Severe physical inactivity in chronic obstructive pulmonary disease: changes in systemic inflammation after pulmonary rehabilitation – a pilot study

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Abstract

Background The purpose was to investigate whether severe physical inactivity (SPI) is associated with altered levels of common inflammatory markers as compared to higher Physical activity levels (PALs), and whether pulmonary rehabilitation would reduce the levels of systemic inflammation in SPI in patients with COPD.

Methods This prospective, cohort study was conducted in four rehabilitation centers in Region Zealand, Denmark. We included patients with COPD referred for 7-12 weeks of pulmonary rehabilitation (2-hours of exercise therapy and education twice weekly). We measured b-eosinophils, p-fibrinogen, p-CRP, s-IL-6, s-CD 163, nasal lavage-IL-8, and daily physical activity, using a validated activity monitor, SenseWear®, at baseline and after rehabilitation. SPI was defined as PAL <1.4.

Results In total, 31 of 57 patients were SPI at baseline, and seven (23%) of these patients improved to non-SPI after pulmonary rehabilitation. We observed no significant differences in the primary endpoint *i.e.* change in systemic inflammation between patients who remained SPI at both time points vs. patients who improved PAL from SPI at baseline to non-SPI at follow-up. At baseline, SPI was associated with significantly higher p-fibrinogen levels ($p=0.04$) than non-SPI, but no other differences were observed between SPI and non-SPI.

Conclusion In a cohort of patients with COPD attending pulmonary rehabilitation, we could not demonstrate any differences or changes in systemic inflammation or PAL following rehabilitation between patients with SPI and non-SPI. This might be a true negative finding or due to a high pro-inflammatory drive in all patients regardless of SPI status or study limitations such as suboptimal levels of rehabilitation intensity and SPI cut-off level.

The study was registered at ClinicalTrials.gov (NCT01700296), <https://register.clinicaltrials.gov>. Registered in November 2012.

Background

Chronic obstructive pulmonary disease (COPD) is associated with sedentary lifestyle especially in advanced stages. A minority of patients with COPD are severely physical inactive (SPI), defined as a total daily energy expenditure/resting energy expenditure ratio <1.4¹. SPI is inversely correlated to disease severity, including lung function decline, disease burden, frequency of hospitalization and mortality in patients with COPD²⁻⁴, and recent evidence suggests that patients with SPI does not improve as much from pulmonary rehabilitation as the general COPD population⁵. Current evidence increasingly supports the association between reduced lung function and systemic inflammation and a possible link with comorbidities such as cardiovascular disorders, skeletal muscle dysfunction, diabetes, and osteoporosis^{6,7}. Stable COPD is associated with elevated levels of systemic inflammatory markers such as leukocytes, eosinophils, CRP, IL-6, IL-8, fibrinogen, and TNF- α ^{6,8-12}. Lifestyle factors such as smoking,

poor nutrition, low physical activity level (PAL) and obesity are known to increase systemic and/or local inflammation in COPD^{10,13,14}. The association between physical inactivity and systemic inflammation is particularly interesting as it is present not only in COPD, but across a range of chronic conditions^{15,16} thereby potentially contributing to the link between systemic inflammation, COPD disease severity and comorbidities. As exercise therapy and other types of physical activity is known to be anti-inflammatory¹⁷, physical inactivity constitutes a highly relevant target for treatment to reduce inflammation and disease symptoms. This is further substantiated by the fact that exercise therapy, typically as part of pulmonary rehabilitation, improves health-related quality of life and exercise capacity in the general population of patients with COPD^{18,19}. It is unknown, whether SPI is associated with worse systemic inflammation as compared to higher PALs in patients with COPD, and whether pulmonary rehabilitation can reduce systemic inflammation in patients with SPI. This is important to know to be able to individualize treatment in patients with COPD and SPI.

Therefore, we aimed at investigating whether SPI is associated with altered levels of common inflammatory markers as compared to higher PALs, and whether pulmonary rehabilitation (exercise therapy and education) would reduce the levels of systemic inflammation in SPI. We hypothesized, that patients with SPI would have increased systemic inflammation and that measurable improvements in PAL after pulmonary rehabilitation – especially changing from SPI to non-SPI – would lead to measurable reduction in systemic inflammation.

