GOLD stages and the major overlap between GOLD stages, we could not show significant differences.

In earlier studies, we demonstrated that dynamic hyperinflation occurs during ADL[6,7] and therefore we presumed a relationship between the amount of dynamic hyperinflation induced during regularly performed activities in daily life and a decline in physical activity.

In general, patients with lower FEV_1 tend to have more resting hyperinflation,[23,24] i.e. IC and thus IRV are already lower at rest. Any extra hyperinflation during physical activity adds to the already elevated end-expiratory lung volume, leaving less room for the expansion of tidal volume that comes with increasing minute ventilation. In severe COPD dynamic hyperinflation is likely to lead to such mechanical constraints on tidal volume. At some point, further increase in the effort to breathe does not result in an equal increase in tidal volume, known as neuromechanical dissociation. This causes a sharp increase in symptoms and impairments that patients experience. In mild-to-moderate COPD this neuromechanical dissociation not necessarily happens, because IC is still large. Despite the fact that, in the present study, a considerable amount of dynamic hyperinflation was shown during ADL, a critical decrease in IRV (to less than 0.5L[20] or less than 10% of TLC[13]) occurred in only ~30% of the subjects. That might explain why lower IRV at the end of ADL did not contribute to a lower level of physical activity, when FEV_1 and hyperinflation were already taken into account. Yet, an increase in inspiratory effort due to the extra elastic and threshold loading of the inspiratory muscles that comes with (dynamic) hyperinflation most likely occurred.[4,25] Especially in patients who have less room to hyperinflate this increasing effort might discourage them to maintain their activities. This is supported by the final model in which both resting and dynamic hyperinflation remain as a unique contributor to mean daily physical activity.

Next to patients' level of physical activity we measured HS. Though the study population mainly consists of patients with mild-to-moderate airflow limitation, 78% of the patients experienced severe problems in one or more sub-domains of HS. This is in line with a recent study of Jones et al., who also found marked impairments in HS in patients with mild COPD.[1] Studies investigating HS showed that sub-domains of HS are poorly related to airflow limitation.[22] Physical activity, important for maintaining health,[26] was found to be an independent predictor of quality of life.[27,28] Whether there is a causal relation between physical activity and sub-domains of HS cannot be concluded from this cross-sectional study.

Clinical relevance

Because physical (in-) activity is related to hospitalization, mortality and lung function decline[29,30] and to the

occurrence of systemic effects[31] and comorbidities,[32] promoting physical activity in patients with COPD is now recommended from an early stage of disease on.[12] Most likely physical inactivity causes deconditioning, leading to more symptoms and impairments and thus more inactivity.[33] Since the decrease in physical activity in patients with COPD cannot be predicted by monitoring FEV_1, it is important to measure resting and operating lung volumes, because these are significant contributors to physical activity in COPD. Likely, the association between airflow limitation and physical activity is mediated through the amount of resting hyperinflation and the occurrence of dynamic hyperinflation. Detecting the occurrence of dynamic hyperinflation during ADL is important, but may be unfeasible in clinical practice. However, this can be determined alternatively during CPET or voluntary hyperventilation. Given that our results indicate that patients who hyperinflate during their own daily activities might be at risk of becoming inactive, early detection and treatment of hyperinflation may be a key aspect in the prevention of inactivity.

In conclusion, resting hyperinflation and the dynamic hyperinflation that occurs during activities that patients perform in daily life explain levels of physical activity in patients with COPD better than FEV_1. Therefore, hyperinflation deserves attention in the monitoring of patients with COPD.

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The study was conceived by HvH, RD, JV and YH. The protocol was developed by AL, HvH and YH. Data collection was performed by AL. Data were analyzed by AL and HvH and interpreted by all contributing authors. Outline of the manuscript was completed by AL, HvH, JV and YH. The manuscript was reviewed and revised by all authors. All authors approved the final version.

AL had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2013.02.017.

Conflicts of interest

No conflicts of interest were reported by the authors of this paper.

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