Methods

Design

We have recently published the clinical data and study design⁵. Briefly, this was a prospective, observational cohort study conducted in 2013-2014 at four pulmonary rehabilitation units in Region Zealand, Denmark. The reporting of this study adheres to the STROBE guidelines²⁰

The study was approved by the Danish National Ethical Committee, and complied with the Declaration of Helsinki. Written and oral informed consent was obtained from all participants.

The study was registered at ClinicalTrials.gov (NCT01700296).

Participants

Patients referred for pulmonary rehabilitation were included if they fulfilled the following eligibility criteria: physician-diagnosed COPD; no exacerbations in the past four weeks prior to inclusion, ability to give informed consent, no life-threatening comorbidity (*eg.* malignancy or severe heart failure), and no history of asthma.

Rehabilitation

The reporting of the rehabilitation adheres to the TIDieR guidelines²¹. Pulmonary rehabilitation was conducted according to Danish national guidelines as a multidisciplinary, non-pharmacological intervention using supervised exercise therapy and patient education²². Patients attended either one of three municipal rehabilitation centers or a hospital-based rehabilitation program. As this was an observational study, the duration of the program varied between seven and twelve weeks due to differences between the individual rehabilitation programs. Other than that, the content of the rehabilitation program was similar according to the national treatment guidelines. The program consisted of two-hour sessions twice weekly: one hour of exercise therapy, equally distributed between endurance and strength training under supervision of a physical therapist, and one hour of patient education by an assigned nurse or other relevant professionals e.g. oxygen specialist. Initially, 30 min of strength training was performed in weight training machines for mm. pectoralis major, deltoid, biceps brachii, triceps and quadriceps. Patients performed 3 x 12 repetitions at 50–80% of one repetition maximum (1-RM). The 1-RM test was repeated halfway to re-establish the workload. Subsequently, 30 min. of endurance training was performed at moderate intensity adjusted individually to level 14–15 on the Borg scale of perceived exertion. The endurance training included either cycling on an ergometer or walking on a treadmill. Education included disease-, nutritional- and pharmacological education in addition to smoking cessation assistance to optimize the performance and autonomy of patients with chronic respiratory impairment.

Outcomes

The participants were examined twice: at first day of the rehabilitation course (before the first rehabilitation session (baseline), and in the week after completing the rehabilitation (follow-up).

Primary endpoint: Between-groups differences in change of inflammatory markers levels between patients with SPI at baseline who at follow-up still have SPI vs. those improving to non-SPI.

Secondary endpoints:

Baseline differences in levels of inflammatory markers between patients with SPI vs. non-SPI.

Protocol deviations

The current study deviates from our original protocol (clinicaltrials.gov number NCT01700296) in two ways. Firstly, the Ethics Committee disapproved of including a control group not attending the physician-requested pulmonary rehabilitation. Secondly, we chose to examine the short-term outcome as long-term systemic inflammation is affected by many non-COPD related factors, such as rhinitis, cardiovascular diseases, chronic liver disease etc., which we could not control or adjust for.

Basic measurements

Our publication on clinical characterization of SPI in COPD included details on measurements of *e.g.* forced expiratory volume in first second (FEV₁), 6-minute walk test, and patient-reported outcomes. For further details on the results of these measurements please refer to reference ⁵.

Objective measurement of physical activity including Severe Physical Inactivity

PAL was measured with an activity monitor (SenseWear[®] Armband, Bodymedia, Pittsburgh, PA) continuously worn for seven days after each study visit. SenseWear[®] has previously been validated for use in COPD¹. The activity monitor is worn on the back of the upper right arm at the level of the triceps. It assesses accelerations in two planes using a bi-axial accelerometer, and measures and stores skin temperature, near body temperature, heat flux, and galvanic skin resistance. Output from the SenseWear[®] includes total energy expenditure, daily time in sedentary-, light-, moderate- and hard activity as well as number of steps.

In the current study, PAL was calculated as total daily energy expenditure divided by resting energy expenditure in kcal measured by the activity monitor. Based on a previous study cut-offs for PAL were defined as PAL ≥ 1.70 : active person, 1.40-1.69: sedentary person; and <1.40 : SPI²³.

Data from patients with $\geq$ two days of $\geq 90\%$ wearing time were included.

Laboratory analyses

Besides measuring leukocytes and eosinophils in blood, CRP, IL-6, IL-8, fibrinogen, and TNF- α in serum, we also measured serum CD163 (overexpression on lung alveolar macrophages may be involved in COPD pathogenesis²⁴, and s-CD163 correlates to sputum-IL8^{14,24}), and nasal lavage-IL-8 (marker of inflammation in lower airways in COPD^{11,25 10,26}).

Serum and plasma samples: 5 mL samples of both serum and plasma were collected in sterile tubes and centrifuged, and the supernatant was kept for later analysis of the inflammatory markers IL-6, IL-8 and CD 163 at -80°C . Levels of biomarkers were measured at The Respiratory Research Unit, Bispebjerg University Hospital, using commercial ELISA kits (Human IL-6, IL-8 and sCD163 Quantikine high sensitivity ELISA; R&D Systems, Minneapolis, MN, USA).

Blood samples: CRP (Dimension Vista, Siemens Healthcare Headquarters GmbH, Erlangen, Germany), eosinophils (Sysmex XE-5000, Sysmex Corporation, Kobe, Japan), and fibrinogen (STAGO, Triolab AS, Brøndby, Denmark) were measured at all visits. All blood samples were analysed at Naestved Hospital, Department of Clinical Biochemistry immediately following each visit.

Nasal lavage

Nasal lavage was performed using a technique adapted from Hilding and Hurst^{10,26}. A 12F Foley catheter, modified by removal of the tip distal to the balloon, was inserted into the nostril and inflated with sufficient volume of 0.9% saline solution to form a comfortable seal, typically 7 to 10mL. With the head of the patient flexed forward, a volume of 7 mL 0.9% saline solution was instilled through the catheter, and was washed in and out of the nasal cavity three times using a 100 mL syringe. The nasal wash was collected in sterile tubes and stored at -80°C , for later analysis of IL-8.

Sample size calculation

The sample size calculation was based on the clinical study⁵. However, assuming a significant level (α) of 0.05, power ($1-\beta$) of 0.80, minimal clinically important difference (MCID) of 20%, and a standard deviation of 2 times MCID, a total number of 34 patient was needed to detect a 20% difference in change in IL-8 levels between patients with SPI at baseline who at follow-up still have SPI vs. those improving to non-SPI.

Statistics

As data were not normally distributed, we used non-parametric statistics. Continuous data were presented as median (range), and categorical data as n (%). Differences were assessed using Wilcoxon signed-rank test (continuous data) resp. Chi2-test (categorical data). Kruskal-Wallis test for trend was performed for coherence between PAL tertiles and inflammation, and Spearman's rho was used for correlation analyses. Statistical significance was defined as $p < 0.05$ and all analyses were performed using professional statistical software (STATA 14.1; StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Results

Patients

In total, 31 patients out of the 57 patients were classified as SPI at baseline. After rehabilitation, seven of these patients (23%) became non-SPI, as they increased their daily level of objectively measured physical activity (PAL) to ≥ 1.4 . None of the study participants were treated with oral corticosteroids or antibiotics within four weeks prior to baseline or follow-up visits. Complete data sets of SenseWear[®] and inflammatory markers were available in 66-76% of patients: nl-IL-8 68% ($n=40$), IL-6 68% ($n=40$), CD-163 66% ($n=39$), and fibrinogen, eosinophils and CRP 76% ($n=45$).

Inflammatory markers at baseline

Table 1 shows that patients with SPI had slightly, yet significantly, higher fibrinogen than patients without SPI, ($p=0.04$), but otherwise no significant differences were observed. Subdividing PAL into tertiles did not result in significant differences for any of the inflammatory marker (Table 2). Figure 1a-c shows the lack of association between baseline PAL and inflammatory markers.

In total, 20 (39%) were current smokers (median pack-years: 41), and 30 (59%) used daily-inhaled corticosteroids (ICS). We observed no association between neither ICS use nor current smoking and levels of inflammatory markers (data not shown). Summarized a large deviation on all inflammatory markers were seen.

Changes in inflammatory markers after pulmonary rehabilitation

Table 3 depicts that shifting from SPI at baseline to non-SPI at follow-up was only associated with significant changes in fibrinogen ($p=0.04$) compared to patients with SPI at both time points. Although a lower CD-163 and nl IL-8 was observed in patients with non-SPI after rehabilitation, the difference was not significant, potentially due to a small sample size and large variation. Figure 2a-c show that improvement in PAL was not associated with significant changes in inflammatory markers.

Discussion

SPI is associated with morbidity and mortality in COPD^{2,3} and reduced lung function is associated with systemic inflammation^{6,7}, highlighting that interventions aimed at SPI and inflammation are needed. However, in this pilot study, including patients with COPD attending pulmonary rehabilitation (exercise and education), we observed that neither Severe Physical Inactivity (SPI) nor improvement in physical activity levels were associated with levels of inflammatory markers.

We used validated motion sensors¹, since recollection of performed physical activity is poor²⁷, and we used well-validated methods for measuring relevant biomarkers¹³. However, even though it might be true negative findings, several reasons might account for the non-significant findings. First, our study sample was small, indicating that the lack of significant findings might be a result of a type II error, yet statistically significant changes in systemic inflammation has previously been demonstrated in a rehabilitation study with even lower number of patients²⁸. Individual variation in inflammatory markers over time¹², or too small changes in physical activity to elicit inflammatory changes might also explain our negative findings^{13,19,29}. There is no well-established cut-off for the minimal exercise intensity or duration to lower systemic inflammation. The pulmonary rehabilitation offered in our study followed national guidelines³⁰. Indeed, we demonstrated at best a modest mean increase in PAL but in the current study we focused on responders to rehabilitation *i.e.* those who actually improved their daily level of physical activity. Even though PAL improved which lead some patients to go from SPI to non-SPI, the patients still fulfilled the criteria of sedentary lifestyle²³. This suggests that further improvements in PAL is needed in order to reduce inflammation.

In COPD, local or systemic inflammation is influenced by phenotype, medication as well as several non-COPD factors, such as comorbidities, smoking status, nutrition, physical activity, age and drugs^{10,31,32}. Participants in our study were stable with respect to treatment, weight, comorbidities and smoking habits. The study design excluded patients with acute exacerbation four weeks prior to baseline or follow-up. Researchers have found no relation between smoking status and inflammatory markers³³, though other studies show an association of smoking and inflammatory status³⁴. It can be speculated that the inflammation in COPD patients with SPI is not primarily driven by the low level of physical activity but by all contributing factors leading to SPI^{6,10}. Thus, improving PAL affects only one of several pro-inflammatory causes, which in our low-volume study resulted in an undetectable alteration in inflammation. Yet, Waschki *et al*/prospectively found in 170 patients with stable COPD that PAL was a

superior predictor for 2 year-mortality compared to cardiovascular, nutritional, respiratory, muscular, depression status or biomarkers²⁵.

Our assessment of inflammation was primarily based on serology. We included no measurements from the lower airways. Nasal lavage served as a proxy marker for lower airway inflammation, using a previously described protocol for sampling, and we found similar levels of nasal IL-8^{25,26}. The nose is not the target organ in COPD, and it is likely that bronchoalveolar sampling by sputum or bronchoscopy would allow detection of higher and more physiologically relevant levels of inflammatory markers^{35,36}. Future studies should incorporate sampling from lower airways, e.g. spontaneous or induced sputum which is obtainable from the majority of patients with COPD¹⁴.

Conclusions

In conclusion, we did not find any differences in systemic inflammation or changes in systemic inflammation or PAL following the rehabilitation between patients with SPI and non-SPI. We speculate that suboptimal intensity and duration of daily physical activity despite improvement as well as measurement of inflammation in clinically irrelevant compartments might play a role for the negative findings. SPI remains a serious challenge in COPD as a grave prognosticator of morbidity and mortality.

List Of Abbreviations

COPD: Chronic Obstructive Pulmonary Disease

PAL: Physical Activity Level

SPI: Severe Physical Inactivity

Declarations

Ethics approval and consent to participate

The study was approved by the Danish National Ethical Committee, and complied with the Declaration of Helsinki. Written and oral informed consent was obtained from all participants.

The study was registered at ClinicalTrials.gov (NCT01700296).

Consent for publication

Not applicable.

Availability of data and materials

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request

Competing interests

Dr. Skou is associate editor of the Journal of Orthopaedic & Sports Physical Therapy, has received grants from The Lundbeck Foundation, personal fees from Munksgaard, all of which are outside the submitted work. He is co-founder of Good Life with Osteoarthritis in Denmark (GLA:D®), a not-for profit initiative hosted at University of Southern Denmark aimed at implementing clinical guidelines for osteoarthritis in clinical practice.

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Authors contribution

MT has as a part of her PhD contributed substantially in all aspects of the work.

UBT has as a main supervisor of the PhD project also contributed substantially in all aspects, except data collection.

AL has made substantially contributions in the interpretations of data as well as having substantially revised the manuscript.

SS has made substantially contributions in the interpretations of data as well as having substantially revised the manuscript.

JL has made substantially contributions in acquisition and analysis of the laboratory samples.

All authors have read and approved the manuscript

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Tables

Table 1. Systemic and airway inflammation at baseline stratified by patients with Severe Physical Inactivity (SPI) (n=31) or non-SPI (n=20)

	Baseline		
	SPI (n=31)	Non-SPI (n=20)	<i>p</i>
s-IL-6 pg/ml (range)	2.7 (1.1-9.1)	2.3 (0.1-9.6)	0.31
nl-IL-8 pg/ml (range)	113.8 (19.2-2572.8)	253.4 (16.8-1571.4)	0.31
s-CD-163 pg/ml (range)	64.2 (26.3-127.3)	64.1 (20.5-123.6)	0.94
CRP mg/L (range)	3.8 (0.4-55.0)	2.8 (0.9-25.0)	0.34
Eosinophils 10 ⁹ /l (range)	0.2 (0-2.1)	0.2 (0.1-0.5)	0.17
Fibrinogen µmol/l (range)	13.3 (6.2-23.6)	11.2 (6.5-16.7)	0.04

nl= nasal lavage,

Table 2. Physical Activity Level tertiles and inflammatory markers at baseline

	Baseline Physical Activity Level			
	Lowest tertile	Middle tertile	Highest tertile	<i>p</i>
PAL (range)	1.2 (1.1-1.2)	1.3 (1.3-1.3)	1.4 (1.4-2.1)	-
s-IL-6 pg/ml (range)	3.2 (1.9-9.1)	2.1 (1.1-6.3)	2.7 (0.1-9.6)	0.40
nl-IL-8 pg/ml (range)	139.3 (26.3-1136.0)	103.2 (19.2-2572.8)	273.8 (16.8-1571.4)	0.40
s-CD-163 pg/ml (range)	71.0 (43.3-76.4)	57.8 (26.3-127.3)	69.5 (20.5-123.6)	0.40
CRP mg/L (range)	6 (0.4-55)	3.3 (0.4-23.0)	2.8 (0.9-25.0)	0.40
Eosinophils 10 ⁹ /l	0.1 (0-0.5)	0.2 (0.0-2.1)	0.2 (0-0.5)	0.07
Fibrinogen μ mol/L (range)	14.4 (9.9-23.6)	12.2 (6.2-16.8)	12.1 (6.5-16.9)	0.40

nl= nasal lavage,

*chi2 >0.05 for trend

Table 3. Patients with Severe Physical Inactivity (SPI) at baseline (n=31): changes in systemic and airway inflammation during pulmonary rehabilitation stratified by change in SPI-status (persistent SPI vs. patients with non-SPI after rehabilitation)

	Follow-up		
	SPI (n=24)	Non-SPI (n=7)	<i>p</i>
s-IL-6 pg/ml (range)	0.3 (-3.0-1.3)	-0.1 (-3.3-1.0)	0.99
nl-IL-8 pg/ml (range)	5.7 (-995.1-568.5)	-83.6 (-2190.3-463.8)	0.47
s-CD-163 pg/ml (range)	2.4 (-52.4-40.4)	-19.2 (-1.6-28.2)	0.08
CRP mg/L (range)	0 (-15.0-20.0)	-0.4 (-48.8-0.9)	0.19
Eosinophils 10 ⁹ /l (range)	0 (-0.3-0.4)	0 (0-0.1)	0.51
Fibrinogen μ mol/L (range)	-0.6 (-16.9-9.9)	-0.4 (-11.2-1.2)	0.04

nl= nasal lavage

Figures

Figure 1

a: Association between PAL an log IL-8 at baseline. b: Association between PAL an log IL-6 at baseline. c: Association between PAL an log CD-163 at baseline.

Figure 2

a: Association between PAL and IL-8 from baseline to follow-up b: Association between PAL and IL-6 from baseline to follow-up c: Association between PAL and CD 163 from baseline to follow-up

Supplementary Files

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- [STROBEchecklistcohort.pdf](#)